THE EPIDEMIOLOGY OF CARDIAC ARREST

IN-HOSPITAL RISK ASSESSMENT, TREATMENT AND OUTCOME

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Cover illustration: "*Still alive"*, a joint venture of my children

The epidemiology of cardiac arrest –
in-hospital risk assessment, treatment and outcome

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"Do one thing every day that scares you."
Eleanor Roosevelt

To my children,
the most meaningful *thing* of all

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ABSTRACT

AIM: To describe and analyse sudden cardiac arrest, both in hospital and out of hospital, from an epidemiological perspective, by early prediction, by comparing changes over time in relation to aetiology, characteristics, treatment, survival or mortality and by identifying factors associated with outcome.

METHODS: This thesis is based on four observational studies, including patient information from the Swedish Registry for Cardiopulmonary Resuscitation, in and out of hospital, and from a local registry on medical emergency team assessment at Sahlgrenska University Hospital.

RESULTS: In ***Paper I***, the 30-day survival after out-of-hospital cardiac arrest in Sweden among patients found in a shockable rhythm increased from 12% in 1992 to 23% in 2009. Strong predictors of survival were a short interval from collapse to defibrillation, bystander cardiopulmonary resuscitation (CPR), female gender and out-of-hospital cardiac arrest outside home. In ***Paper II***, in Sahlgrenska University Hospital, the 30-day survival after an in-hospital cardiac arrest, on monitoring wards, increased significantly from 43.5% in 1994 to 55.6% in 2013. There was a significant reduction in the delay from collapse to the start of CPR and an increase in the proportion of patients defibrillated before the cardiac arrest team arrived. On the non-monitoring wards, there were no significant changes in survival; there was nonetheless a significant decrease in the proportion of patients found in shockable rhythms, from 46% in 1994 to 26% in 2013. In ***Paper III***, adjusted trends indicated an overall increase in 30-day survival after in-hospital cardiac arrest in Sweden, from 24.7% in 2008 to 32.5% in 2018 (monitoring wards, 32.5% to 43.1%, and non-monitoring wards, 17.6% to 23.1%). The proportion of patients found in shockable rhythms decreased in overall terms from 31.6% in 2008 to 23.6%

in 2018 (monitoring ward 42.5% to 35.8%, and non-monitoring wards, 20.1% to 12.9%). In ***Paper IV***, the overall 30-day mortality among patients assessed by a medical emergency team in Sahlgrenska University Hospital was high (29.0%) and almost twice as high on medical wards as on surgical wards (37.1% vs 19.8%). Factors associated with increased 30-day mortality were reflected in age, type of ward, vital parameters, laboratory biomarkers, previous medical history and acute medical condition.

CONCLUSIONS: Over the past few decades, the overall survival after a sudden cardiac arrest has increased, both in and out of hospital, despite a declining trend in the proportion of shockable cardiac arrests. Part of the reason appears to be a shorter delay from collapse to treatment. Several factors associated with an increased risk of dying of a sudden cardiac arrest have been identified and, if appropriately risk stratified and immediately treated, the fatal outcome may be averted.

KEYWORDS: cardiac arrest; co-morbidity; CPC score; CPR; defibrillation; delay; deteriorating patient; epidemiology; in-hospital cardiac arrest; medical emergency team; mortality; outcome; out-of-hospital cardiac arrest; rapid response system; rapid response team; survival; vital signs

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SAMMANFATTNING PÅ SVENSKA

Syftet med den här avhandlingen var att analysera hjärtstopp, både på och utanför sjukhus, ur ett epidemiologiskt perspektiv genom tidig prediktion och genom att jämföra förändringar över tid avseende etiologi, karaktäristika, behandling och överlevnad eller mortalitet, samt genom att identifiera faktorer associerade med utfallet. Avhandlingen baseras på fyra observationsstudier, tre på registerdata från Svenska Hjärt-lungräddnings-registret, på respektive utanför sjukhus, och en på registerdata från ett nyskapat register över patienter som handlagts av den mobila intensivvårdsgruppen (MIG) på Sahlgrenska Universitetssjukhuset.

Arbete I beskriver förändringar i 30-dagars överlevnad (från 1992 till 2009) efter bevittnat hjärtstopp utanför sjukhus, med defibrillerbar rytm och av förmodad kardiell etiologi samt faktorer associerade med utfallet, ur ett svenskt nationellt perspektiv. Sammanfattningsvis ökade överlevnaden. Bäst förutsättning för överlevnad hade kvinnor, de som drabbades av hjärtstopp utanför hemmet, och de som fick tidig bystander-hjärtlungräddning och tidig defibrillering.

Arbete II beskriver förändringar i 30-dagars överlevnad efter hjärtstopp med påbörjad hjärtlungräddning på Sahlgrenska Universitetssjukhuset, utifrån avdelningens monitoreringsgrad (från 1994 till 2013). Sammanfattningsvis karaktäriserades förändringar avseende hjärtstoppsverksamheten av en generellt kortare tid från kollaps till behandling, vilket ledde till en signifikant ökad överlevnad bland patienterna på de monitorerade avdelningarna.

Arbete III beskriver förändringar i 30-dagars överlevnad (från 2008 till 2018) efter hjärtstopp med påbörjad hjärtlungräddning på sjukhus, utifrån avdelningens monitoreringsgrad och första registrerade rytm, samt förändringar i förekomst av defibrillerbar rytm, ur ett svenskt nationellt perspektiv. Sammanfattningsvis ökade överlevnaden, oavsett monitorerings-grad på avdelningen, trots att andelen defibrillerbara hjärtstopp minskade.

Arbete IV identifierar och beskriver riskfaktorer för 30-dagarsmortalitet hos inneliggande, kliniskt försämrade patienter som handlagts av den mobila intensivvårdsgruppen (MIG) på Sahlgrenska Universitetssjukhuset (från 2010 till 2015). Sammanfattningsvis bidrog ålder, komorbiditet och akut sjukdom, i kombination med avvikelser i vitalparametrar och laboratorieprover, samt typ av vårdavdelning, till att identifiera patienter med stor risk för död inom

30 dagar. Risken att dö var störst för medicinpatienter, andningspåverkade patienter och patienter med ett lågt blodsockervärde.

Slutsatsen är att oväntat, plötsligt hjärtstopp är ett allvarligt tillstånd med dålig prognos, men att överlevnaden har ökat under de senaste decennierna, både på och utanför sjukhus, trots en minskande trend av andelen defibrillerbara hjärtstopp. En del av förklaringen tycks vara att tids-fördröjningen från kollaps till behandling har blivit kortare. Ett flertal faktorer som är associerade med en ökad risk att drabbas och dö av ett plötsligt hjärtstopp har identifierats. Om dessa riskfaktorer upptäcks i tid och adekvata behandlingsåtgärder vidtas, kan det kliniska förloppet vändas och möjligheterna till överlevnad förbättras.

LIST OF PAPERS

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

I. Adielsson A, Hollenberg J, Karlsson T, Lindqvist J, Lundin S, Silfverstolpe J, Svensson L, Herlitz J

Increase in survival and bystander CPR in out-of-hospital shockable arrhythmia: bystander CPR and female gender are predictors of improved outcome - Experiences from Sweden in an 18-year perspective

Heart 2011; 97:1391-1396

II. Adielsson A, Karlsson T, Aune S, Lundin S, Hirlekar G, Herlitz J, Ravn-Fischer A

A 20-year perspective of in hospital cardiac arrest - Experiences from a university hospital with focus on wards with and without monitoring facilities

International Journal of Cardiology 2016; 216:194–199

III. Adielsson A, Djärv T, Rawshani A, Lundin S, Herlitz J

Changes over time in 30-day survival and the incidence of shockable rhythms after in-hospital cardiac arrest - A population-based registry study of nearly 24,000 cases

Manuscript submitted, 2020

IV. Adielsson A, Danielsson C, Forkman P, Karlsson T, Pettersson L, Herlitz J, Lundin S

Risk factors for 30-day mortality in medical emergency team patients - A retrospective cohort study

Manuscript submitted, 2020

CONTENTS

ABBREVIATIONS

CCOT	Critical Care Outreach Team
CCRT	Critical Care Response Team
CPC	Cerebral performance categories
CPR	Cardiopulmonary resuscitation
ICU	Intensive care unit
IQR	Interquartile range
MET	Medical emergency team
MIG	Mobil intensivvårdsgrupp (mobile intensive care group)
OR	Odds ratio
RRT	Rapid response team
RRS	Rapid response system
SD	Standard deviation
SMD	Standardised mean difference

1 INTRODUCTION

Sudden cardiac arrest continues to be a serious public health problem with an often fatal outcome. In Sweden, approximately 9,000 people suffer a sudden cardiac arrest where cardiopulmonary resuscitation (CPR) is initiated each year. About 70% of the arrests occur outside hospital. In Sweden, the survival rate from sudden cardiac arrest outside hospital is around 10%. The corresponding number for sudden cardiac arrest in-hospital is just over 30%. In all, almost 7,500 people die from sudden cardiac arrest each year [1, 2].

Sudden cardiac arrest is a multifaceted phenomenon; it is not caused by a single underlying condition, nor is it caused by a single risk factor. A large proportion of the people who suffer sudden cardiac arrest are seemingly healthy and comparatively active. Although children and the young can be affected, most people who die from sudden cardiac arrest are middle-aged or older.

Sudden cardiac arrest is characterised by an abrupt and unexpected loss of consciousness with the absence of respiration and systemic circulation. The cessation of circulation is usually caused by an electrical disturbance in the heart, resulting in an arrhythmia, which interrupts the pumping action of the heart and stops the blood flow to the body. Sudden cardiac arrest differs from a myocardial infarction, characterised by a blockage that partially stops the blood flow to the heart. However, a myocardial infarction can trigger an electrical disturbance in the heart that may cause a sudden cardiac arrest. If left without action, sudden cardiac arrest inevitably leads to death. With immediate, appropriate medical care, survival is possible. If CPR is performed, by starting chest compressions and, when applicable, using a defibrillator to shock the heart, a normal heart rhythm can be restored and the chances of survival will increase substantially.

Since this kind of event is unexpected, the majority of sudden cardiac arrests occur outside hospital. Even if the sudden cardiac arrest is unforeseen, it is often preceded by warning symptoms such as chest pain or discomfort, dyspnoea, palpitations, weakness and syncope, for minutes to hours before the respiration and circulation cease [3-5].

Consequently, the outcome may be considerably improved if these ominous preceding symptoms are detected early in the course, and adequate measures are taken. In these circumstances, the imminent and potentially life-threatening situation may be prevented [6].

"…as the physicians say it happens in hectic fever, that in the beginning of the malady it is easy to cure but difficult to detect, but in the course of time, not having been either detected or treated in the beginning, it becomes easy to detect but difficult to cure."

- Niccolo Machiavelli, The Prince

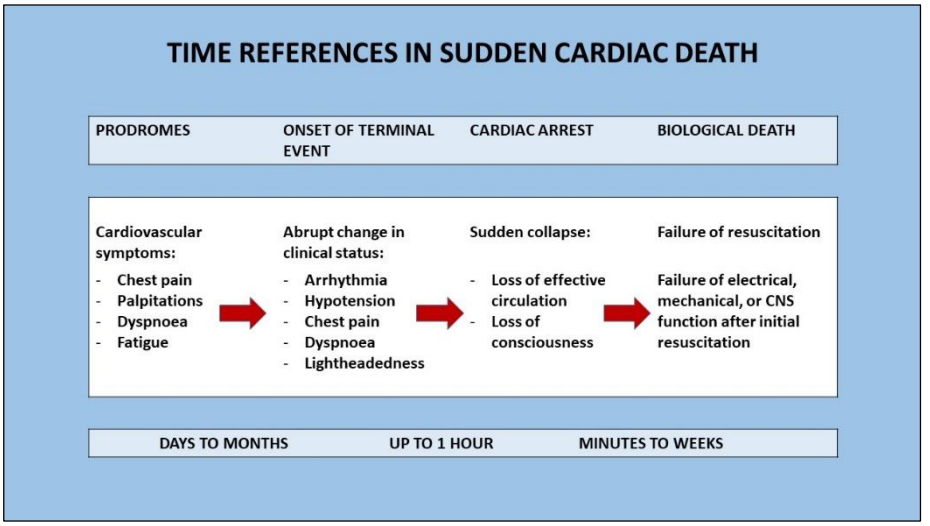
DEFINITION OF CARDIAC ARREST

Over the years, the definition of cardiac arrest has been the subject of extensive debate. The descriptions have varied in relation to the prevailing circumstances in focus, in particular, whether the cardiac arrest was sudden, unexpected, witnessed, or of cardiac aetiology. Usually, the term "cardiac arrest" refers to a condition of unconsciousness, including the absence of respiration and systemic circulation. The temporal aspect is not specified or whether or not the cardiac arrest was expected or witnessed.

Sudden cardiac arrest or sudden cardiac death, on the other hand, implies a rapid and unexpected occurrence of unconsciousness with the absence of adequate respiration movements or a perceptible pulse, representing a systemic circulation [7]. A cardiac arrest is presumed to be of cardiac aetiology when the possibility that it was caused by trauma, drowning, respiratory failure or asphyxia, electrocution, drug overdose, or any other non-cardiac cause has been ruled out [7]. Sudden cardiac death is a natural death from an underlying cardiac cause and is preceded by a sudden loss of consciousness, usually within one hour of the onset of symptoms, or occurs in patients found dead within 24 hours of being asymptomatic, presumably due to cardiac arrhythmia or haemodynamic catastrophe [7, 8].

Sudden cardiac arrest most frequently occurs outside hospital, far from advanced care. In many cases, sudden cardiac arrest is the first and only symptom of manifest heart disease, commonly ischaemic heart disease. In some cases, however, prodromal signs may be present up to one hour before the terminal event. The direct cause of sudden cardiac arrest is usually ventricular arrhythmia, such as ventricular fibrillation or ventricular tachycardia [9]. By definition, a patient suffering a sudden cardiac death does not survive. In spite of this, because of irreversible neurological impairment and prolonged life-support care, some patients may live for several weeks

after resuscitation before the actual biological death occurs. These circumstances complicate the interpretation of the one-hour definition of sudden cardiac death (*Figure 1*).



** CNS, central nervous system*

Figure 1. *The four different phases of sudden cardiac death: 1) warning signs (prodromes), 2) onset of the terminal event, 3) cardiac arrest and 4) progression to biological death. Modified from the ABCDs of emergency cardiovascular care by Thoracickey*

It is worth noting that the overall concept of sudden cardiac arrest does not include any consideration of the aetiology, i. e. whether the cardiac arrest was triggered by a pure cardiac condition or by other preceding circumstances [10-13].

AETIOLOGY OF SUDDEN CARDIAC ARREST

An array of mechanisms can cause sudden cardiac arrest. The aetiology is usually divided into two main subgroups, cardiac or non-cardiac. The causes of cardiac arrest are often uncertain, and it is not rare for the clinical and post-mortem diagnoses to differ [14]. Sudden cardiac arrest, with no other obvious aetiology, is generally classified as cardiac related [15]. In order to reduce the degree of misclassification, it has been suggested in recent years that sudden cardiac arrest of cardiac, respiratory, other non-cardiac and unknown

aetiology is instead classified as medical (in contrast to trauma, drowning, asphyxia, electrocution and drug overdose) [16, 17]. In overall terms, the most common cause of sudden cardiac arrest is cardiac aetiology, such as acute myocardial infarction, arrhythmia, or heart failure, with a prevalence of more than 50% [18]. Cardiac diseases associated with sudden cardiac arrest vary in different age groups. In young individuals, there is an overrepresentation of cardiomyopathies and primary electrical diseases (channelopathies) [19-21], congenital coronary anomalies [22], myocarditis [23] and substance abuse [24]. However, in older individuals, chronic diseases, such as ischaemic heart disease, valvular heart disease and heart failure, predominate. The second most common cause of sudden cardiac arrest, particularly in in-hospital patients, has a non-cardiac aetiology, specifically respiratory insufficiency [18, 25]. Other common causes of sudden cardiac arrest of non-cardiac aetiology are non-traumatic haemorrhage, pulmonary embolism, intracranial processes, intoxication, trauma and drowning [26].

The early identification of underlying causes of a sudden cardiac arrest may play an important role in resuscitation. If the treatment of potential and reversible causes is promptly initiated, the outcome could possibly be improved [27]. Reversible causes of sudden cardiac arrest can be categorised into 4 Hs and 4 Ts (*Table 1*) [28]. Recently, however, the 4 Hs and 4 Ts have been expanded to include hydrogen ion (acidosis), hypoglycaemia and trauma as well.

4 Hs	4 Ts
Hypo-/hyperkalaemia	**Tamponade**
Hypothermia	**Tension pneumothorax**
Hypovolaemia	**Thrombosis, coronary or pulmonary**
Hypoxia	**Toxins ("tablets")**
(Hydrogen ion = acidosis)	**(Trauma)**
(Hypoglycaemia)	

Table 1. *Reversible causes of cardiac arrest, categorised into 4 Hs and 4 Ts*

Identifying the cause of a sudden cardiac arrest can also be of great value in tailoring post-cardiac arrest treatment early in the process, as the conditions before and during the sudden cardiac arrest determine the subsequent organ dysfunction and need for interventions. The management of sudden cardiac arrest in the post-resuscitation period generally focuses on the trigger mechanism, circulatory and respiratory support and neuroprotective strategies.

LOCATION OF SUDDEN CARDIAC ARREST

The characteristics of sudden cardiac arrest in relation to setting vary, in that in-hospital cardiac arrests often result from a gradual deterioration in previous diseases, in contrast to out-of-hospital cardiac arrests, which are generally more sudden and less predictable. This dissimilarity thus implies fundamentally different conditions for preventing and recognising an event resulting in sudden cardiac arrest.

OUT-OF-HOSPITAL CARDIAC ARREST: According to past research, the majority of patients suffering an out-of-hospital cardiac arrest suffer from heart disease and supposedly have a cardiac aetiology to the arrest. The most common cause of out-of-hospital cardiac arrests is ischaemic heart disease [29, 30]. Only about 30% are thought to have a non-cardiac aetiology [26, 29, 31]. The epidemiology of out-of-hospital cardiac arrests with a non-cardiac aetiology has been reported to differ from those with a cardiac aetiology, in that patients with a non-cardiac aetiology tend to be younger and more frequently of female gender. The arrests are less frequently witnessed and also less frequently present with shockable arrhythmias, resulting in much lower survival rates [26, 29].

IN-HOSPITAL CARDIAC ARREST: An in-hospital cardiac arrest is an acute event that can affect any hospitalised patient. An in-hospital cardiac arrest is defined as an unexpected or sudden loss of circulation and is differentiated from the expected in-hospital death by the initiation of resuscitation with chest compressions and defibrillations. Previously, the survival rates after in-hospital cardiac arrest were so poor that resuscitation was considered virtually pointless by some [32-34]. However, survival has improved considerably over the last few decades. [35]. Despite the improved outcome, in-hospital cardiac arrest remains an overlooked appearance to a certain degree, in comparison with out-of-hospital cardiac arrest [36]. In order to prevent in-hospital cardiac arrest and improve the overall in-hospital survival, extensive efforts have been devoted over the past few years to structuring

the measures for identifying deteriorating patients and the initiation of appropriate interventional actions.

DIAGNOSING OF CARDIAC DISORDERS

About half of all sudden cardiac arrests in the general population occur in individuals without a known heart disorder, while, in fact, most of them suffer from hidden ischaemic heart disease [30]. Most disorders associated with an increased risk of sudden cardiac arrests, such as cardiomyopathies and primary electrical diseases (channelopathies), can be shown by abnormal findings on a resting 12-lead electrocardiogram [7, 9]. Findings indicating underlying cardiomyopathy or arrhythmogenic diseases include pathological Q-waves, T-wave inversion, ST depression, left axis deviation, conduction delays and signs of primary electrical disorders (for instance, long QT syndrome and Wolff-Parkinson-White syndrome). Although, even if the electrocardiogram is correctly interpreted, not all signs of conditions potentially at risk of cardiac arrest may be captured. Depending on the symptomatology and extent of disease suspicion, additional diagnostic testing is then required, including echocardiography and exercise electrocardiogram monitoring, and less frequently coronary angiography, electrophysiological studies or genetic testing [9].

PREVENTION OF CARDIOVASCULAR DISEASE

Because the majority of sudden cardiac arrest occur in individuals without known heart disease, prevention efforts should be directed towards the conventional risk factors, similar to those of cardiovascular disease [7]. Cardiovascular disease is a unifying concept for conditions involving the circulatory system, which consists of the heart (cardio) and the blood vessels (vascular). In the past few decades, an increasing number of preventive measures for cardiovascular disease have been established in the developed countries in order to reduce the prevalence of risk factors.

Over the years, hundreds of risk factors have been reported to be associated with cardiovascular disease. Some risk factors are fixed, or non-modifiable risk factors and others are modifiable risk factors. There are also risk factors that are assumed to be associated with an increased risk of cardiovascular disease, even if their exact role has not yet been clarified (*Table 2*).

NON-MODIFIABLE FACTORS	MODIFIABLE FACTORS	CONTRIBUTORY FACTORS
Age	**Cardiovascular diseases**	**Alcohol abuse**
Gender	**Diabetes**	**Inflammatory markers**
Heredity	**Hypercholesterolaemia**	**Psychosocial factors**
	Hypertension	**Stress**
	Obesity	
	Physical inactivity	
	Smoking	

Table 2. *Risk factors for cardiovascular disease*

At public health level, extensive education programmes have emphasised the importance of balancing diet, weight control, exercise and smoking cessation in order to avoid the formation of atherosclerosis. Lowering cholesterol levels and improving cardiovascular fitness are believed to play essential roles in reducing the risk of sudden cardiac arrest [37].

At healthcare level, several preventive measures have evolved, including pharmacotherapy for lowering high blood pressure, heart rate and cholesterol levels, along with regulating blood clotting and ventricular arrhythmias. In preventing and treating ventricular arrhythmias and acute coronary syndrome, invasive measures have also become available in the form of implantable cardioverter defibrillators, coronary angioplasty with vascular stenting, catheter ablation and, more rarely, surgical by-pass or ablation. The successful prevention of sudden cardiac arrest includes the active management of diseases and co-morbidities, potentially predisposing to ventricular arrhythmias [38].

Despite the increasing treatment options for reducing cardiovascular disease, acute coronary syndrome and ventricular arrhythmias remain a common cause of sudden cardiac arrest. The incidence of ventricular arrhythmias within the hospital perimeter has declined in recent decades, due presumably

to the increasing availability of revascularisation strategies and the immediate introduction of adequate pharmacological treatment in acute coronary syndrome [35, 39, 40]. Similar reductions in the incidence of ventricular arrhythmias have also been reported in the out-of-hospital setting [41-44]. The reason for this change is not stated, but it may be related to a more aged population with a higher prevalence of co-morbidities, including heart failure. The initial rhythm in a sudden cardiac arrest often derives from the underlying cause, in that ventricular fibrillation is commonly triggered by ischaemia, and asystole is commonly caused by heart failure [45].

Then again, a considerable number of sudden cardiac arrests occur in non-hospital environments, offering limited treatment alternatives, which underlines the value of screening programmes for the prior identification of patients at risk. However, in this context, it should be mentioned that, currently, no convincing data support broad screening programmes in the general population (without the presence of warning symptoms, an increased risk of arrhythmias or suspected heredity), from a cost-benefit perspective.

PREVENTION OF IN-HOSPITAL CARDIAC ARREST

> *"Patients who are admitted to the hospital believe that they are entering a place of safety. They feel confident that, should their condition deteriorate, they are in the best place for prompt and effective treatment. Yet there is evidence to the contrary."*
>
> – National Institute for Health & Care Excellence in the UK, 2007 [46]

Preventable deaths on hospital wards are still far too common. Patients who are, or become, acutely ill in hospital may indeed receive suboptimal care. In fact, in retrospect, many in-hospital cardiac arrests are considered avoidable with the appropriate actions or interventions [6]. The prevention of in-hospital cardiac arrest will thus be best achieved by addressing the underlying mechanisms of the sudden cardiac arrest. Clinical deterioration is a prevalent fact some hours before the event of in-hospital cardiac arrest. Progressive deterioration and the acute worsening of underlying conditions must be recognised and treated early in the process to avoid them developing into in-hospital cardiac arrest and possible death. However, identifying critical illness

and preventing sudden cardiac arrest are complex tasks, requiring several essential steps to ensure clinical success. In facilitating the prevention and detection of patient deterioration and cardiac arrest within the hospital, the care process can be structured into a chain of prevention, where the five rings in the chain represent: staff education, monitoring of patients, recognition of patient deterioration, a system to call for help and an effective response (*Figure 2*) [47].

Figure 2. *The chain of prevention. © Gary Smith [47]*

The chain of prevention can be seen as a simplified description of the process of the rapid response system (RRS), designed to detect and respond to deteriorating patients outside the intensive care unit (ICU) [48]. The identification of at-risk patients in combination with early interventions, to prevent a clinical deterioration developing into a sudden cardiac arrest, is essential for success.

RAPID RESPONSE SYSTEM

The term RRS refers to the system of monitoring vital signs in general ward patients and responding to abnormal findings, indicating critical illness. These systems were created in the early 1990s, primarily in Australia, the USA and the UK. The different RRS were an attempt to improve the outcome of in-hospital cardiac arrest by defining medical emergencies at an early stage in general ward patients [49]. The first description in the literature was from an Australian centre in Sydney, in 1995 [50]. Since then, the RRS has been widely described and, in many observational studies, it has shown benefits in terms of a decrease in the prevalence of in-hospital cardiac arrest and mortality rates [51-55]. However, the only multicentre randomised, controlled trial, the Medical Early Response Intervention and Therapy (MERIT) study performed in Australia, in 2005, was unable to demonstrate the same benefits [56].

Instead, the MERIT study investigators concluded that *"the implementation of RRS greatly increased emergency team calling but did not substantially affect the incidence of cardiac arrest, unplanned ICU admissions, or unexpected death"* [56], which has generated a debate about the efficacy of RRS and its ability in fact to reduce hospital mortality [57, 58].

THE STRUCTURE OF RAPID RESPONSE SYSTEMS

The concept of RRS was formally introduced in 2005 at the First International Conference on Medical Emergency Teams [59]. The structure of RSS was defined as the entire system and not just the individual components of the system. It was then established that the RRS is based on four components (*Figure 3*) [59].

1) **Afferent limb** for crisis detection and triggering a response. Recognising patients at risk of further deterioration by monitoring and frequently measuring vital signs

2) **Efferent limb**, the response algorithm, i.e. the response team, with expertise in critical care and medical resources

3) **Administrative limb** oversees and supports the entire system with resources, training and education

4) **Quality improvement limb** for data collection, feedback and evaluation

The rationale of RRS is that, among patients outside the ICU, a clinical deterioration causes an imbalance between the urgent need for treatment and available resources [59]. As a result, there is a need for a hospital system to detect and treat patients in crisis before serious adverse events develop, including unplanned admission to the ICU, sudden cardiac arrest and unexpected death. These events are frequently preceded by abnormal vital signs hours to days before they occur [60-62]. The RRS is designed to function as a safety net for critically ill patients, as a means of preventing progression to cardiac arrest on general hospital wards, by optimising the level of care and treatment measures [63].

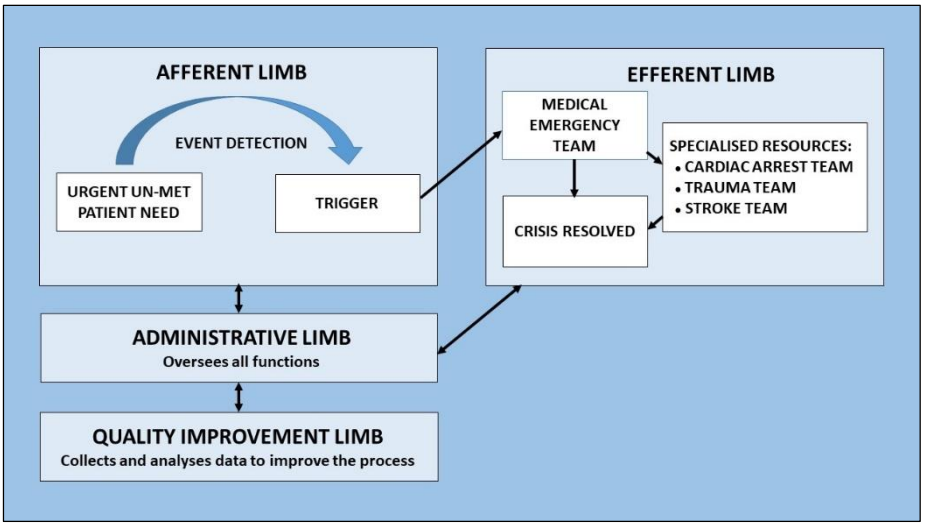


Figure 3. *Rapid response system structure. Modified from [59]*

RAPID RESPONSE SYSTEMS WORLDWIDE

Over the years, the concept of RRS has spread all over the world. Depending on team composition, the reference of the efferent limb of the RSS varies between countries. Regardless of the denotation, the RRS teams are generally composed of healthcare practitioners specialising in critical care or intensive care medicine, with the skills to identify urgent needs and provide adequate medical care [48]. They operate 24 hours a day, seven days a week, and the common denominator is the skills to improve patient outcome by initiating more advanced medical therapy and escalating the level of care when needed.

MEDICAL EMERGENCY TEAM (MET): Was introduced at Liverpool Hospital in Sydney, Australia, in 1989, in order to identify and treat patients at risk on general wards [64]. In the first description, the name and function of the cardiac arrest team was changed to MET [50], the crucial difference being that the MET is supposed to be activated before the patient has deteriorated into multiorgan failure and developed an in-hospital cardiac arrest [65, 66]. The MET consists of intensive care nurses and physicians and has the capacity to 1) prescribe medical treatment, 2) provide advanced airway management, 3) establish central venous access and 4) start ICU level of care at the patient's bedside [67].

RAPID RESPONSE TEAM (RRT): Was described in 1997, in the USA. The RRT can be led by nurses (most common), respiratory therapists or physicians. It has the same basic functions as the MET and the ability to call in additional resources to provide ICU level of care [67].

CRITICAL CARE OUTREACH TEAM (CCOT): Was introduced in the UK in 2000 [68]. The CCOT is generally nurse led and physician supported. It functions as a traditional RRT for in-hospital emergencies and, in addition, it provides an outreach service to discharged ICU patients and high-risk patients to prevent crises [67]. The CCOT also plays a role in educating and training the ward staff in critical care [69].

CRITICAL CARE RESPONSE TEAM (CCRT): Was introduced in Ontario, Canada, in 2006, and was a component of the general "Critical Care Strategy" formulated at the time. The CCRT is typically led by a physician, but otherwise it works in a manner similar to the CCOT [70].

MOBIL INTENSIVVÅRDSGRUPP (MIG (mobile intensive care group)): Is the equivalent of RRS teams in Sweden. The MIG was first introduced in 2003 at Lund University Hospital [71]. At Sahlgrenska University Hospital, the concept of MIG was implemented on the surgical wards in 2005 for a trial period. Since 2007, the MIG service has operated at full scale on all nursing wards, with a few exceptions, such as the thoracic surgery wards. The MIG is comparable to the MET and RRT in composition and function.

"TRACK AND TRIGGER" WARNING SYSTEMS

The RRS is a track and trigger warning system, developed for the detection and management of critically ill patients at risk outside the intensive care units. These systems, also known as early warning scores, are designed to be activated in patients displaying a gradual clinical deterioration. In cases of acute deterioration, the cardiac arrest team should be alerted. The track and trigger warning systems can be activated by any member of the staff when patients develop predefined clinical alterations, or when any member of the staff feels concerned about the patient. Several trigger mechanisms for the risk assessment of hospitalised ward patients have been adopted over the years.

Critical illness is generally preceded by physiological deterioration, and the predominantly used track and trigger systems rely on the periodic observations of these basic physiological signs, such as oxygen saturation, respiratory rate, heart rate, systolic blood pressure and level of consciousness

[72]. The objective of any track and trigger warning system is the early recognition (track) of adverse events and the activation (trigger) of predetermined action plans when certain thresholds of the vital parameters are reached [73]. There is a plethora of different track and trigger systems for identifying patients at risk and estimating their risk score [74-76]. Most are modifications or hospital-specific adaptations of scoring systems. The various track and trigger systems can be broadly categorised into 1) single-parameter systems, 2) multiple-parameter systems and 3) aggregate weighted scoring systems [74, 75, 77].

SINGLE-PARAMETER SYSTEMS: Single-parameter systems rely on the observation of several individual physiological signs. If the predefined threshold of any of these signs is reached by a particular patient, a clinical response strategy is activated. The first of these systems was initially developed at Liverpool Hospital in Sydney, in the early 1990s [50]. The original MET calling criteria included physiological abnormalities, laboratory values, specific conditions and general concern (*Table 3*). The parameters were based on clinical intuition and no formal evaluation against defined outcomes was conducted. Since then, a variety of surveillance systems based on the Liverpool MET calling criteria have developed [75].

The majority of the single-parameter systems continue to be based on subjective parameters selected through clinical intuition rather than through validation studies. There are only a few solid primary studies of the diagnostic accuracy of single-parameter systems. A couple of Australian studies have demonstrated a reduction in the incidence of in-hospital cardiac arrest and death from in-hospital cardiac arrest in medical patients [51, 52], as well as a reduction in the incidence of postoperative adverse outcomes and in-hospital mortality in surgical patients [78]. In spite of this, these before-and-after studies have their limitations and the findings stand in contrast to the results of the MERIT multicentre study, which was not able to prove similar benefits of the RRS when relying on a single-parameter system [56]. Nowadays, single-parameter systems tend to be used less often.

PARAMETER	VALUE
Abnormal physiology	
Temperature (°C)	<35.5 or >39.5
Systolic blood pressure (mmHg)	<100 or >200
Respirations (bpm)	<10 or >30
Pulse rate (bpm)	<40 or >120
Urine output over 24 h (ml)	<500
Reduced or altered level of consciousness	
Abnormal pathology	
Serum potassium (mmol/l)	<3 or >6
Serum sodium (mmol/l	<125 or >155
Blood sugar (mmol/l)	<2 or >20
Arterial pH	<7.2 or >7.55
Base excess (mmol/l)	<-15 or >+10
SPECIFIC CONDITIONS	
Cardiovascular	
Cardiopulmonary arrest	
Pulmonary oedema	
New arrhythmia	
Respiratory	
Acute severe exacerbation of asthma	
Acute respiratory failure	
Upper airway obstruction	
Shock	
Hypovolaemic shock	
Cardiogenic shock	
Anaphylactic shock	
Septic shock	
Metabolic	
Acute diabetic emergencies	
Poisoning/trauma	
Near drowning	
Carbon monoxide poisoning	
Severe drug overdose	
Obstetrics	
Amniotic fluid embolism	
Pre-eclampsia	
Neurological	
Status epilepticus	
Acute psychiatric disturbance	
Surgical	
Excessive bleeding	
Excessive drainage	

Table 3. *The original medical emergency team calling criteria from Liverpool Hospital, Sydney, Australia. Data from [50]*

Also demonstrated are the single-parameter calling criteria introduced at Sahlgrenska University Hospital, Sweden, in 2005, referred to in Paper IV of this thesis (*Table 4*).

PARAMETER	VALUE
Threatened airway*	
Saturation despite O_2 (%)	<90%
Respiratory rate (breaths/minute)	<8 or >30
Systolic blood pressure (mmHg)	<90
Heart rate (beats/minute)	<40 or >130
Decreased level of consciousness	≥RLS** 4
Serious concern regarding the patient's health	

** The criterion was removed in 2013, to be handled by the cardiac arrest team instead, due to the seriousness of the condition.*
*** RLS; reaction level scale*

Table 4. *The medical emergency team calling criteria at Sahlgrenska University Hospital, Gothenburg, Sweden*

MULTIPLE-PARAMETER SYSTEMS: Multiple-parameter systems use combinations of various physiological criteria to activate the rapid response system, without the calculation of a score. Triggering depends on the deviation of multiple physiological parameters and has the potential to allow for a graded response. The simultaneous occurrence of multiple critical parameters allows for mortality risk stratification without complex calculations [79]. The multiple-parameter system can be difficult to use for assessment, however, which may explain why it is not used to the same extent as the other systems.

AGGREGATE WEIGHTED SCORING SYSTEMS: Aggregate weighted scoring systems categorise and distribute points to the measured variables depending on the degree of physiological deviation. The points are combined into a score and correlated to predefined trigger thresholds, which are then

used to activate designated interventions [75]. Aggregated weighted systems are the most complex of the early warning systems. Examples include the original Early Warning Score [80] with its further developed variations, for instance; the Modified Early Warning Score [81], the Standardised Early Warning System [82] and the National Early Warning Score [83]. National Early Warning Score was first introduced in 2012 by the Royal College of Physicians of London, with the addition of supplementary oxygen treatment as one of the parameters. In 2017, the National Early Warning Score was updated to produce a second version (National Early Warning Score 2), including several modifications to the vital sign weightings and the addition of a diversified SpO2 scale with an adjusted section for patients with hypercapnic respiratory failure [84].

CONTINUOUS MONITORING

Early warning systems have been globally adopted since their introduction. Even though a number of different versions exist, the core for the early detection of derangements in simple physiological parameters and the identification of patients at high risk of deterioration, by intermittent observations, is consistent [85]. However, the most pronounced limitation of early warning systems is precisely their intermittent nature. Periodic checks tend to result in the delayed detection of deranged vital signs and the subsequent late alerting of clinicians when clinical deterioration occurs in patients on general wards [86]. For this reason, possible solutions with the monitoring of continuous vital signs on general wards have begun to be considered in recent years. So far, solutions of this type have been limited to critical care wards and other specialist care units, including coronary care units, coronary angiography laboratories, and operating rooms, with reference to costs and the impaired mobilisation of recovering patients. It may therefore be worth noting that the rapid development of wireless and portable surveillance sensors is currently ongoing. Several monitoring tools for this purpose have already received clearance for further clinical studies and evaluation [87-89]. In spite of this, even if emerging technologies have the potential to help improve the quality of in-hospital care and safety, their clinical efficacy and benefits remain to be proven [90].

ANTECEDENTS AND SERIOUS ADVERSE EVENTS

In the past, resuscitation following in-hospital cardiac arrest demonstrated disappointingly high mortality rates and significant neurological morbidity

[91-93]. The post-resuscitation outcome was so discouraging that several clinicians questioned whether CPR should be regarded as meaningless in certain patient populations, given the few functional survivors and the high costs involved [32-34]. In this context, other researchers began to consider the number of serious adverse events in hospitals, resulting in permanent disability and possible death [94], and the course of events preceding the actual cardiac arrest [95, 96]. The occurrence of serious adverse events and iatrogenic injuries in the hospitalised patients had been known for a long time. Back in the 1960s, it was reported that 20% of the patients admitted to the medical wards at a university hospital in the USA suffered one or more episodes of iatrogenic medical complications, of which 8% ended fatally [97] In an Australian quality review study from 1992, it was revealed that almost 17% of the admitted patients suffered serious adverse events. In almost 14% of the cases, the disability was permanent and, in 5%, the patient died. Fifty-one per cent of the serious adverse events were assessed to result from substandard medical care and were thus considered preventable [98].

By then, the idea had been raised that it might be possible to establish clinical strategies to predict and prevent cardiac arrest in hospitalised patients by identifying and managing potentially serious adverse events early in the process [95]. It was demonstrated that closer monitoring, the more rapid identification of clinical deterioration and more accessible critical care, including more aggressive medical interventions, could substantially reduce cardiac arrest and deaths on general wards [99].

Since then, several studies have shown that serious adverse events and unexpected deaths are preceded by a period of physiological instability, detectable by abnormalities in commonly measured vital parameters and laboratory samples [95, 100, 101]. These warning signs, also referred to as prodromal symptoms or antecedents, have been confirmed in several studies to be present up to between eight and 48 hours prior to serious adverse events, defined as cardiac arrest, unanticipated ICU admission or hospital death [62, 95, 101-104]. Given these conditions, there should be sufficient time to identify patients at risk and target the interventions and if needed, escalate the level of care. Moreover, many serious adverse events appear to be a direct consequence of insufficient, delayed, or incorrect medical care [105]. This assessment is also supported by previous findings indicating that in-hospital cardiac arrests often appear to be related to non-cardiac processes, such as respiratory, circulatory and metabolic issues, with the cardiac arrest only representing the common final pathway of a combination of underlying disturbances [95, 106].

ARRHYTHMIA AND SUDDEN CARDIAC ARREST

Sudden cardiac arrest is a disorder in which heart contractions suddenly and unexpectedly cease, resulting in the abrupt cessation of blood supply to the brain and other vital organs. Death will inevitably occur within minutes if life-saving treatment is not rapidly initiated.

The heart rate and rhythm are determined by an internal electrical system in the heart. Problems in the electrical system cause irregular heartbeats, also referred to as arrhythmias. There are many types of arrhythmia, of varying degrees of seriousness. If the arrhythmia leads to insufficient pumping capacity, the blood supply and thereby also the oxygen supply will be inadequate, resulting in a sudden cardiac arrest.

Sudden cardiac arrest can result from four different arrhythmias, further categorised into two principal groups based on possible treatment strategies, i.e. shockable and non-shockable arrhythmias. The term “shockable” implies that delivering an electrical shock to the heart by using a defibrillator may terminate the arrhythmia. Ventricular tachycardia and ventricular fibrillation are both shockable arrhythmias, whereas asystole and pulseless electrical activity are non-shockable arrhythmias.

The cardiac arrest survival rate following initial shockable arrhythmias is substantially higher than the survival rate following initial non-shockable arrhythmias. In spite of this, the survival rate following pulseless electrical activity has been shown to be slightly higher than that following asystole [107].

SHOCKABLE ARRHYTHMIA

VENTRICULAR TACHYCARDIA: Due to incorrect electrical activity, a fast ventricularly triggered, yet regular, heart rate, can occur. Shorter periods may not cause any symptoms, whereas longer periods can be fatal, eventually resulting in ventricular fibrillation and sudden cardiac death. Some ventricular tachycardias are associated with sufficient cardiac output, but, when there is no effective cardiac output, i.e. no pulse, it is regarded as a pulseless ventricular tachycardia and it is then recognised as one of the shockable arrhythmias on the cardiac arrest protocol, treated with high-energy, unsynchronised defibrillation [108].

VENTRICULAR FIBRILLATION: Is most frequently a fatal arrhythmia. Due to disorganised electrical activity, there are no significant or co-ordinated

ventricular contractions. The heart ventricles quiver without generating cardiac output. Without a pulse, agonal breaths or apnea, unconsciousness and cardiac arrest occur, resulting in sudden cardiac death in the absence of immediate advanced cardiac life support, including defibrillation [109].

NON-SHOCKABLE ARRHYTHMIA

ASYSTOLE: Is caused by the cessation of electrical activity, resulting in the total absence of ventricular contractions and cardiac output; this presents clinically with no palpable pulse, no blood pressure, no respiration, unconsciousness and unresponsiveness. Asystole, usually irreversible, is the most serious form of sudden cardiac arrest with a very poor prognosis. In current routine protocols, asystole is treated by CPR in combination with high doses of intravenous adrenaline. Previously recommended treatment with atropine is no longer included in the cardiac arrest protocol. However, underlying reversible causes (Hs and Ts) may sometimes be treated, when identified early in the course [109].

PULSELESS ELECTRICAL ACTIVITY: Is a condition with co-ordinated electrical activity in the absence of palpable central pulses. Despite the presence of electrical activity, the heart does not contract, or, for some other reason, does not produce sufficient cardiac output to generate a pulse. Collapse and unconsciousness occur, with agonal respiration or apnea. Pulseless electrical activity is primarily treated by CPR and adrenaline, while potential underlying causes are investigated and possibly treated. Pulseless electrical activity is commonly triggered by reversible conditions (Hs and Ts) that may be reversed if identified and corrected. The most common cause of pulseless electrical activity is hypoxia, secondary to respiratory failure [109, 110].

CHAIN OF SURVIVAL

OUT-OF-HOSPITAL CHAIN OF SURVIVAL: The majority of sudden cardiac arrests occur outside hospital, with mainly poor outcomes. Despite comprehensive improvement measures over the years, designed to accomplish more immediate resuscitation efforts, the survival rates to hospital discharge are generally lower than 10% [7, 111]. The first step towards improving the outcomes of out-of-hospital cardiac arrest involved the chain of survival, a descriptive metaphor for the different elements of emergency cardiovascular care, developed by Mary M Newman in the 1980s [112]. Since then, the concept has been elaborated and globally implemented in the standard CPR guidelines for the emergency cardiovascular care of out-

of-hospital cardiac arrest. Like the chain of prevention, the chain of survival consists of five key steps, or links, that are interrelated.

In accordance with the 2015 guideline update for CPR and emergency cardiovascular care by the American Heart Association, the five links in the adult out-of-hospital chain of survival are [113]:

1) **Immediate recognition of cardiac arrest and activation of the emergency response system**
   Recognise the emergency and call the local emergency number to activate the emergency response system
   Retrieve the nearest automated external defibrillator.

2) **Early CPR with the emphasis on chest compressions**
   Start CPR immediately

3) **Rapid defibrillation**
   When applicable, defibrillate as soon as an automated external defibrillator is available

4) **Basic and advanced emergency medical services by professional responders**
   Perform high-quality CPR, early defibrillation, medical therapy and device interventions

5) **Advanced life support and integrated post-cardiac arrest care**
   The comprehensive and multidisciplinary care before and after hospital admission, including mild therapeutic hypothermia, percutaneous coronary intervention, coronary by-pass surgery, implantable defibrillators and intensive care treatments

The rationale behind the chain of survival concept is a potentially higher survival rate when a specific sequence of the included actions occurs as rapidly as possible. All the links must be connected and, in order to develop strength in each individual link, separate specialised programmes are crucial. Weakness or delay in any link will inevitably cause poor results in the resuscitation efforts, thereby reducing the likelihood of a positive outcome [114].

A similar chain of survival is illustrated within the framework of the European Resuscitation Council guidelines for resuscitation [115]. Just like for the American Heart Association chain of survival, the most crucial goal is reducing the time from cardiac arrest to the initiation of life-saving treatment. The most notable difference is the structure of four links instead of five. The first three steps are essentially the same, whereas the fourth and last step broadly contains both the previously described fourth and fifth steps, including advanced life support with airway management, drugs and additional necessary interventions for correcting causal factors, as well as post-resuscitation care [116, 117]. The Swedish Resuscitation Council is part of the European Resuscitation Council and therefore also refers to this chain (*Figure 4*).

Figure 4. *The out-of-hospital chain of survival, as illustrated by the European Resuscitation Council. Image by European Resuscitation Council guidelines for resuscitation [115]*

IN-HOSPITAL CHAIN OF SURVIVAL: In the 2015 guideline update for CPR and emergency cardiovascular care by the American Heart Association, a new separate chain of survival for in-hospital cardiac arrest was introduced, identifying a different pathway relative to out-of-hospital cardiac arrest. The update draws a clear distinction between the two systems, establishing that out-of-hospital cardiac arrest is most commonly the result of an unforeseen event with a responsive element. Whereas the focus on in-hospital cardiac arrest, in contrast, is shifting from active resuscitation to the prevention of cardiac arrest, including the activation of the emergency response system [113].

The five links in the adult in-hospital chain of survival comprise [113]:

1) **Surveillance and prevention**

2) **Recognition of cardiac arrest and activation of the emergency response system**

3) **Immediate high-quality CPR**

4) **Rapid defibrillation**

5) **Advanced life support and post-arrest care**

RESUSCITATION

In Sweden, more than 6,000 people every year suffer an out-of-hospital cardiac arrest in which resuscitation is attempted and about 600 survive [118]. The cornerstones of CPR are chest compressions, ventilation and early defibrillation, when applicable, and immediate measures to deal with potentially reversible causes, for instance, hyperkalemia or hypoxia [18]. The early initiation of CPR is associated with improved outcomes for both out-of-hospital cardiac arrest and in-hospital cardiac arrest [119, 120]. The quality of CPR and in particular chest compressions has been shown to be associated with improved outcomes in patients with cardiac arrest [121]. Although the proportion of cardiac arrest patients presenting with an initial shockable arrhythmia is relatively small and is decreasing [44], approximately some 20-25% for both in-hospital cardiac arrest and out-of-hospital cardiac arrest [107, 122], rapid defibrillation is crucial to survival, when indicated [107, 120, 122]. The value of a short delay from collapse to defibrillation to increased survival chances has long been established [123]. In fact, early defibrillation is regarded as the most important factor for survival in sudden cardiac arrest with shockable rhythms [124-127]. When defibrillation is provided immediately in conjunction with the onset of a shockable rhythm, the success rate can be impressively high [124]. Survival of 74 per cent to hospital discharge has been reported for patients receiving their first defibrillation within three minutes after a sudden cardiac arrest in a gambling casino [128]. However, for every minute that defibrillation treatment is delayed, the chance of survival is reduced by 10-12% [129].

In Sweden, approximately 80% of the in-hospital cardiac arrest cases are defibrillated within three minutes [1]. In the case of out-of-hospital cardiac arrest, the delay time from collapse to defibrillation is tripled [118]. The widespread deployment of automated external defibrillators in hospitals, healthcare centres, and other strategic places in the community represents a large-scale effort in attempting to reduce the delay from collapse to life-saving measures. The comprehensive and recurrent CPR training of both laypersons and medical professionals is a complementary approach to improving the quality of CPR, as well as reducing the delay to the start of CPR [118].

Substantiated support for the effectiveness of medication in in-hospital cardiac arrest is sparse. Currently, the use of adrenaline and amiodarone (in ventricular tachycardia or ventricular fibrillation) is recommended. Both have been shown to improve short-term outcomes in the out-of-hospital cardiac arrest. There is, however, only limited evidence to support substantial neurological benefits when these medications are used [130, 131]. Considering the different circumstances between CPR in in-hospital cardiac arrest and out-of-hospital cardiac arrest, particularly the much earlier administration of medication in the in-hospital setting, the extent to which findings from studies of out-of-hospital cardiac arrest can be applied to in-hospital cardiac arrest is uncertain. For in-hospital cardiac arrest with non-shockable arrhythmias, the early administration of adrenaline has been associated with better outcomes [132]. On the other hand, the early administration of adrenaline in shockable arrhythmias has been associated with poorer outcomes [133].

Although medication and airway management are still included in cardiac arrest advanced life support, they are of secondary importance compared with early defibrillation and high-quality, continuous chest compressions. For a long time, endotracheal intubation has been the commonly preferred approach to establishing adequate ventilation and oxygenation. Recent evidence, in relation to both out-of-hospital cardiac arrest [134, 135] and in-hospital cardiac arrest [136], indicates nonetheless that alternative approaches, i.e. supraglottic airways (bag-mask ventilation or laryngeal mask airways), might be equally or even more effective. There are, however, many advantages to endotracheal intubation during resuscitation, including ventilation during continuous chest compressions and protection from aspiration. Then again, the disadvantages include an unidentifiable laryngeal entrance resulting in prolonged intubation attempts, endotracheal tube dislodgement and unrecognised oesophageal intubation, with a possibly fatal outcome [116]. These difficulties are mainly correlated to inexperienced

healthcare practitioners. In the 2019 summary from the International Liaison Committee on Resuscitation, it is stated that; *"overall, there is no high-certainty evidence to recommend an advanced airway strategy over bag mask ventilation and no high-certainty evidence to recommend a specific advanced airway device over another"* [137].

Ultimately, the best airway technique for ventilation and oxygenation appears to depend on the specific clinical characteristics of the patient, the clinical circumstances, the availability of appropriate equipment and the skills of the rescuer.

OUTCOME

Sudden cardiac death remains one of the leading causes of death worldwide, accounting for 15-20% of all deaths [9, 45]. Most sudden cardiac deaths are unwitnessed and caused by cardiac arrhythmias, including those resulting from acute myocardial infarction, with ventricular fibrillation as the final underlying mechanism [9, 45]. The majority of the patients are, however, found in asystole or pulseless electrical activity [9]. Although the survival rates are gradually improving, the prognosis for surviving a sudden cardiac arrest is still very poor. The average survival rate to hospital discharge, following an out-of-hospital cardiac arrest, has been reported to vary from 3% in Asia to almost 10% in Australia [138]. For in-hospital cardiac arrest, the common estimate for survival rates has been around 20% [139], with a fairly wide variation between different regions and hospitals. The survival rate for in-hospital cardiac arrest is believed to be higher than that for out-of-hospital cardiac arrest, due partly to patient selection through the limitation of medical therapy decisions and do not attempt resuscitation orders and partly to the earlier recognition and initiation of treatment with the aid of the emergency response system [140].

Factors associated with the outcome of in-hospital cardiac arrest have traditionally been divided into two subcategories: 1) Non-modifiable, such as age, gender, co-morbidity, aetiology and time of day and 2) Modifiable, such as place of in-hospital cardiac arrest and monitoring level, witnessed or unwitnessed cardiac arrest, the delay from detection to action and also to some extent the initial rhythm and type of treatment provided, as well as treatment limitations (do not intubate or do not attempt resuscitation orders). Previous studies have shown that gender, co-morbidity, aetiology, location in relation to monitoring level and the circumstances at resuscitation can affect outcome [25, 141, 142].

Independent of location, several prognostic parameters for a successful outcome of sudden cardiac arrest have been identified, including witnessed events, short delays between collapse and the arrival of the cardiac arrest team, short duration of CPR, including short delays from collapse to chest compressions and defibrillation, and a shockable arrhythmia as the first registered rhythm [107, 143]. Moreover, a cardiac aetiology of the sudden cardiac arrest has been shown to be associated with a much better outcome [25]. In overall terms, the survival rates for sudden cardiac arrest have improved over the last few decades, both out of hospital [144], and in hospital [140, 145].

2 AIM

The overall aim of this thesis was to describe and analyse sudden cardiac arrest, both in hospital and out of hospital, from an epidemiological perspective, by early prediction, by comparing changes over time in relation to aetiology, characteristics, treatment, survival or mortality and by identifying factors associated with outcome.

From the overall aim, the following specific aims for each paper were formulated.

PAPER I

The aim was to describe changes in 30-day survival, from 1992 to 2009, after bystander-witnessed out-of-hospital cardiac arrest, with a shockable rhythm and of presumed cardiac aetiology, including factors associated with the outcome, from a nationwide perspective.

PAPER II

The aim was to describe changes in 30-day survival, from 1994 to 2013, after in-hospital cardiac arrest where CPR was initiated, in relation to the monitoring level of the ward, including factors associated with the outcome, at Sahlgrenska University Hospital.

PAPER III

The aim was to describe changes in 30-day survival, from 2008 to 2018, after in-hospital cardiac arrest where CPR was initiated, in relation to the monitoring level of the ward and the initially registered rhythm, including changes in the incidence of shockable rhythms, from a nationwide perspective.

PAPER IV

The aim was to identify factors associated with 30-day mortality in clinically deteriorating patients, assessed by the MET while hospitalised in 2010-2015 at Sahlgrenska University Hospital.

3 PATIENTS AND METHODS

The papers in this thesis are based on four observational studies. Three of the studies include data from the Swedish Registry for Cardiopulmonary Resuscitation, on sudden cardiac arrest in- and outside hospitals, from both a local and a nationwide perspective. The fourth paper includes data from an independently created registry of patients assessed by the MET while hospitalised at Sahlgrenska University Hospital.

OVERVIEW OF PAPERS

An overview of the papers included in this thesis is given (*Table 5*).

	PAPER I	**PAPER II**	**PAPER III**	**PAPER IV**
Design	Retrospective and prospective observational cohort study	Retrospective and prospective observational cohort study	Retrospective and prospective observational cohort study l	Retrospective observational cohort study
Population	All patients suffering a witnessed OHCA with a shockable rhythm, of presumed cardiac aetiology	All patients suffering an IHCA where CPR was initiated	All patients suffering an IHCA where CPR was initiated	All patients assessed by the MET while hospitalised
Study period	1992-2009 (18 years)	1994-2013 (20 years)	2008-2018 (11 years)	2010-2015 (6 years)
Setting	Out-of-hospital, multicentre, Sweden	In-hospital, single-centre, Sahlgrenska	In-hospital, multicentre, Sweden	In-hospital, single-centre, Sahlgrenska
Database	OHCA-SRCR	IHCA-SRCR	IHCA-SRCR	MET registry
Included (*n*)	(*n*=7,187)	(*n*=2,340)	(*n*=23,950)	(*n*=2,601)
Primary outcome	30-day survival; time from OHCA to survival	30-day survival; time from IHCA to survival	30-day survival; time from IHCA to survival	30-day mortality; time from MET assessment to death

*** MET, medical emergency team; CPR, cardiopulmonary resuscitation; OHCA, out-of-hospital cardiac arrest; IHCA, in-hospital cardiac arrest; SRCR, the Swedish Registry for Cardiopulmonary Resuscitation*

Table 5. *Overview of Paper I-IV*

PAPER I

STUDY DESIGN: A retrospective and prospective, observational, multicentre study based on outcome data from the out-of-hospital Swedish Registry for Cardiopulmonary Resuscitation

STUDY POPULATION: All patients in Sweden, suffering a bystander-witnessed out-of-hospital cardiac arrest, found in a shockable rhythm of presumed cardiac aetiology, where an ambulance was called and CPR was initiated, from 1 January 1992 to 31 December 2009 (*n*=7,187). Patients <18 years were excluded.

SETTING: Out of hospital, nationwide in Sweden

OUTCOME: Two study outcomes were recorded; 1) admission to hospital with spontaneous circulation and the primary outcome 2) survival at 30 days. Changes over time were analysed and factors associated with outcome were identified by analysing its relationship with patient characteristics and resuscitation-related variables. In addition, the cerebral performance category (CPC) score was recorded on discharge from hospital among the 30-day survivors in a subset analysis in 2008-2009.

PAPER II

STUDY DESIGN: A retrospective and prospective, observational, single-centre study based on outcome data from the in-hospital Swedish Registry for Cardiopulmonary Resuscitation

STUDY POPULATION: All patients admitted to Sahlgrenska University Hospital, on monitoring and non-monitoring wards, suffering an in-hospital cardiac arrest in which CPR was initiated, from 1 January 1994 to 31 December 2013 (*n*=2,340). The study population was subdivided into two groups, depending on the monitoring level of the ward, and further stratified into four subgroups of five-year intervals, based on the occurrence of in-hospital cardiac arrest. Patients <18 years were excluded.

SETTING: In hospital, on monitoring and non-monitoring wards, at Sahlgrenska University Hospital

OUTCOME: The primary outcome was survival at 30 days, in relation to the monitoring level of the ward. Changes in survival and the incidence of shockable rhythms over time were analysed. Factors associated with the

outcome were identified by analysing its relationship with patient characteristics and resuscitation-related variables. In addition, the CPC score was recorded on discharge from hospital among the 30-day survivors and compared over time.

PAPER III

STUDY DESIGN: A retrospective and prospective observational, multicentre study based on outcome data from the in-hospital Swedish Registry for Cardiopulmonary Resuscitation

STUDY POPULATION: All patients in Sweden, suffering an in-hospital cardiac arrest in which CPR was initiated, on monitoring and non-monitoring wards, from 1 January 2008 to 31 December 2018 (*n*=23,950). The study population was subdivided into four groups, depending on the monitoring level of the ward and the initially registered rhythm. Each group was further stratified into two time periods, 2008-2013 and 2014-2018, and compared. Patients <18 years were excluded.

SETTING: In hospital, on monitoring and non-monitoring wards, nationwide in Sweden

OUTCOME: The primary outcome was survival at 30 days, in relation to the monitoring level of the ward and the initially registered rhythm. Changes in survival and the incidence of shockable rhythms over time were analysed. In addition, factors associated with the outcome were identified by analysing its relationship with patient characteristics and resuscitation-related variables.

PAPER IV

STUDY DESIGN: A retrospective, observational, single-centre study based on registry data on MET-assessed patients at Sahlgrenska University Hospital.

STUDY POPULATION: All patients assessed by the MET while hospitalised at Sahlgrenska University Hospital, from 1 January 2010 to 31 December 2015 (*n*=2,601). Patients <18 years were excluded. In the event of repeated MET assessments, only the first MET assessment during each hospital episode was included.

SETTING: In hospital, primarily on general wards, at Sahlgrenska University Hospital

OUTCOME: The primary endpoint was death within 30 days. Patient characteristics, including age and co-morbidity, and the acute medical condition, along with vital signs and laboratory biomarkers, as well as the type of ward for admission, were analysed to identify factors associated with the outcome.

DEFINITIONS

The following sections comprise general descriptions and definitions of the prevalent concepts and conditions deemed necessary to further elaborate or explain various concerns for a better comprehension of the studies included in this thesis.

THE SWEDISH REGISTRY FOR CARDIOPULMONARY RESUSCITATION

The Swedish Registry for Cardiopulmonary Resuscitation started in 1990. In the beginning, the collection of data was restricted to CPR in out-of-hospital cardiac arrest. Only more than a decade later was the registry expanded to include CPR in in-hospital cardiac arrest as well. At Sahlgrenska University Hospital, serving as a model for the future national in-hospital registry, the sudden cardiac arrests occurring at the hospital started to be entered in a local, hospital-based registry, as early as 1994. In Paper II of this thesis, data from this limited registry edition are used exclusively. However, since 2006, the Swedish Registry for Cardiopulmonary Resuscitation has consisted of two sub-registries; cardiopulmonary resuscitation outside hospitals and cardiopulmonary resuscitation inside hospitals [118].

The Swedish Registry for Cardiopulmonary Resuscitation is a national quality registry with the highest degree of certification. At present, there are more than 100 national quality registries in operation in Sweden, with joint financial support from the state and healthcare authorities. All national quality registries contain individual-based information on problems, measurements and results in healthcare. The aim of the Swedish Registry for Cardiopulmonary Resuscitation is to include all cases of sudden cardiac arrest, in which CPR is initiated. These days, virtually all cases of out-of-hospital cardiac arrest in which CPR was attempted are included in the registry, with nearly 100% coverage. In the sub-registry of in-hospital cardiac arrest, where CPR was initiated, 71 of 73 hospitals in Sweden are included. As a result, a few per cent remain until the goal of full coverage is reached [118].

The primary purpose of the registry is to outline in detail the care involved with sudden cardiac arrests, in order to identify weak links in the chain of survival. By analysing registry data, all the steps included in the CPR process can be observed and, by extension, optimised with the further aim of increasing the chances of survival after sudden cardiac arrest, in and out of hospital. In addition, registry data provide the units in the emergency medical service, as well as the hospitals, with detailed information on the outcome of their resuscitation efforts, individually and in comparison to others. This basis of objective knowledge is a prerequisite for sectional improvement work [118].

MEDICAL EMERGENCY TEAM REGISTRY

The MET registry referred to in Paper IV of this thesis is an independently created registry of patients assessed by the MET while hospitalised at Sahlgrenska University Hospital, from 1 January 2010 to 31 December 2015. The registry was designed and established by our research group, with the addition of some technical support. Patient data were then collected from the patients' records with the assistance of three medical students, in the process of writing their master's theses. The data were registered on an electronic form created in Microsoft Access®, at the Centre of Registers (*Registercentrum*) of the Västra Götaland Region. In total, the register form comprised somewhere in the order of magnitude of 100 epidemiological variables.

UTSTEIN-STYLE DEFINITIONS

In 1990, the American Heart Association and the European Resuscitation Council reached consensus on a uniform way of reporting data following a sudden cardiac arrest. The agreement was framed at an international multidisciplinary conference, at Utstein Abbey, on the island of Mosterøy, near Stavanger, Norway.

In 1991, the foundation of the Utstein-style guidelines was first published [146]. Initially, Utstein reporting focused on the concept of out-of-hospital cardiac arrest. The primary aim was to standardise the definitions and data recordings, to enable the comparison of cardiac arrest epidemiology and outcomes between different emergency medical service systems. The secondary aim was to improve the quality of resuscitation by identifying knowledge gaps and facilitating clinical research by systematising the reporting and definitions used.

Six years later, in 1997, the first Utstein reporting guideline for in-hospital cardiac arrest was published. It established four categories of variables for documenting in-hospital resuscitation: 1) hospital, 2) patient, 3) cardiac arrest and 4) outcome [147]. Since then, the Utstein guidelines have been elaborated and regularly updated.

In 2004, the definitions and data elements for both out-of-hospital cardiac arrest and in-hospital cardiac arrest were incorporated in the guidelines, in an attempt to reduce the complexity of data collection and address the inconsistencies in terminology between in-hospital and out-of-hospital Utstein templates [148].

In 2015 and 2019, the Utstein reporting guidelines for sudden cardiac arrest were further revised. However, the updates were restricted to exclusively out-of-hospital cardiac arrest [16] or in-hospital cardiac arrest [149] respectively, due to considerable differences in the precondition, on account of the setting of the incident. In the 2015 guidelines, the former Utstein reporting definitions and templates for out-of-hospital cardiac arrest were updated to five data element domains: 1) system factors, 2) dispatch and recognition, 3) patient variables, 4) process variables and 5) outcomes (*Figure 5*) [16].

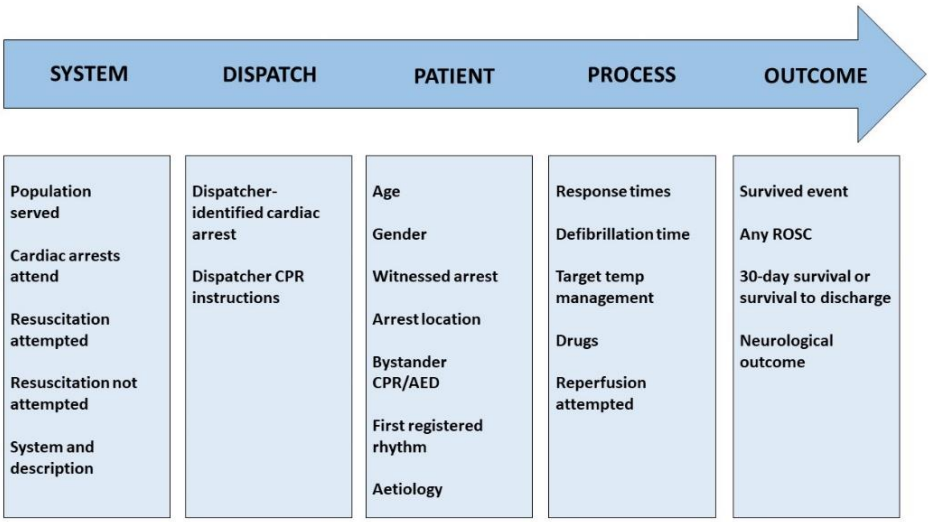


Figure 5. *The out-of-hospital cardiac arrest core elements are shown for each of the five domains. AED indicates automated external defibrillator; CPR, cardiopulmonary resuscitation; ROSC, return of spontaneous circulation. Modified from [16]*

With the introduction of new definitions in 2015, different categories of aetiology were suggested. The former presumed cardiac, respiratory, other non-cardiac and unknown aetiology were now all defined as medical. Additional categories included asphyxia, traumatic cause, drowning, drug overdose and electrocution [16, 17].

In the in-hospital cardiac arrest guidelines from 2019, the Utstein elements for reporting were further elaborated and grouped into six domains for documenting in-hospital resuscitation. As a result, the four original categories (hospital factors, patient variables, cardiac arrest and outcomes) were expanded to include the "pre-event" and "post-resuscitation" phases (*Figure 6*) [149].

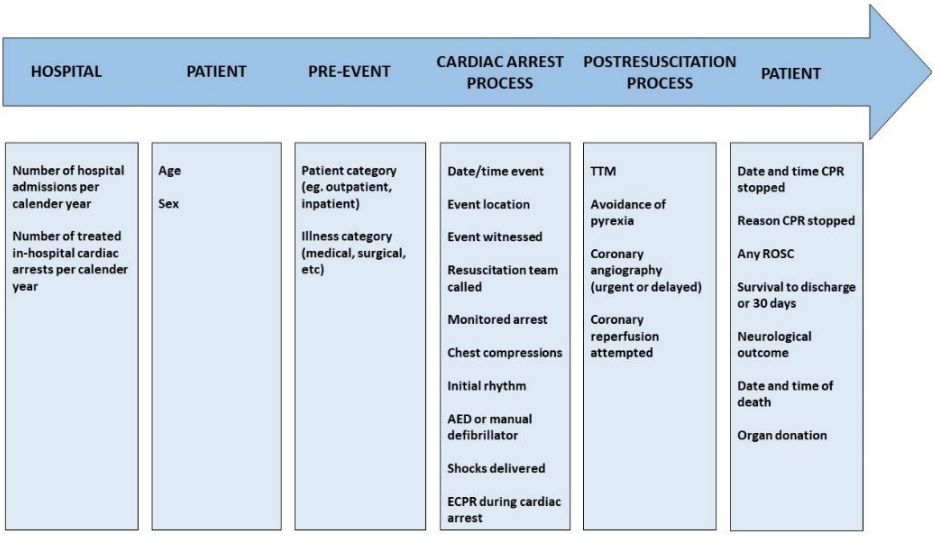


Figure 6. *The in-hospital cardiac arrest core elements are shown for each of the six domains. AED indicates automated external defibrillator; CPR, cardiopulmonary resuscitation; ECPR, extracorporeal cardiopulmonary resuscitation; ROSC, return of spontaneous circulation; TTM, targeted temperature management. Modified from [149]*

WARDS WITH OR WITHOUT MONITORING FACILITIES

The concept of monitoring is, by definition, the repeated or continuous observation of vital signs or physiological functions to ensure patient safety and to guide medical treatment. The most advanced monitoring systems depend on cables and bulky monitors to recognise and display the monitored vital signals. For this reason, continuous advanced monitoring is mainly

limited to the ICU, the operating room and post-operative care units. Most other monitoring options at the hospital are of a more simplified nature, including intermittent monitoring on general wards [150]. Current ward monitoring protocols usually include periodic checks by a ward nurse about every four to eight hours, which in reality leave the patients unmonitored for the majority of their hospital stay [151, 152]. As a result, the patients on wards without continuous monitoring, typically entailing long gaps between checks of vital signs, are most vulnerable and at the highest risk of suffering serious adverse events [150].

Due to the described differences in preconditions and opportunities to detect and act upon clinical deterioration developing into a sudden cardiac arrest, we subdivided the in-hospital cardiac arrest patient population into two groups, based on the monitoring facilities on wards, and studied them separately in Papers II and III. In both papers, the monitoring wards included the ICU, coronary care units, coronary angiography laboratories, operating rooms and emergency departments. The remaining wards, including intermediate care units, were defined as non-monitoring wards.

EMERGENCY TEAMS

MEDICAL EMERGENCY TEAM: The RRS at Sahlgrenska University Hospital includes a MET, referred to as *"mobil intensivvårdsgrupp"* (MIG (mobile intensive care group)). The MET at Sahlgrenska University Hospital utilises a single parameter trigger system and is supposed to be activated in deteriorating patients when abnormal vital parameters are detected. The MET is available 24 hours a day, seven days a week and typically includes an intensive care specialist at consultant level and an intensive care nurse. Nevertheless, staffing has varied around the clock, primarily by replacing the intensive care specialist with an intensive care trainee at night.

CARDIAC ARREST TEAM: Sahlgrenska University Hospital, like many other emergency hospitals with an RRS, is equipped with a separate cardiac arrest team in addition to the MET. The cardiac arrest team operates in a similar manner but is primarily intended to respond to patients with acutely life-threatening conditions and in-hospital cardiac arrests. The composition of the cardiac arrest team differs from that of the MET and also varies between hospitals, depending on the location and hospital profile. At Sahlgrenska University Hospital, the cardiac arrest team consists of three doctors trained in intensive care, internal medicine and cardiology, respectively, with the addition in recent years of an anaesthetic nurse.

RESUSCITATION EQUIPMENT AND SERVICE

The available resuscitation equipment has varied over time, both in and out of hospital. The preferred technical devices have changed, due partly to the prevailing expertise and medical developments but also to local traditions. One of the most significant changes in CPR, in all settings, has most definitely been the widespread distribution of portable automated external defibrillators, with the stated objective of saving lives by reducing the time from collapse to defibrillation in sudden cardiac arrests.

With regard more specifically to in-hospital cardiac arrest, Sahlgrenska University Hospital was one of the first hospitals in Sweden to introduce automated external defibrillators on almost all non-monitoring wards, in 1996. In about the same period, standardised emergency equipment, including medical treatment and intubation kits, was distributed to all hospital wards. In addition, the extensive CPR training of the medical staff was regularly conducted to improve the conditions and knowledge of resuscitation still further. Similar changes have since been implemented at all the hospitals in Sweden.

In the out-of-hospital environment, corresponding efforts have been made in the management of out-of-hospital cardiac arrest. In the emergency medical service, the primary focus has been shortening the delay from collapse to treatment, partly by raising staff competence and equipping all ambulances with automated external defibrillators, thereby making advanced CPR more readily available. Another crucial part of improving the out-of-hospital cardiac arrest situation has naturally been the extensive CPR training invested in laypersons. By educating the public in CPR and raising awareness of early treatment, the initiation of bystander CPR in out-of-hospital cardiac arrest has significantly increased over the years. Rapidly initiated bystander CPR has been shown to be associated with improved survival in several studies [119, 153-155].

For many years, the dominant approach to maintaining an airway and providing ventilation in patients undergoing CPR was endotracheal intubation. Nowadays, however, the general perception is that supraglottic airway strategies, such as laryngeal mask airways, are at the very least equally effective when securing respiratory function in a cardiac arrest situation [134, 135], without including the previously described disadvantages of endotracheal intubation [116]. Moreover, the outcome of endotracheal intubation tends to be more dependent on the experience of the practitioner compared with supraglottic airways. In the past few years, the general out-

of-hospital cardiac arrest (and to a certain extent also in-hospital cardiac arrest) guidelines in Sweden have therefore leaned more towards advocating laryngeal mask airways over endotracheal intubation, although regional differences occur.

CEREBRAL PERFORMANCE CATEGORY SCORE

From the patient's perspective, the critical outcome of a resuscitation attempt is not solely cardiac survival but also long-term neurological and functional outcome [156]. Survival following a sudden cardiac arrest depends upon both heart and brain resuscitation. The recovery from anoxic brain injuries varies in patients who undergo cardiac resuscitation. The neurological impact extends from complete recovery to coma and brain death [157, 158]. Considering the functional and neurological disability is therefore essential when assessing the status of cardiac arrest survivors to evaluate the outcome of resuscitation efforts. The CPC has been the prevailing standard outcome measurement and can be determined through patient records. The CPC score is also widely used in research and quality assurance when assessing neurological outcome following a sudden cardiac arrest [159]. The CPC score estimates were incorporated in the Swedish Registry for Cardiopulmonary Resuscitation in 2008.

A *"good"* outcome is generally defined as a CPC score of 1 (=good neurological performance) or 2 (=moderate neurological disability), while a *"poor"* outcome is defined as a CPC score of 3 (=severe neurological disability), 4 (=unconsciousness or persistent vegetative state), or 5 (=brain death) [160]. It is worth noting that a good CPC score on hospital discharge usually predicts a better long-term survival prognosis.

DATA COLLECTION

The stepwise and systematic process of gathering and analysing epidemiological information to answer the hypotheses set for each paper, and subsequently to present the results, is described in detail on the basis of the respective registries.

THE SWEDISH REGISTRY FOR CARDIOPULMONARY RESUSCITATION - OUT-OF-HOSPITAL CARDIAC ARREST

The data collection is based on the out-of-hospital cardiac arrests reported to the Swedish Registry for Cardiopulmonary Resuscitation by the emergency

medical service crew. For each case, the ambulance crew completed a form with information on age, location of the cardiac arrest, probable aetiology and a standardised description of the CPR procedure, including the various intervention times, bystander CPR, defibrillation and medical treatment. In ambulances with manual defibrillators, the first registered rhythm was defined as ventricular fibrillation, ventricular tachycardia, pulseless electrical activity or asystole. For automated external defibrillators, the first recorded rhythm was defined as shockable or non-shockable. In order to establish the time of cardiac arrest in witnessed cases, the emergency medical service crew interviewed the bystanders about delays from arrest to call. The aetiology of the cardiac arrest was based entirely on the assessment of the emergency medical service crew and bystander information, without autopsy confirmation or further clinical data. In the bystander CPR analyses, the profession of the bystander (layperson or healthcare practitioner off duty) was described. The immediate outcome was reported by the emergency medical service as dead on arrival, dead in the emergency room or admitted alive to the hospital. A follow-up on survival to 30 days was conducted. The out-of-hospital Swedish Registry for Cardiopulmonary Resuscitation applies standardised Utstein-style definitions to all variables and outcomes [159].

THE SWEDISH REGISTRY FOR CARDIOPULMONARY RESUSCITATION - IN-HOSPITAL CARDIAC ARREST

Data are collected in two steps, at the actual event and more than 30 days later. In the first step, baseline information, patient characteristics, circumstances surrounding the cardiac arrest and treatment interventions performed, including specific times, are recorded by a nurse or physician attending the event. In the second step, follow-up data, co-morbidities, probable aetiology of the cardiac arrest and 30-day survival data are recorded by a nurse or physician associated with the registry. In all survivors, the mental and physical level of functioning, including a CPC score, are obtained. The in-hospital Swedish Registry for Cardiopulmonary Resuscitation applies standardised Utstein-style definitions to all variables and outcomes [159]. At participating units, designated staff are responsible for the registration of the information in a shared online system [118].

MET REGISTRY

Data were collected from the MET assessment protocol, supplemented with electronic medical records, laboratory biomarker analyses and, in some cases, ward archive information, supplemented with 30-day survival status from the Swedish population registry. Baseline characteristics, type of ward, previous

medical history, the reason for MET call, vital parameters at MET arrival, laboratory biomarkers from up to 48 hours before and six hours after MET activation, acute medical condition, limitation of medical therapy decisions, potential ICU admission and primary diagnosis, were recorded.

ETHICAL CONSIDERATIONS

Due to the rapid course and severe condition, clinically deteriorating patients or patients suffering a sudden cardiac arrest are unable to give their conscious permission to participate in clinical studies or be included in registries, following the event. Informed consent can therefore only be granted after the event, in the event of survival, or by next of kin who are present.

The Swedish Registry for Cardiopulmonary Resuscitation follows the medical ethical principles in the World Medical Association Declaration of Helsinki from 1964, revised in 2013 [161]. The administration and documentation of the Swedish Registry for Cardiopulmonary Resuscitation are thus adapted to ethical research principles, including the policies for informed consent and confidentiality. In the 2013 amendment of the Declaration of Helsinki, in paragraph 30 regarding research involving persons incapable of giving consent, it is stated, in summary, that; "*when a subject is physically or mentally incapable of giving consent, informed consent from a legally authorised representative must be obtained*", i.e. from a research ethics committee [161].

Several ethical approvals within the frameworks of the Swedish Registry for Cardiopulmonary Resuscitation have been applied for and obtained from various ethical review boards in Sweden. All the data are analysed at group level, meaning the privacy and anonymity of the individuals are secured. Moreover, all survivors are informed about their inclusion in the Swedish Registry for Cardiopulmonary Resuscitation. If they so wish, they are further given the opportunity to withdraw their data from the registry. When it came to Papers I, II and III included in this thesis, there were no deviating ethical considerations in association with the Swedish Registry for Cardiopulmonary Resuscitation, beyond those commonly identified.

The ethical considerations for Paper IV mainly revolved around balancing the acquisition of knowledge and patient integrity. Obtaining patient approval was not possible due to the generally impaired condition of patients at the MET assessment, the poor long-term prognosis and the fairly long delay to data collection. However, given the development opportunities for the

management of this very ill patient group, priority was given to knowledge acquisition and the perspective of optimising the MET operation and patient care, with estimated future benefits. Appropriate measures were nonetheless taken to secure patient integrity by only acquiring relevant information from the treatment period, handling the medical records and additional information carefully by keeping it in a protected space and deidentifying all patient data.

As a result, all four studies obtained approval from the ethical review board at the University of Gothenburg. Because of the predominantly retrospective nature of the studies and the fact that many of the study participants were already incapacitated or deceased, the need for informed consent was waived by the committee. In addition, neither of the studies involved any interventions that could harm or influence the outcome. Instead, the potential future benefits, from a broader population perspective, were assumed to outweigh the eventual individual disadvantages, especially when considering the dominantly poor prognosis for these patient groups.

OVERVIEW OF STATISTICAL METHODS

In Table 6, an overview of the statistical methods used in the papers in this thesis is reported schematically.

ANALYSES	PAPER I	PAPER II	PAPER III	PAPER IV
Univariable analysis:				
Fisher's exact test	X			
Mann-Whitney U test	X	X		
Spearman's rank correlation test	X	X		
Log-rank test			X	
Multivariable analysis:				
Multiple logistic regression	X	X	X	X
Missing data:				
Multiple imputations			X	X
Complete case analysis	X	X	X	X

Table 6. *Summary of statistical methods applied in Papers I-IV*

PAPER I

DESCRIPTIVE STATISTICS: Percentages, mean ±SD or median (IQR) were reported.

STATISTICAL ANALYSES: Fisher's exact test was used for the comparison of proportions between groups. The Mann-Whitney U test was used for the evaluation of continuous variables. For association trends over time, the Mann-Whitney U test was used for dichotomous variables and Spearman's rank correlation for continuous variables. All tests were two-sided and a p-value of <0.01 was considered statistically significant.

MULTIVARIABLE STATISTICAL ANALYSES: A forward stepwise logistic regression was applied to identify independent predictors of dichotomous dependent variables.

PAPER II

DESCRIPTIVE STATISTICS: Percentages, mean ±SD or median (IQR) were reported.

STATISTICAL ANALYSES: For association trends over time, on monitoring and non-monitoring wards respectively, the Mann-Whitney U test was used for dichotomous variables, whereas Spearman's rank correlation was used for continuous or ordered variables. All tests were two-sided and a p-value of <0.05 was considered statistically significant.

MULTIVARIABLE STATISTICAL ANALYSES: For interaction analyses between the time period and the type of ward for cardiac arrest, logistic regression was used, with continuous variables dichotomised by the overall median value, comparing the difference in the -2 log-likelihood of the models, with and without the interaction term included.

PAPER III

DESCRIPTIVE STATISTICS: Percentages, mean ±SD or median (IQR) were reported.

STATISTICAL ANALYSES: Complete case analyses were performed throughout the study. Standardised mean differences (SMD) were used to compare groups. The Kaplan-Meier estimator was used to delineate survival curves and the log-rank test was used to test for differences.

MULTIVARIABLE STATISTICAL ANALYSES: Logistic regression was used to calculate the adjusted probability of 30-day survival, where adjustment was made for age, gender and calendar year.

PAPER IV

DESCRIPTIVE STATISTICS: Percentages, mean ±SD or median (IQR) were reported.

STATISTICAL ANALYSES: The Kaplan-Meier estimator was used to delineate mortality curves. All tests were two-sided and a p-value of <0.01 was considered statistically significant.

MULTIVARIABLE STATISTICAL ANALYSES: Logistic regression was used to calculate age-adjusted p-values for the association of each variable with 30-day mortality. Due to the amount of missing data for several of the variables, multiple imputations were used. Multiple logistic regression analyses with a backward stepwise selection of variables were performed, both using multiple imputations and as a sensitivity analysis, using complete case analysis to see whether the findings were consistent without multiple imputations.

4 RESULTS

PAPER I

OUT-OF-HOSPITAL CARDIAC ARREST IN SWEDEN

During the study period, 1992-2009, there were a total of 52,275 cases of out-of-hospital cardiac arrest in Sweden, in which CPR was attempted. Of these, 7,187 cases fulfilled the inclusion criteria of probable cardiac aetiology, bystander-witnessed arrest and a registered shockable initial rhythm.

BASELINE CHARACTERISTICS

AGE, GENDER, LOCATION AND RESUSCITATION: The mean age was 69, SD 12 years (median, 71 years), of which 19% were female, and 45% of the out-of-hospital cardiac arrest occurred outside the home. Bystander CPR was performed in 55% of the cases, in 69% by a layperson and in 31% by a medical professional, not at work. The median delay from collapse to defibrillation was 12 minutes.

CHARACTERISTICS OF 30-DAY SURVIVORS: Compared with patients who died before hospital admission, patients who survived to 30 days were younger (66 SD 13 years vs 69 SD 12 years), more commonly female (21% vs 17%), and significantly more frequently suffered the cardiac arrest outside of the home (67% vs 41%). Bystander CPR was performed significantly more frequently (73% vs 52%) and the delay from collapse to defibrillation was significantly shorter (median 9 minutes vs 13 minutes).

CHARACTERISTICS IN RELATION TO GENDER: In comparison, patients of the female gender were older, more frequently suffered the sudden cardiac arrest at home and received bystander CPR less frequently. With regard to the delay from collapse to defibrillation, there were no gender differences. However, the number of defibrillations performed was significantly higher for males (mean±SD 4.8±4.6 vs 4.4±4.3; p=0.005).

OUTCOME

CHANGES OVER TIME: During the study period, there was no change in age, gender distribution or place of the cardiac arrest. Bystander CPR, however, increased from 46% to 73% (p for trend <0.0001). In patients receiving bystander CPR, the proportion of lay bystander CPR increased from 56% to

80% (p for trend <0.0001). Moreover, the median delay from collapse to defibrillation increased from 12 minutes to 14 minutes (p for trend 0.0004).

IMMEDIATE AND 30-DAY SURVIVAL: The proportion admitted to the hospital with spontaneous circulation increased from 28% to 45% (p for trend <0.0001). The proportion alive at 30-days increased from 12% to 23% (p for trend <0.0001) (*Figure 7*).

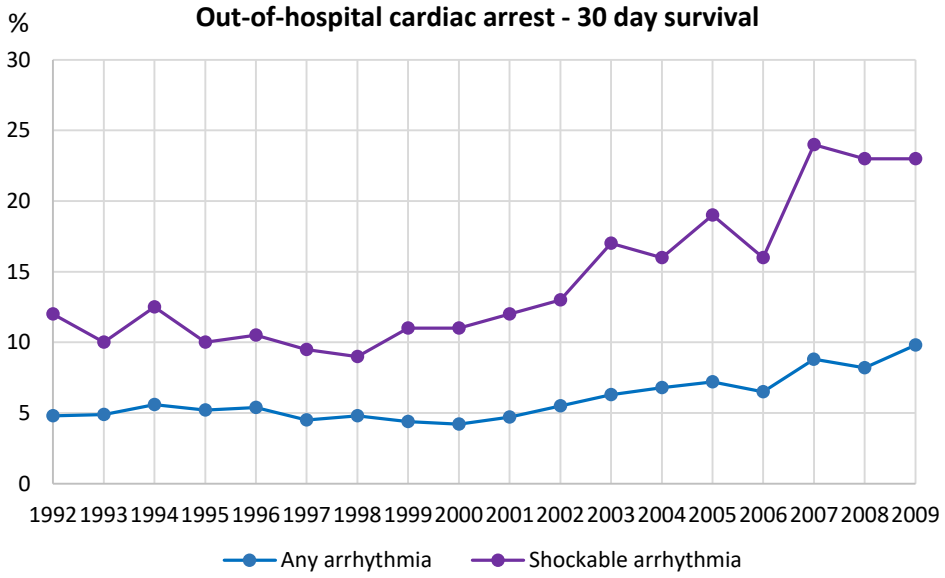


Figure 7. *Unadjusted trends of the proportion of patients who were alive at 30 days after out-of-hospital cardiac arrest with shockable arrhythmia and, for comparison, any arrhythmia*

FACTORS ASSOCIATED WITH OUTCOME: In the multivariable analyses, increasing age was associated with higher survival to hospital admission but lower survival to 30 days. Female gender, cardiac arrest outside the home, bystander CPR and a shorter delay from collapse to defibrillation were all independently associated with both increased survival to hospital admission and survival to 30 days.

CEREBRAL PERFORMANCE CATEGORY: In a subset analysis of CPC, performed in 2008 to 2009, in patients discharged alive from hospital (*n*=98), the outcome was *"good"* in 94% of the cases, CPC 1 (76%) and CPC 2 (18%), and *"poor"* in 7% of the cases, CPC 3 (4%) and CPC 4 (3%).

PAPER II

IN-HOSPITAL CARDIAC ARREST AT SAHLGRENSKA UNIVERSITY HOSPITAL

During the study period, 1994-2013, there were a total of 2,340 in-hospital cardiac arrests, where 53% occurred on wards with monitoring facilities.

BASELINE CHARACTERISTICS

AGE, GENDER AND PREVIOUS MEDICAL HISTORY: On monitoring wards, the median age increased from 70 years in the first period to 71.5 years in the last period. On non-monitoring wards, there was no significant change in age. Nor did the proportion of gender change significantly over time on any of the wards (33.5% and 38.0% were female on monitoring and non-monitoring wards respectively).

On monitoring wards, there were no significant changes in the previous history, whereas, on non-monitoring wards, there was a significant decrease in previous myocardial infarction and heart failure.

CIRCUMSTANCES AT RESUSCITATION: On non-monitoring wards, the recording of an initial shockable rhythm decreased significantly, 46% to 26% ($p<0.0001$ for trend). Similar changes on monitoring wards were not observed.

On both types of ward, the start of CPR prior to the arrival of a rescue team increased significantly, whereas defibrillation prior to the arrival of a rescue team only increased significantly on monitoring wards.

In patients with a witnessed collapse, the delay from collapse to calling for the cardiac arrest team was reduced on wards with monitoring facilities but did not change significantly on other wards.

The delay from collapse to the start of CPR decreased significantly on monitoring wards but not on non-monitoring wards. On the other hand, the delay from collapse to defibrillation only decreased significantly on non-monitoring wards.

OUTCOME

30-DAY SURVIVAL: 30-day survival increased significantly on monitoring wards, 43.5% to 55.6% (p=0.002 for trend). However, on non-monitoring wards, a similar increase in survival was not observed.

CEREBRAL PERFORMANCE CATEGORY: In 30-day survivors, the estimated CPC score at discharge from the hospital did not change significantly over time. On the other hand, already in the first five-year period of the study, the cerebral performance outcome was *"good"* (CPC 1 or 2) in 94% of the survivors on monitoring wards and 89% on non-monitoring wards.

PAPER III

IN-HOSPITAL CARDIAC ARREST IN SWEDEN

During the study period, 2008-2018, 23,186 unique patients suffered a total of 23,950 in-hospital cardiac arrests at Swedish hospitals, where 45.1% occurred on wards with monitoring facilities.

BASELINE CHARACTERISTICS

AGE, GENDER AND PREVIOUS MEDICAL HISTORY: The overall mean age was 72.6, SD 13.2 years (monitoring wards 70.9, SD 13.3 years, and non-monitoring wards 74.0, SD 13.0 years). The proportion of gender did not change significantly over time on any of the wards (36.8% and 40.1% were female on monitoring and non-monitoring wards respectively). Patients found in a shockable rhythm were younger; 70.6, SD 12.6 years, compared with those found in a non-shockable rhythm; 73.3, SD 13.3 years. With regard to the previous history, there was a clinically relevant increase over time of respiratory insufficiency on non-monitoring wards (SMD=0.12). Moreover, among patients found in a shockable rhythm, the proportion of patients with a previous history of heart failure decreased (SMD=0.12). Among patients found in a non-shockable rhythm, on the other hand, a previous history of respiratory insufficiency increased (SMD=0.10).

CIRCUMSTANCES AT RESUSCITATION: Among patients found in a shockable rhythm, the proportion of patients defibrillated before the arrival of the cardiac arrest team increased over time (from 71.0% to 80.9%, SMD=0.23). In addition, the use of buffering agents decreased over time, independent of initial rhythm and type of ward.

OUTCOME

30-DAY SURVIVAL: Overall 30-day survival was 30.0 %, (female 27.9%, and male 31.3 %). The overall adjusted 30-day survival increased over time from 24.7% to 32.5% (from 33.5% to 43.5% on monitoring wards and from 17.6% to 23.1% on non-monitoring wards) (*Figure 8*). The adjusted 30-day survival increased at both academic and non-academic hospitals.

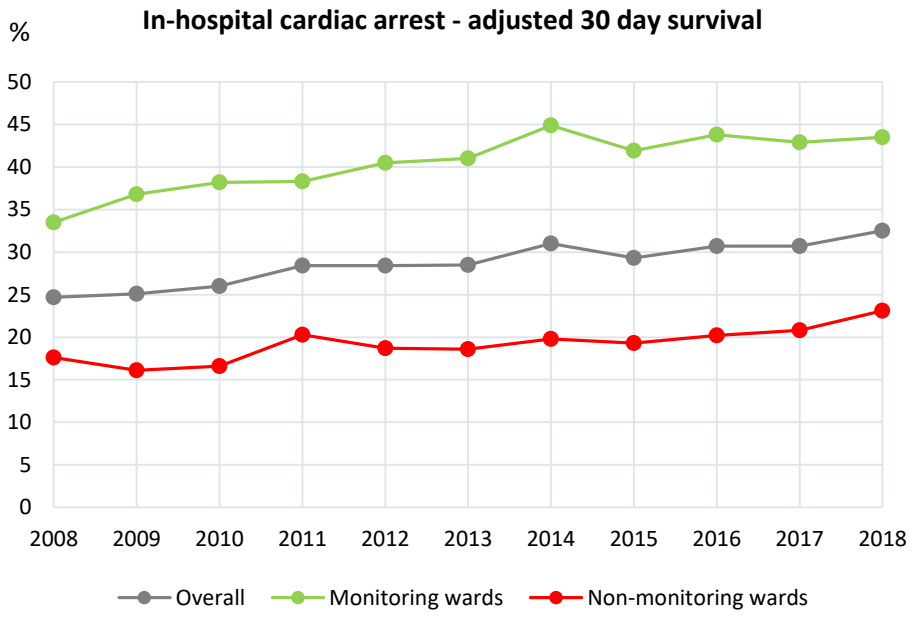


Figure 8. *Adjusted trends of the proportion of patients who were alive at 30 days, distributed by monitoring level of the wards*

In relation to the first registered rhythm, the adjusted 30-day survival increased considerably among patients with both a shockable and a non-shockable rhythm (from 53.7% to 64.9% for shockable rhythm and from 14.2% to 22.0% for non-shockable rhythm).

The increase in adjusted 30-day survival appeared to be more marked in younger patients than among the elderly. For patients >85 years of age, the adjusted 30-day survival did not change at all.

In a follow-up, up to 10 years, it was revealed that the long-term survival prognosis among patients suffering an in-hospital cardiac arrest was poor.

PROPORTION OF SHOCKABLE RHYTHMS: In 26.3% of the total cases, the first registered rhythm was shockable. Men collapsed more often in a shockable rhythm than women, with a proportion of 69.5%. Overall, the proportion of patients found in shockable rhythms decreased from 31.6% to 23.6% (on monitoring wards, from 42.5% to 35.8%, and on non-monitoring wards from 20.1% to 12.9%).

PAPER IV

MEDICAL EMERGENCY TEAM-ASSESSED PATIENTS AT SAHLGRENSKA UNIVERSITY HOSPITAL

During the study period, 2010-2015, there were 3,553 MET assessments at Sahlgrenska University Hospital, of which 2,601 individual patients fulfilled the inclusion criteria.

BASELINE CHARACTERISTICS

AGE AND GENDER: Patients age varied from 18 to 99 years of age (mean=65.7, SD 16.8), of which 44.3% were female. Fewer than half the patients (42.5%) were transferred to the ICU.

OUTCOME

30-DAY MORTALITY: Overall 30-day mortality was 29.0%. Patients with palliative or limitation of medical therapy decisions demonstrated a significantly higher 30-day mortality (65.5%), in comparison to patients without any treatment restrictions (21.2%). There were, however, no significant differences in 30-day mortality with regard to gender or level of care (age-adjusted p=0.37 and 0.31 respectively).

30-DAY MORTALITY IN RELATION TO:

Type of ward: The highest 30-day mortality was found in patients on geriatric wards, followed by patients on respiratory medicine and oncology wards. The MET-assessed patients on surgical wards had significantly lower 30-day mortality.

Previous medical history: Previous medical conditions associated with the highest 30-day mortality were heart failure, followed by haematological disease, angina pectoris and pulmonary disease. The following previous

medical conditions were significantly associated with increased age-adjusted 30-day mortality: cancer, haematological disease, pulmonary disease and liver disease.

Acute medical condition: Acute conditions associated with the highest 30-day mortality were gastroenteritis, acute coronary syndrome, heart failure and renal failure. The following acute medical conditions were associated with increased age-adjusted 30-day mortality: heart failure, pneumonia and renal failure.

Laboratory biomarkers: Laboratory biomarkers associated with the highest 30-day mortality were hypoglycaemia, hypernatraemia, hyperkalaemia, acidosis and hyperlactataemia. The same laboratory findings were also associated with a significant increase in age-adjusted 30-day mortality, along with elevated serum creatinine and hypoxaemia.

Status on arrival of MET: Patients who presented with hypoxia and tachypnoea had the highest 30-day mortality. The following vital parameters were associated with a significant increase in age-adjusted 30-day mortality: hypoxia, tachypnoea, tachycardia and unconsciousness.

INDEPENDENT FACTORS ASSOCIATED WITH 30-DAY MORTALITY: When using multiple imputations in logistic regression analyses, age and factors related to type of ward, vital parameters, laboratory biomarkers, previous medical history and acute medical condition all contributed to the prediction of death. Of these factors, the highest odds ratios (OR) for death within 30 days were found for hypoglycaemia, haematological disease and hypoxia.

THE TIMING OF DEATH IN RELATION TO DAYS AFTER MET ASSESSMENT: In overall terms, approximately half the deaths occurred within the first four days after an MET assessment.

5 DISCUSSION

OUT-OF-HOSPITAL CARDIAC ARREST
PAPER I

WHO IS THE CPR BYSTANDER?

Basic life support is defined as medical care given in the event of life-threatening illnesses or injuries outside medical facilities, pending full medical care at a hospital. Basic life support refers to the initial care that first responders, or bystanders, can provide to anyone who is experiencing a cardiac or respiratory arrest, drowning or choking. Bystanders may be trained healthcare practitioners off duty, present at the scene, or qualified laypersons [159].

In the Utstein publication from 2015, the term "bystander CPR" is defined as *"CPR performed by a person not responding as part of the organised emergency response system to a cardiac arrest. Physicians, nurses and paramedics may be described as performing bystander CPR if they are not part of the emergency response system involved in the victim's resuscitation"* [16]. Despite this, there is still some confusion about whether the term "bystander" only applies to those witnessing the collapse and initiating CPR on the scene or also to the first-tier response such as police officers, firefighters and smartphone app-dispatched rescuers [162]. Due to this uncertainty, the incidence of "true bystander CPR" may be overestimated when including cases with CPR performed by the first-tier response in the analyses.

In the Swedish Registry for Cardiopulmonary Resuscitation analyses of bystander CPR, in Paper I, the profession of the bystander was described as a layperson or healthcare practitioner off duty. However, at the time of the study, we were not able to distinguish CPR initiated by a "true bystander" on the scene from CPR initiated by police officers or firefighters, dispatched from the dispatch centre and part of the first-tier response. When dispatched, they were in fact involved in the organised response system and were not by definition "true bystanders". The correct definition of bystander CPR in Paper I should therefore have been "CPR started before the arrival of the emergency medical service", including all kinds of CPR before the arrival of the emergency medical service, irrespective of whether or not an organised response system was involved. In later publications on the same topic, this definition has been used instead [119].

Overall, there was a significant increase in the frequency of bystander CPR over time and explicitly so in the proportion of laypersons performing bystander CPR. A fact which, at least in part, can be traced to the purposeful public CPR education efforts made during the study period [163].

WHY IS BYSTANDER CPR ASSOCIATED WITH AN INCREASE IN SURVIVAL AFTER OUT-OF-HOSPITAL CARDIAC ARREST?

When basic life support is performed in the field, it increases the time margins for medical professionals to arrive and provide advanced life support. Bystander CPR has been shown to improve survival chances by two to three times [115, 164]. Traditionally, bystander CPR has included both manual chest compressions and mouth-to-mouth ventilation. In recent years, however, bystander CPR has been limited, in many cases, to only chest compressions [165, 166]. Part of the reason may be the fact that bystanders are instructed to perform CPR by an operator at the dispatch centre, over the phone. These instructions are more easily adhered to when limited to only chest compressions, which is in accordance with guideline recommendations when bystander-supported CPR is performed [167]. It has been argued that the blood is most probably well oxygenated immediately after the circulatory collapse. As a result, focusing on providing circulating oxygen to the brain is therefore regarded as far more critical, in order to avoid brain and tissue damage, than losing time on adding more oxygen through mouth-to-mouth ventilation. One positive side-effect of the changed “chest compressions only” recommendation may be more CPR-motivated bystanders, as mouth-to-mouth ventilation results in some resistance in the resuscitation of strangers. However, the question of whether “chest compressions only” is as effective as chest compressions plus mouth-to-mouth ventilation is still the subject of discussion [168].

Promptly initiated and ongoing bystander CPR, until the arrival of the emergency medical service, increases out-of-hospital cardiac arrest survival significantly [153, 154, 169]. It is assumed that bystander CPR through chest compressions maintains the circulation and thus prolongs the ventricular fibrillation, resulting in an extended shockable phase [170-173]. Another reason for increased survival may be the broader availability of automated external defibrillators outside medical facilities, accessible for bystander CPR and early defibrillation. Publicly available automated external defibrillators have been proven to increase survival in out-of-hospital cardiac arrests significantly [151-153]. Other mechanisms, in addition to the prolongation of shockable rhythms, also appear to be of great significance. Among victims of

out-of-hospital cardiac arrests not found in a shockable rhythm, bystander CPR still appears to be associated with increased survival [174-176].

It is crucial to recognise that, in all cases, regardless of aetiology, the best effect of bystander CPR is achieved within a fairly short time window (i.e. minutes) after the collapse. In other words, the earlier CPR is started, the higher the survival [173, 177].

WHY WAS SURVIVAL HIGHER IF OUT-OF-HOSPITAL CARDIAC ARREST OCCURRED OUTSIDE THE HOME?

Basic life support requires knowledge and training in CPR, the use of automated external defibrillators and relieving airway obstructions. Most people expressing an interest in basic life support education tend to be younger and usually not living with anyone likely to be affected [178]. So, despite extensive training efforts among laypersons, the average bystander is a person in a position similar to that of the victim, such as a partner or related party, with limited CPR training [179]. The lack of experience means the bystander will often need guidance to manage an unusual and stressful situation of this kind. Coaching efforts have therefore been made in many places to educate operators at dispatch centres to instruct first responders in CPR over the phone, until the emergency medical service arrives, with good results [180].

In Paper I, we concluded that the location of collapse was associated with outcome; as a result, the survival rate was significantly higher for those suffering a sudden cardiac arrest outside the home. The reason for this could be that fewer people in the elderly population have taken part in CPR training. Another explanation is the pure size ratio between men and women. When a sudden cardiac arrest occurs at home, the patient is more frequently a man and the bystander is a member of the opposite gender, causing an imbalance in physical qualifications. Simply put, a small, slender woman will not be able effectively to perform deep chest compressions on a large man, to the same extent as the reverse. For this reason, the quality of bystander CPR and thereby the survival chances should reasonably be substantially higher outside the home with the assistance of more robust and skilled bystanders.

Another aspect is that, when a person collapses outside the home, there are often more people attending the event. One bystander can dial 112 and the others can start CPR. Among those performing CPR, one can perform chest compressions and the other can perform mouth-to-mouth ventilation. When the bystander performing chest compressions is exhausted, he or she can be

replaced by a fresh bystander. As a result, during out-of-hospital cardiac arrest outside the home, bystanders often perform successful teamwork together as opposed to at home, where the bystander is generally alone.

IS THE PATIENT'S GENDER IMPORTANT FOR THE CHANCES OF SURVIVING AN OUT-OF-HOSPITAL CARDIAC ARREST?

It has previously been stated that women are less likely to develop and survive an out-of-hospital cardiac arrest compared with men [181]. However, according to the findings in Paper I, the chance of survival to 30 days was significantly higher for women. In addition to the obvious physical dissimilarities, other differences in relation to gender, of relevance for survival, can be speculated upon.

In the field of out-of-hospital cardiac arrest, it has been stated that women have a different cardiac arrest profile than men, with more aggravating prognostic factors affecting survival. Women are usually older, more frequently collapse at home and commonly present with a non-shockable rhythm of non-cardiac aetiology. Women also appear to be less likely to have a witnessed cardiac arrest and therefore receive bystander CPR less often [182, 183]. Our results in Paper I demonstrated similar findings, in that women were significantly older when suffering a sudden cardiac arrest, more frequently collapsed at home and less frequently received bystander CPR. These characteristics have almost consistently been reported globally, while the survival reports, in relation to gender, are far more inconsistent.

Various studies have indicated an association between female gender and increased survival after out-of-hospital cardiac arrest [184-186]. In contrast, other studies have not been able to demonstrate the same beneficial association, not even when adjusting for the imbalance in unfavourable predictors [187-190]. In spite of this, some studies have shown that women in their reproductive period experience increased survival after sudden cardiac arrest compared with men of the same age or older women, suggesting that there may be a neuro- and cardioprotective effect from their hormonal levels, referred to as the "oestrogen effect" [189, 191-193].

Beyond the hormonal protective effect of oestrogen, other explanations have been speculated upon. They include diverse responses of the autonomic nervous system and cardiac cells to ischaemia, resulting in a lower oxygen requirement in women, as well as a more pronounced vagal activation with possibly beneficial antiarrhythmic effects [194]. Moreover, our finding in Paper I that women require significantly fewer defibrillations may indicate a

more favourable response to electrical treatment when presenting with a shockable rhythm, possibly due to a smaller heart and thorax volume.

Even though several studies have addressed possible differences between genders in the chance of survival after out-of-hospital cardiac arrest, no conclusion on the subject has emerged. It appears that about the same number of studies report no gender difference in survival after out-of-hospital cardiac arrest, improved survival for men or improved survival for women. These inconsistencies may be explained in part by different inclusion criteria or different subsets of the study population, such as limitations to only initial shockable rhythms, or only cardiac aetiology (as in Paper I), or limitations to specific age categories. In addition, the survival endpoint varies between different studies, e.g. the return of spontaneous circulation, survival to admission to hospital, survival to discharge from hospital, survival to 30 days and long-term survival. So, to answer this question, the relationship between gender and survival warrants further investigation. An investigation of large sample size was recently performed using a machine learning technique on the Swedish Registry for Cardiopulmonary Resuscitation [195]. In this study, the victims' gender did not appear to have any impact on the chances of surviving an out-of-hospital cardiac arrest. One interesting observation in the Swedish Registry for Cardiopulmonary Resuscitation is that, during the last decade, it appears that 30-day survival has increased more markedly in men than in women [196], for which we have no explanation.

WHICH ARE THE POSSIBLE MECHANISMS BEHIND THE INCREASED DELAY FROM COLLAPSE TO DEFIBRILLATION?

During the study period in Paper I, we found a significant increase in the delay from collapse to defibrillation, with a median delay of up to 14 minutes. There appears to be a general trend towards increasing delays from cardiac arrest to defibrillation generated by prolonged response times by the emergency medical service. The reason, leading to an insufficient supply or reduced availability of paramedics, is probably multifactorial. Among other things, it is reasonable to assume a relationship between the steadily growing population and the lack of a corresponding increase in resources, creating an imbalance which inevitably results in a reduced density of the emergency medical service, i.e. the number of ambulances per capita, and a heavier workload for the paramedics. Another consequence of population growth is an increasing number of cars and traffic congestion, leading to longer transportation times for the emergency medical service.

An additional mechanism, which possibly generates extended emergency medical service response times, is the implementation of so-called “fast tracks” for various time-sensitive and non-time-sensitive alarm conditions. The goal of the emergency medical service’s “fast tracks” is to achieve more rapid pathways for patient care from the event to the final destination for treatment, or examination, within the hospital. The emergency medical service’s “fast-tracks” are, for example, applicable to patients suffering an acute myocardial infarction [197], stroke [198], or hip fracture [199] and frail elderly, for whom hospital admission is inevitable without considering whether or not the condition is time sensitive [200]. The processing of these “fast tracks” involves a greater workload and more time for the emergency medical service, causing a reduction in the availability of paramedics for future assignments, independently of the degree of prioritisation.

Due to the value of early defibrillation for survival after shockable out-of-hospital cardiac arrest, in combination with the described changes in society, substantial investments have been made in recent years to reduce delays by implementing automated external defibrillators in the community, together with the active recruitment of bystanders through smartphone applications.

As a side note, the reported decline in the incidence of shockable rhythms could be due to longer delays from cardiac arrest to defibrillation [39, 201]. Since ventricular fibrillation is an extremely energy-consuming condition, it will eventually transition into asystole. In other words, the favourable treatment window with defibrillation is limited and narrow. It is therefore essential to understand that delayed interventions will rapidly reduce the chances of survival.

IN-HOSPITAL CARDIAC ARREST
PAPERS II AND III

WHY WAS THERE A DECLINE IN INITIAL SHOCKABLE RHYTHMS IN IN-HOSPITAL CARDIAC ARREST?

By now, the declining incidence of initial registered shockable rhythms outside hospital is a well-known fact, even though the underlying causes are not fully understood [41-44]. A change of factors in patient characteristics, such as increased age at the onset of cardiac arrest, a higher prevalence of co-morbidities and decreased cardiac aetiology or at least cardiac ischemic diseases, has been reported as a probable reason. It has thus been speculated that, when patients collapse in cardiac arrests nowadays, they have reached the end-stage of their heart disease and more frequently present with non-shockable rhythms. However, this hypothesis has never been confirmed. As previously mentioned, resuscitation-related reasons have also been discussed, primarily increased delays from collapse to the arrival of the emergency medical service and defibrillation [39, 201].

Other possible causes, also applicable to in-hospital cardiac arrest, are more prevalent pharmacological prevention and treatment regimens for cardiovascular disease, including ischaemic heart disease, with the extensive use of beta-blockers and angiotensin-converting enzyme inhibitors [193]. These medications may reduce the duration of ventricular fibrillation [202]. In this context, however, it is important to emphasise that beta-blockers are also able to reduce the risk of sudden cardiac disease and cardiovascular death in patients with acute coronary syndrome, or those presenting with chronic heart failure [203].

More specific explanations for the decline in initial shockable rhythms in in-hospital cardiac arrests, in particular, include more readily available opportunities for revascularisation interventions, in addition to the urgent introduction of adequate pharmacological treatment, when admitted to hospital with acute coronary syndrome [39, 40]. Another possible contributory factor may be the increasingly more common secondary prevention with implantable cardioverter defibrillators [44, 204, 205].

Even if the search for a universal explanation of the decline in initial shockable rhythms in in-hospital cardiac arrests, as well as out-of-hospital cardiac arrests, is likely to continue, there is currently good reason to suspect that the cause is plausibly multifactorial and a clear answer probably does not exist.

WHY WAS THE DECLINE IN INITIAL SHOCKABLE RHYTHMS MORE MARKED ON NON-MONITORING WARDS?

In line with the above reasoning relating to possible explanations of the declining trend in the proportion of initial ventricular fibrillation, there is no single, obvious variable that stands out in the analyses of our material, either in patient characteristics or in resuscitation efforts. However, there are some changes over time that deserve to be highlighted and discussed in more detail.

It has long been known that men suffer sudden cardiac arrests to a greater extent than women and also more frequently present with an initial shockable rhythm [182, 183]. It is therefore worth pointing out that there were no changes in the gender distribution over time, on any of the wards, possibly explaining the decrease in the incidence of initial shockable rhythms. The trend for average age when suffering a sudden cardiac arrest was a decrease rather than an increase, implying that the age factor can also be eliminated.

When searching for answers relating to baseline characteristics, the most probable explanation would be a change in the co-morbidity perspective, such as an increase in general co-morbidity on non-monitoring wards. Based on the reported findings in Papers II and III, it is not, however, possible to draw this conclusion with any certainty. What could be demonstrated, however, was a significant decrease in previous myocardial infarction and a corresponding increase in respiratory insufficiency, which was even more pronounced on non-monitoring wards. Both variables could serve as possible contributory factors to the decrease in the proportion of initial shockable rhythms. What, on the other hand, would suggest a different outcome for the first recorded rhythm was the accompanying reduction in heart failure, on both types of ward, since it has previously been reported that heart failure, in particular, will cause asystole [45].

When analysing the reported resuscitation efforts, there is nothing to indicate a connection with the change in rhythm distribution. Instead, rescue attempts have improved over time. Overall, there was an increase in the proportion of patients receiving CPR and defibrillation before the arrival of the cardiac arrest team, as well as a reduction in the delay from collapse to defibrillation.

One factor that could be of significance, but about which we lack information for obvious reasons, is the delay from collapse to discovery in the unwitnessed cases. This delay may conceivably have increased over time,

resulting in a larger proportion of initial ventricular fibrillations devolving into asystole before discovery.

Another possible association between the decrease in initial shockable rhythms and non-monitoring wards specifically could be that the patients on general wards are in potentially poorer condition now than before. Medical practitioners appear to have become more diligent about issuing limitation of medical therapy decisions such as do not intubate, no intensive care or no dialysis orders, possibly resulting in more affected patients remaining on non-monitoring wards. As a result, declining patients suffering an in-hospital cardiac arrest of non-cardiac (non-ischaemic) aetiology are less likely to present with shockable rhythms [107].

In addition, there could be many other possible explanations, mostly applicable to patients on the non-monitoring wards, such as alterations in medical prevention and treatment regimens, with reference to pharmaceuticals, and cardiovascular interventions through angiographic and surgical techniques. We have not included any of these variables in our analyses and are therefore unable to comment on possible associations.

WHICH ARE THE MOST PLAUSIBLE EXPLANATIONS FOR THE INCREASED SURVIVAL RATE AFTER IN-HOSPITAL CARDIAC ARREST?

Although rhythm conditions and baseline characteristics associated with increased survival chances have not improved, on the whole, survival after in-hospital cardiac arrest has nevertheless increased significantly. The most striking change in baseline characteristics for improved survival rate was the moderate reduction in average age. According to previous reports, the survival rate gradually increases with decreasing age [1, 206, 207].

With regard to previous medical history, co-morbidity appears to be primarily associated with the initial rhythm and, by extension, survival. As the proportion of shockable in-hospital cardiac arrest has evidently decreased, it seems unlikely that a decrease in myocardial infarction and an increase in respiratory insufficiency would have affected the survival outcome in a positive direction. Moreover, in previous studies, a history of respiratory insufficiency has been significantly associated with reduced survival [208, 209]. However, it may be possible that the reduced prevalence of heart failure, on both monitoring and non-monitoring wards, could have contributed to the increased survival rate. By triggering non-shockable in-hospital cardiac arrest to a lesser extent, an even more significant increase in non-shockable in-hospital cardiac arrest may have been prevented [45].

Nonetheless, it seems more plausible to assume that the increased survival rate, accompanied by mostly impaired aetiological conditions, is likely to depend on advances in resuscitation efforts among healthcare practitioners. Notably, the critical rescue interventions mostly improved over time, i.e. a larger proportion of patients received CPR and were defibrillated before the arrival of the cardiac arrest team and the delay from collapse to defibrillation, and also to some extent CPR, decreased. In addition, the use of buffering agents decreased significantly over time, due to revised guidelines for resuscitation. Nevertheless, there is no reason to assume that this alteration has had a major impact on improved survival rates.

In addition, two other potential confounding factors may explain the increased survival rate after in-hospital cardiac arrest. Firstly, there is a knowledge gap relating to the procedures involving do not attempt resuscitation orders. We do not know whether do not attempt resuscitation orders have increased over time and thereby created problems with selection bias by altering the characteristics of the study cohort available for resuscitation. Secondly, there is also a knowledge gap relating to the proportion of patients resuscitated after an in-hospital cardiac arrest without alerting the rescue team, principally on monitoring wards such as ICU, coronary angiography laboratories and operating rooms. If the reporting of these cases to the registry has improved over time, an artificial increase in the survival rate may have occurred, since the majority are most likely survivors. The observation that the proportion of patients found in shockable rhythms decreased over time speaks against but does not completely rule out either of these two hypotheses.

WHY WAS THE SURVIVAL MUCH LOWER AMONG PATIENTS SUFFERING AN IN-HOSPITAL CARDIAC ARREST ON NON-MONITORING WARDS?

The underlying reason for dividing the study population into two subgroups becomes apparent when comparing the survival rate for patients on non-monitoring wards with that of patients on monitoring wards. Then, if not before, the widely differing circumstances of patient care between the two types of ward emerge with clarity. The preconditions differ in terms of not only accessible monitoring equipment but also the numerical ratio of patients to nurses, resulting in a much higher witnessed status for in-hospital cardiac arrest on monitoring wards and thereby the more immediate availability of advanced life support. Further, the competence profile of the staff varies between the two types of ward, which would imply that the staff on monitoring wards are more accustomed to performing CPR and managing

patients with life-threatening conditions. Given these fundamental differences in the conditions of patient care, our findings of higher survival outcome following an in-hospital cardiac arrest on wards with monitoring facilities compared with wards without these facilities are not particularly surprising. Moreover, when searching the literature, our findings are in accordance with the reports from other studies [210-212], with only a few exceptions [213].

In addition to the structural differences on the wards, the patient population differs in terms of some crucial basic characteristics. On non-monitoring wards, for example, the average age for suffering an in-hospital cardiac arrest was substantially higher than on monitoring wards. In many studies, increased age is regarded as a predictive factor for reduced survival following cardiac arrest, especially above 70 years [18, 207, 214]. Furthermore, patients on non-monitoring wards had significantly more co-morbidities, such as previous stroke, diabetes, renal failure, respiratory insufficiency and cancer. Several of these medical conditions have previously been reported to be associated with decreased survival rates following cardiac arrest, specifically respiratory insufficiency, renal dysfunction and active malignancy [25, 142, 143, 209]. It is worth noting the relatively smaller proportion of patients with previous myocardial infarction on the non-monitoring wards, possibly indicating a higher frequency of non-cardiac (non-ischaemic) aetiology in in-hospital cardiac arrest, associated with poorer survival [25, 107, 212, 215]. Cardiac morbidity before and on hospital admission has previously been associated with the almost doubling of the survival rate compared with non-cardiac morbidity [208]. With regard to heart failure, a condition associated with asystole and subsequently more unsatisfactory survival outcome [45, 142], the proportion of patients with this condition was large. More than a third of the patients on non-monitoring wards had heart failure in their medical history. However, the proportion of patients with heart failure on monitoring wards was almost equally large. As a result, the substantial proportion of heart failure in the patient population is unable to explain the lower survival on non-monitoring wards, in particular.

Following previously discussed associations between co-morbidity and first registered rhythm in cardiac arrest, it can be concluded that patients on non-monitoring wards with higher co-morbidity, possibly suffering an in-hospital cardiac arrest of non-cardiac aetiology more frequently, will collapse in a non-shockable rhythm to a larger extent than patients on monitoring wards. Accordingly, the patients on non-monitoring wards did suffer an in-hospital cardiac arrest with initial shockable rhythm less than half as often as the patients on monitoring wards.

Upon closer examination of the efforts involved in resuscitation, a few essential differences appear. Perhaps the most critical difference is the degree of witnessing status, where non-monitoring wards reported a much lower percentage of witnessed in-hospital cardiac arrest. The most evident consequences of unwitnessed cardiac arrest are presumably the delayed discovery of collapse and subsequently the delayed initiation of treatment. These effects could be observed in both Papers II and III. The delay from collapse to call and from collapse to CPR appeared to be somewhat longer, whereas the delay from collapse to defibrillation was considerably longer on non-monitoring wards. Other causes, apart from the degree of witnessing, may explain this delay, such as a less well-tuned organisation and less experienced staff to act in emergency situations, as well as a possible lack of close access to equipment, e.g. defibrillators.

When comparing treatment, in-hospital cardiac arrest patients on non-monitoring wards were treated with adrenaline more frequently. In-hospital cardiac arrest patients on monitoring wards, on the other hand, were defibrillated and treated with anti-arrhythmic drugs and buffering agents more frequently. In all probability, these differences in treatment are not primarily associated with the outcome but are instead an expression of the underlying aetiology and initial registered arrhythmia of the cardiac arrest.

Last but not least, on non-monitoring wards, there is no refined selection of patients, as there is on monitoring wards, for which not all patients qualify as a result of limitations in medical therapy decisions. As a result, many patients suffering an in-hospital cardiac arrest on non-monitoring wards have a much poorer prognosis from the start due to more advanced age and greater co-morbidity, as previously discussed.

If do not attempt resuscitation orders are not issued, in-hospital patients suffering a cardiac arrest must receive CPR, even if the cardiac arrest is only the final event in the dying process. As a result, if the do not attempt resuscitation policy is not effectively used before the in-hospital cardiac arrest occurs, CPR must inevitably be performed until an active decision about discontinuation is made. All in-hospital patients, in whom CPR was initiated, were included in the study population. It is therefore possible that several patients for whom do not attempt resuscitation orders should have been issued were included. It is not entirely inconceivable that legitimate do not attempt resuscitation orders failed to be issued to a greater extent on non-monitoring wards. However, we have no objective support for this assumption.

WHICH ARE THE WEAK LINKS IN THE CHAIN OF SURVIVAL FOLLOWING IN-HOSPITAL CARDIAC ARREST?

In the updated guidelines for CPR and advanced cardiovascular life support from 2015, a different pathway for in-hospital cardiac arrest in relation to out-of-hospital cardiac arrest was presented. By shifting the focus from the active resuscitation of an unexpected cardiac arrest outside hospital to the more vigorous prevention of avoidable cardiac arrest inside hospital, i.e. detecting and improving clinical deterioration prior to the arrest, the objective was to reduce the number of in-hospital cardiac arrests [113].

Despite partially overlapping study periods in Papers II and IV, we have not been able to find any evidence to suggest that the number of cardiac arrests has been reduced following the implementation of the MET at Sahlgrenska University Hospital. However, this assumption is only a rough estimate, as we have not explicitly analysed and compared this outcome. There could be many reasons why the desired reduction in in-hospital cardiac arrests has not occurred. Moreover, the effect of preventive measures such as the introduction of a new system may be delayed and only appear later.

With regard to survival following in-hospital cardiac arrest in Sweden, there are some weaker links in the chain of survival and this deserves to be further elucidated.

SURVEILLANCE AND PREVENTION: Given the marked differences in the overall outcome between non-monitoring wards and monitoring wards, there is significant potential for improvement in this area on the non-monitoring wards. By increasing the monitoring level and nurse density on general wards, the rapid identification of ominous warning signs would be facilitated through improved surveillance. It should be noted that the term “surveillance” includes not only technological monitoring equipment but also the interpretation of clinical data and measurements, as well as data-driven decision making. If patients at risk for potential serious adverse events are recognised early in the course, appropriate measures can be initiated, including the escalation of the level of care (if needed), in order to prevent further clinical deterioration developing into a cardiac arrest.

RECOGNITION OF CARDIAC ARREST AND ACTIVATION OF THE EMERGENCY RESPONSE SYSTEM: If an in-hospital cardiac arrest occurs despite adequate medical efforts being made, the chances of the immediate detection of the collapse should be greatly improved by the implementation of increased surveillance and nurse density. Witnessed cardiac arrest is a previously known

predictor of higher survival, provided CPR is promptly initiated, regardless of location [107, 143]. Increasing the proportion of witnessed in-hospital cardiac arrests is therefore a desirable aim in order to increase the survival rate, particularly on general (i.e. non-monitoring) wards with currently highly sporadic and limited monitoring capabilities.

IMMEDIATE HIGH-QUALITY CPR: Due to the dedicated work and extensive efforts made with recurrent CPR training for all medical professionals in recent decades, very satisfactory results in CPR performance have been achieved in overall terms. These endeavours have substantially increased the initiation of CPR before the arrival of the cardiac arrest team and reduced the delay from collapse to CPR, specifically on non-monitoring wards. In Papers II and III, we only measured the actual time of starting CPR and the delays from collapse. As we have not performed any quality checks on CPR performance, it is worth pointing out that, in order for the resuscitation to be effective, chest compressions have to be of the correct depth and rate and with minimal interruption.

RAPID DEFIBRILLATION: Based on the reported findings, there should still be scope for improvement in in-hospital cardiac arrests with shockable rhythms, especially on non-monitoring wards. In overall terms, more than half the patients with a shockable rhythm were defibrillated before the arrival of the cardiac arrest team. Over time, there was also an increase in the proportion of patients with a shockable rhythm defibrillated before the arrival of the cardiac arrest team on non-monitoring wards (61.8% during the first period and 65.6% during the second period) and a corresponding decrease on monitoring wards (64.2% and 56.1% respectively). However, the delays from collapse to defibrillation were significantly shorter on monitoring wards compared with non-monitoring wards and did not change on either ward during the study period. Given that the median time for defibrillation was four times longer on the non-monitoring wards, there should reasonably be opportunities for improvement through an optimised resuscitation organisation and a further increase in the availability of automated external defibrillators.

ADVANCED LIFE SUPPORT AND POST-ARREST CARE: This final link has not been thoroughly investigated in our studies, except for treatment measures performed during or in direct proximity to the resuscitation. More in-depth analyses of these variables from a survival perspective are likely to be highly uncertain as they reflect several variables, including the underlying causes of the cardiac arrest, the initial rhythm and the skills resources of the resuscitation service.

In this link in the chain of survival, it is crucial to realise that resuscitation does not stop with the return of spontaneous circulation. The cornerstones of post-arrest care include the identification and treatment of factors triggering the arrest, the improvement of neurological recovery and outcome and also the limitation of injury and tissue damage associated with the cardiac arrest.

HOW SHOULD WE IMPROVE SURVIVAL EVEN FURTHER AFTER IN-HOSPITAL CARDIAC ARREST?

In Paper III, the overall percentage of patients who survived to 30 days following an in-hospital cardiac arrest in Sweden was 30%. One year after the in-hospital cardiac arrest, the percentage dropped to 25%. The most common initial rhythms registered at the in-hospital cardiac arrest were pulseless electrical activity and asystole. Taken as a whole, non-shockable rhythms constituted 76% of all in-hospital cardiac arrests. With this in mind, is it acceptable that three-quarters of all hospitalised patients who suffer a sudden in-hospital cardiac arrest during the care of medical management are dead within a year after the event? In any case, these survival rates are considered relatively high in an international comparison. Can we still improve long- and short-term survival? If so, in which way?

From the findings in Paper II and III, and with the addition of recommendations proposed by the subject-matter expertise, there are some key areas that warrant further attention for improvement:

RESUSCITATE THE RIGHT PEOPLE: It may seem obvious in theory, but, in the stressful and time-demanding care environment, it is easy to miss positions on reasonable level of care and life-saving efforts, before the cardiac arrest occurs. The value of the timely issuing of treatment limitation orders, when indicated, in well-founded forms and in agreement with patients and/or their relatives, cannot be sufficiently emphasised. In this way, the initiation of unnecessary and unethical resuscitation is avoided and poor outcome due to selection bias is counteracted [216].

PROVIDE EFFECTIVE RESUSCITATION: It is worth bearing in mind that resuscitation quality is not only determined by the competence of the rescue team. If the clinicians do not feel the right patient is being resuscitated, it becomes a self-fulfilling prophecy that marks the entire care process from CPR to post-resuscitation care, resulting in an impaired outcome. For this reason, it is also essential to make joint, legitimate decisions about the level of care for the individual patient.

CARDIOPULMONARY RESUSCITATION: Prioritise the immediate initiation of CPR and focus on continuously maintaining perfusion to vital organs [217]. Limit interruptions when checking for a pulse, securing the airway, or placing central intravenous lines [218]. Do not ventilate the patient excessively, as excessive ventilation may lead to a reduced survival rate [219]. Make sure the CPR provider is replaced before fatigue occurs and CPR quality drops.

DEFIBRILLATE SHOCKABLE RHYTHMS QUICKLY: If the patient presents in a shockable rhythm, the aim is to defibrillate within two minutes of onset to avoid a reduction in survival chances [122, 217]. For the most part, patients suffering an in-hospital cardiac arrest with a shockable rhythm on monitoring wards were defibrillated within two minutes, whereas, on non-monitoring wards, the delays were substantially longer. In other words, there should be scope for improving the delays from collapse to defibrillation significantly on non-monitoring wards.

INCREASE SURVEILLANCE ON GENERAL WARDS: By increasing the monitoring level and nurse density on general wards, thereby increasing surveillance, the proportion of witnessed in-hospital cardiac arrest would most certainly increase. Immediate detection is the most crucial prerequisite for the prompt initiation of CPR and defibrillation and thus, by extension, survival.

MEASURE OUTCOMES AND EVALUATE THE PERFORMANCE: Measure and record all variables relevant to the outcome of in-hospital cardiac arrest. Use the data to evaluate the performance and provide feedback to the resuscitation team members. Continue to build on the scope and content of the in-hospital Swedish Registry for Cardiopulmonary Resuscitation. The three cornerstones for improving outcome after in-hospital cardiac arrest still further may very well be: 1) Feedback 2) Reflection and 3) Improved attitude to CPR.

MEDICAL EMERGENCY TEAM ASSESSMENT
PAPER IV

HOW SHOULD WE ADDRESS THE FINDING THAT THE TYPE OF WARD FOR MET ASSESSMENT IS ASSOCIATED WITH RISK?

One of the most significant findings in Paper IV was that in-hospital patient mortality after MET assessment was high and unevenly distributed, i.e. a large number of patients died at a small number of treatment facilities. Almost 30% of the patients who were assessed by the MET died within 30 days. More than half of these patients were cared for on medical wards. The general medical wards had the largest number of patients who died, whereas the geriatric wards had the highest proportion of patients who died. On the geriatric wards, more than half the patients assessed by the MET died within 30 days. In all probability, this outcome reflects the MET population complexity with regard to advanced age and numerous co-morbidities, rather than the caregivers' treatment skills.

When specifically comparing medical ward patients with surgical ward patients, the surgical patients more frequently had fewer prognostically unfavourable co-morbidities and instead presented an isolated organ disorder, such as malignancy and gastrointestinal or liver disease, requiring surgical intervention. It appeared that the surgical procedures remedied the primary problems to a certain extent and that the MET assessment was often triggered by a post-operative complication with a relatively good prognosis if correctly treated. The medical patients, on the other hand, often presented a more aggregated disease profile, with a higher frequency of cardiac, pulmonary and haematological diseases. Put simply, in overall terms, general medical wards admitted more high-risk patients, dealing with long-term conditions. Previous studies have reported similar findings, in that general medical wards were overrepresented in terms of in-hospital mortality [54, 220, 221]. Moreover, when adjusting for co-morbidities, a significant decrease in mortality among the medical ward patients was shown [54]. With these diverse conditions in mind, greater vigilance is encouraged when assessing medical ward MET patients.

IS THE PREVIOUS MEDICAL HISTORY VALUABLE IN RISK ASSESSMENT AND, IF SO, HOW SHOULD THAT INFORMATION IMPROVE THE MET PATIENT PROCESSING?

In accordance with the above reasoning, underlying conditions and co-morbidities appear to play a crucial role in the outcome, in terms of mortality.

Moreover, some medical conditions show a more apparent association with death within 30 days than others. The previous medical history with the poorest survival prognosis was predominantly found among internal medicine disorders, such as cancer, haematological disease, pulmonary disease, liver disease, heart failure and angina pectoris.

Back in the 1980s, it was shown that deterioration rates were highest among patients with co-morbidities and that most cardiac arrests occurred in deteriorating patients who were unstable on admission [96]. Patients who arrested as a consequence of clinical deterioration were also known to have very poor survival rates [222]. The absolutely highest risk of deterioration and subsequent cardiac arrest was found in patients who were admitted with acute dyspnoea, usually accompanied by chronic lung disease [96]. Other prognostically poor co-morbidities associated with high in-hospital mortality rates, in addition to respiratory insufficiency and pneumonia, were haematological disorders, cancer, heart failure and renal failure [91, 223]. In contrast, stable patients on admission who deteriorated with newly acquired complications did not suffer cardiac arrests to anything like the same extent. More recent studies have also shown similar associations between co-morbidities and poor outcome, with the addition of ischaemic heart disease and liver disease [221]. These relationships indicate that our finding of the association between previous medical history and in-hospital mortality is a well-known fact with high credibility.

The value of obtaining a comprehensive picture of the patient's previous and present medical conditions can therefore not be over-emphasised when assessing the patient's clinical difficulties and prognosis. Consequently, in high-risk patients with substantial co-morbidity, there is every reason to take even a minor physiological decline seriously and intervene earlier in the deterioration process with targeted treatment measures – not forgetting the immediate escalation of the level of care when necessary.

HOW DO VITAL PARAMETER ABNORMALITIES AFFECT THE OUTCOME AND THEREBY THE RISK ASSESSMENT?

There was a considerable difference when it came to the extent to which the various trigger criteria and vital parameters were associated with outcome. The most frequently used trigger criterion, POX <90% despite oxygen treatment, also demonstrated the highest 30-day mortality rate. In addition, we identified two other trigger criteria which were significantly associated with death within 30 days, i.e. abnormal respiration rate and serious concern on the part of the staff. Upon further analysis of the vital parameters recorded

at MET arrival, similar findings were encountered. Hypoxia, tachypnoea and unconsciousness were all significantly and independently associated with 30-day mortality. Curiously, abnormal circulatory parameters did not appear to play as important a role in predicting the outcome in critically ill patients. These findings are consistent with reports from previous studies [102, 104, 221, 224]. The difference between the physiological variables in association with outcome further emphasises the importance of evaluating not only the degree of deviation but also the kind of deviating variable.

Another prognostically relevant factor to consider in patient assessment is the number of deviating vital parameters. Even if tachycardia did not emerge as an independent predictor in the multivariate analysis, it was still significantly associated with death within 30 days in the age-adjusted analysis. A possible synergistic impact on the outcome cannot therefore be ruled out. Having multiple trigger criteria fulfilled simultaneously has previously been shown to be associated with increased in-hospital mortality, possibly showing the increased severity of illness [221, 224]. This information may be particularly crucial for the risk stratification and prioritisation of patients during the MET assessment.

WHY IS IT THAT ABNORMALITIES IN RESPIRATORY PARAMETERS APPEAR TO BE MORE ALARMING THAN ABNORMALITIES IN CIRCULATORY PARAMETERS?

The value of repeatedly measuring respiratory rate as an indicator of clinical deterioration is so far well established in clinical practice. An increasing respiratory rate implies developing respiratory distress [95, 96]. A declining respiration function has been shown to be associated with cardiopulmonary arrest and has therefore been suggested as a useful predictor in identifying patients at risk of cardiopulmonary arrests on hospital wards [95, 225]. Similar associations between hypotension or tachycardia and cardiac arrest have also been demonstrated, albeit not as pronounced [222, 225]. It may be that abnormal circulatory parameters signal more limited and specific problems and are thus easier to remedy.

On the other hand, there has been widespread speculation about possible explanations of why tachypnoea is so strongly associated with cardiac arrest. It appears that tachypnoea is an expression of acute pathophysiological derangements caused by underlying illnesses, such as sepsis, intracranial catastrophe or abdominal pathology [95, 101]. Some disease states can induce elevated respiratory rates; they include hypoxaemia, hypercarbia, hypovolaemia, hypotension and metabolic acidosis, all of which have the

potential to develop into a cardiac arrest [226]. Since the respiratory rate may indicate severe derangements in several body systems, not only the respiratory system, it is a crucial predictor for detecting clinical deterioration and threatening adverse events [227]. For that reason, it was worrying that the respiratory rate was missing in more than every fifth patient in Paper IV and, in overall terms, it was the vital parameter that was least frequently recorded by the MET.

Regarding hypoxia, reduced oxygen saturation has proven to be common in hospitalised patients. Oxygen saturation of less than 90% has been found in about 10% of patients [228]. In spite of this, it is worth pointing out that the measurement of oxygen saturation through pulse oximetry alone is not considered to be sufficient monitoring of ventilation. Since the specificity of pulse oximetry measurement has been shown to be inadequate, it is not regarded as a satisfactory indicator of serious illness [85, 106]. For example, pulse oximetry readings may be inaccurate due to reduced peripheral circulation at the site of measurement, as in hypothermia, shock, carboxy-haemoglobinaemia, anaemia, skin pigmentation, nail polish and other disturbing artefacts [229]. In addition, there have been problems with the clinical interpretation of the measured values, in that a substantial proportion of staff members did not fully understand the underlying significance of the pulse oximetry result [230, 231]. Given these shortcomings and the fact that respiratory rate provides other types of information than pulse oximetry, the two measurements should be complementary and not substituted for one another [227].

WHICH LABORATORY ABNORMALITIES ARE OF CRUCIAL IMPORTANCE FOR THE EARLY RISK ASSESSMENT?

In recent years, the question of whether it would be possible to add another tool to enable the easier identification of high-risk patients, such as a system based on electronically collected data, has been the subject of debate. The data are already available in the form of routine laboratory biomarkers, i.e. venous blood samples and arterial blood gases, and they are often used in addition to clinical information in risk assessment and the prognostication of ward patients [232]. Moreover, it has already been demonstrated that simple models based on patient characteristics and routine biomarkers are able to accurately predict the risk of in-patient mortality in general medical patients [232-235].

Accordingly, biomarkers are valuable components of risk assessment and guidance in treatment, aiming to reverse the potentially fatal outcome.

Suitably enough, all laboratory abnormalities with a high ability to predict in-hospital death can be found in routine arterial blood gases, with the sole exception of creatinine. Obtaining relevant biomarker data as a decision-making basis for the risk assessment of clinically impaired patients is therefore neither complicated nor costly. In this context, it is worth noting that our data in Paper IV revealed that arterial blood gases were missing in 40% of the MET patients throughout the entire care period. The value of the generous sampling of arterial blood gases in deteriorating patients must therefore be emphasised.

The findings in Paper IV identified several routine biomarkers significantly associated with death within 30 days, among which hypoglycaemia distinguished itself by being independently associated with the highest 30-day mortality risk of all identified risk factors. Other studies also confirm the association of hypoglycaemia with increased mortality risk [236, 237], as well as a similar association for hyperglycaemia [238, 239]. It has been suggested that the association between hypoglycaemia and mortality is most probably related to spontaneous hypoglycaemia as opposed to iatrogenic hypoglycaemia, which would indicate that hypoglycaemia is a biomarker of disease rather than an actual cause of fatality [237, 240]. However, the exact pathogenesis has not been established. In terms of hyperglycaemia, on the other hand, it has been assumed to be due to stress-related causes in exposed patients undergoing surgery, being admitted to the ICU, or developing a critical illness. In spite of this, it is unclear whether stress hyperglycaemia is the causal reason for the adverse outcome or merely a marker of illness severity [239, 241]. In conclusion, regardless of the glucose abnormality, disturbed glucose metabolism appears to be a prognostically poor sign, signifying an increased risk of mortality among critically ill patients.

Other laboratory abnormalities found to be significantly associated with 30-day mortality, in addition to hyperglycaemia, were hyperlactataemia, hyperkalaemia, hypernatraemia, acidosis, hypoxaemia, and elevated creatinine, of which the first three also proved to be independent risk factors. The prognostic significance of these routine biomarkers is consistent with previous findings, indicating that several of the biomarkers are associated with serious adverse events, including mortality, in critically ill patients [233-235]. However, in other studies, some of the biomarkers, such as serum sodium, have, in analogy to glucose, been shown to predict mortality with a U-shaped mortality distribution [242, 243].

Nevertheless, it has not yet been determined whether abnormal laboratory biomarkers are solely markers of disease progression or whether they are in

themselves deleterious. So far, there have been certain indications that some biomarker alterations appear to be more an expression of underlying pathophysiology rather than independent deleterious causes [244-246].

In disorders commonly presenting with hyperlactataemia, such as severe sepsis, shock and ischaemia, there has been speculation about various underlying causes of the lactate increase. Among others, a connection with tissue hypoxia has been suggested, following hypovolaemia, hypotension, tissue hypoperfusion due to circulatory dysfunction, or mitochondrial dysfunction [247-249]. In addition, liver dysfunction may also lead to the increased production and reduced clearance of lactate [248].

With regard to electrolyte abnormalities, severe hyperkalaemia can be fatal and the rate at which hyperkalaemia accumulates impacts the severity of physiological damage [250, 251]. Increased potassium levels may occur either with disorders affecting the acid-base status or the Na-K-ATPase pump at cellular level or with the reduced excretion of potassium due to renal failure or aldosterone-related disorders [250-253]. Hyperkalaemia may then induce alterations in cell membrane potentials, primarily in cardiac and neuromuscular cells, potentially causing cardiac arrhythmias and death [253].

Moreover, with reference to hypernatraemia, it has been shown that the sodium level in itself is not related to mortality but to a higher co-morbidity risk index [244]. In contrast, others have demonstrated an independent association between hypernatraemia [254, 255], as well as hyponatraemia [243], and mortality, even after adjustment for co-morbidities and other risk factors. Severe hypernatraemia commonly manifests in neurological events, including seizures, intracerebral haemorrhage, and unconsciousness. However, death following hypernatraemia appears to result from primarily the underlying disease, while the causal effect of hypernatraemia on increased mortality is uncertain [255]. Seemingly, it remains in many ways to be determined whether critically ill patients die from or with biomarker abnormalities.

HAS THE TIME COME TO DEVELOP A RISK SCORE AS A DECISION-SUPPORT TOOL FOR MET?

Given the high mortality risk in these critically ill patients, there is a pressing demand to improve the conditions for early detection and well-founded positions for further treatment. The urge for more advanced care is extensive and admission to the ICU following MET assessment is common among these patients. In Paper IV, the proportion of patients transferred to the ICU

exceeded 40%. Since resources are limited and a shortage of hospital beds is an ever-present problem, the patients with the most urgent medical need must be given the highest priority. Assessing the severity of illness and probable outcome, as well as identifying the mortality risk factors, are of significant prognostic value for the clinician. In order to increase the assessment accuracy and reliability, a scoring model with risk stratification based on objectively defined variables would most likely be beneficial as decision-making support. At the same time it should be remembered that, in the past, physicians outperformed the currently available scoring systems in predicting the likelihood of hospital death when assessing high-risk patients in a critical care environment [256, 257]. However, the difficulty is not in identifying patients who are doing very poorly or very well, as the outcome is more evident in these groups. The challenge instead lies in scoring the in-between group of patients, in whom outcome prediction is seemingly more complex. In these particular circumstances, an objective risk-scoring model as decision support would undoubtedly be a valuable predictive tool, not least when deciding on different management strategies and resource allocation.

Development work is already in progress within this field. For instance, research groups have shown that combinations of vital signs and additional clinical data, such as demographics and biomarker results, in scoring model systems are able to increase the ability to detect general ward patients at risk of adverse outcomes [258-260]. Even though the complexity of different scoring systems varies, from artificial intelligence algorithms and large machine learning approaches [259, 261] to more simple risk index models, it has been shown that even elementary risk-prediction models can increase the performance above that of a regular track-and-trigger system alone, such as the National Early Warning Score [262].

To summarise, it can be stated that risk-scoring models have the potential to increase the detection of deteriorating high-risk patients and enhance clinical decision-making with regard to the further management and level of care, in specific patient categories. As all risk-scoring models are based on already accessible electronic medical records, it will, however, be a challenge to develop detection approaches also available for patients for whom data are scarce due to an estimated lower baseline risk. Additional research will still be needed to determine whether risk stratification based on model scoring systems will translate into targeted treatment strategies and, if so, whether they will improve the clinical outcome of critically ill patients.

CAN THE MET SERVICE BE FURTHER IMPROVED?

The overall 30-day mortality in Paper IV was almost 30% in patients assessed by the MET, including patients with palliative and limitation of medical therapy decisions. Even when excluding patients with treatment limitations, 30-day mortality still exceeded 20%. The MET patient population is vulnerable, with many co-morbidities and a high risk of adverse outcomes including in-hospital mortality. Although a great deal of concern has focused in recent decades on improving the strategies for early detection and timely actions in the event of clinical deterioration, there is still potential for further enhancement. Based on the findings in Paper IV and previous discussions, some areas deserve further attention in this context.

CONTINUOUS MONITORING ON GENERAL WARDS: One of the most significant weaknesses of the current system is, as previously pointed out, the intermittent monitoring on general wards. Even if patients are hospitalised and cared for, this engenders a false sense of security in many ways. Since the surveillance system is limited to periodic checks of vital functions, this means that the patients are, in fact, unattended most of the day. By implementing a surveillance system predominantly composed of continuous wireless monitoring, the chances of detecting clinical deterioration earlier in the course would substantially improve and, as a result, the improvement of patient safety would subsequently increase.

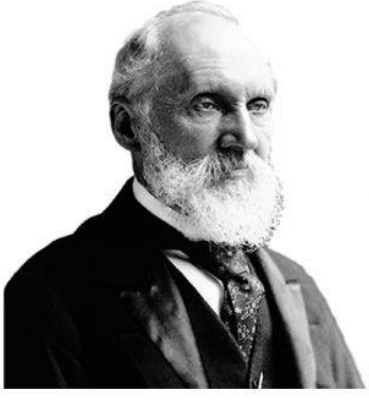
CLEARER WEIGHTING OF VITAL PARAMETERS: Given the plethora of available track-and-trigger systems, with different pros and cons, there is no clear answer about which is preferable. Nonetheless, it is probably not unreasonable to assume that one of the aggregated systems is more comprehensive and that, by simultaneously weighting several variables, it will capture physiological abnormalities earlier in the course. Regardless of the system used to identify critical patients at risk, more focus on the implication of the deranged vital parameters, and their clinical interpretation, is urged when assessing the patient. As previously pointed out, respiratory variables are more strongly associated with mortality than circulatory variables, which thus means that respiratory rate or saturation abnormalities are more ominous findings deserving a greater level of attention. Greater alertness is also advised when several vital signs deviate, as this is often in itself a prognostically unfavourable sign.

MORE GENEROUS BLOOD GAS SAMPLING: The importance of routine laboratory testing in clinical assessment and outcome prediction cannot be overemphasised. It is by now a well-recognised tool when managing critically

ill patients and several routine biomarkers have been shown to be associated with mortality. Most of the predictors of death in the analyses in Paper IV, such as hypoglycaemia, hyperlactataemia, hypernatraemia, hyperkalaemia, acidosis and hypoxaemia, can be recognised through standardised arterial blood gas sampling. With reference to its significant predictive value, generous blood gas sampling is encouraged in clinically deteriorating and high-risk patients.

IMPLEMENT A RISK-SCORING MODEL: As previously stated, risk-scoring models have the potential to increase the detection of critically ill patients and enhance clinical decision-making with regard to clinical management and level of care. By accommodating and implementing an appropriate risk-scoring model that weighs up all the prognostically important variables together, such as age, co-morbidities, abnormal vital parameters and routine biomarkers, greater predictive sensitivity and specificity should be obtained. In addition to potential earlier detection and subsequent assessment of the critically ill patient, a model of this kind could also enable more rapid interventions and serve as guidance in further clinical management and resource allocation.

MEASURE OUTCOMES AND EVALUATE PERFORMANCE: In analogy with the proposals for the quality improvement of the management of in-hospital cardiac arrest, it is suggested that outcomes should be measured and the performance of MET assessment and actions evaluated. Ensure the regular collection and analysis of all relevant patient data with regard to MET assessment, treatment and outcome, in a standardised manner. Use data to provide relevant feedback to the MET members, as well as the ward staff. Educate all team members and seek to improve achievements when indicated. Establish a joint MET patient registry for further research. We cannot improve what we do not measure.



METHODOLOGICAL CONSIDERATIONS

As this thesis exclusively constitutes registry-based research, there are, in conclusion, some urgent methodological considerations and limitations to address regarding the accuracy and representativeness of the presented data. In short, registry-based research generally refers to studies with a retrospective, observational design, based on registry data collected from protocols and medical records. Retrospective registry studies commonly examine relevant factors in relation to an outcome, with the objective of identifying risk factors associated with a disease or an adverse outcome. The results can usually be translated into action more rapidly, as the researcher typically does not collect the data single-handedly.

The advantages of retrospective registry research include 1) obtaining reliable studies of sufficient size and statistical strength, provided solid databases with accurate, complete variables are used, 2) more manageable, time- and cost-efficient than prospective studies, 3) no significant problem with loss to follow-up. On the other hand, the disadvantages include 1) a low level of evidence in comparison to prospective studies, 2) patients are often recruited by convenience sampling, meaning they are not representative of the general population, 3) data are afflicted by many biases, such as selection bias and misclassification bias, as well as confounders, 4) it is not possible to determine causation, only association and 5) larger sample sizes are required, especially if outcomes are rare.

DOES THE SWEDISH REGISTRY FOR CARDIOPULMONARY RESUSCITATION MEASURE UP?

OUT-OF-HOSPITAL CARDIAC ARREST: The Swedish Registry for Cardiopulmonary Resuscitation derives from the former CPR training registry, founded in 1983, which was far from comprehensive. When the out-of-hospital Swedish Registry for Cardiopulmonary Resuscitation was set up in 1990, the reporting frequency was low and the quality similar. Over the years, the coverage and reporting frequency have increased and with them also the completeness and quality. In addition to a greater degree of participation, the reporting methods have improved substantially from manual paper registration to digital web-based input. Before electronic registration was introduced in 2008, the completed paper forms were mailed to an evaluation centre and compiled into a database, entailing significant risks of incorrect entries and delays in registration. Despite improved reporting routines, the validity of the reported variables needs to be addressed.

A previous unpublished internal comparison of documented variables in the emergency medical service's medical records with the out-of-hospital Swedish Registry for Cardiopulmonary Resuscitation revealed that the registry data widely corresponded to source data, or sometimes even with greater detail. Moreover, in 2008-2010, a comparative study of prospective and retrospective out-of-hospital cardiac arrest registry data was performed [263]. The analyses revealed that 25% of the out-of-hospital cardiac arrest patients in whom CPR was initiated failed to be prospectively reported by the emergency medical service crew. After reviewing the local ambulance registry and retrospectively reporting all omitted patients to the out-of-hospital Swedish Registry for Cardiopulmonary Resuscitation, significant differences emerged between the patient groups. The retrospectively recorded patients appeared to be older, received bystander CPR less often and, despite these findings, had a higher survival rate [263]. It is, of course, possible that omitted patients may influence the overall findings. However, in this context, it is essential to realise that the omitted patients represent only a subset of the total study population. For this reason, the impact on overall data should be less significant and most likely of minor clinical relevance, if any. Nevertheless, since then, more advanced registration practices have been developed. As a result, all cases not prospectively reported are retrospectively reported nowadays by a regional co-ordinator.

IN-HOSPITAL CARDIAC ARREST: It should primarily be clarified that there is no clear response to the uncertainty relating to the validity and representativeness of data derived from the in-hospital Swedish Registry for Cardiopulmonary Resuscitation. No one knows for sure the exact coverage and consistency of registry data in relation to source data. Although almost all hospitals have joined the registry in recent years, there is still reason to suspect a substantial number of missing reports; for instance, in-hospital cardiac arrest with the immediate initiation of resuscitation without alerting the cardiac arrest team at coronary angiography laboratories, the OR and the ICU. In addition, there is a considerable amount of missing variables in individual cases, as well as significant hesitation relating to the precision of time registrations associated with different rescue operations.

In an attempt to achieve clarity in some of this incertitude, a validation of the reported data was conducted in 2013-2018. In all, 34 of 71 hospitals were verified, comprising a total of 1,338 patients. When comparing recorded data with hospital case data, information about the place of in-hospital cardiac arrest and survival was consistent with source data in 99% of cases. Furthermore, witnessed status was consistent with source data in 96% of cases, whereas information on the first registered rhythm was consistent with

source data in 94% of cases. In overall terms, coherence between registry data and source data was authentic and of high quality, even though it was somewhat surprising that the information on arrhythmia was not even more accurate. While it can be stated that the in-hospital Swedish Registry for Cardiopulmonary Resuscitation has its weaknesses and contains several areas of uncertainty, it is easy to understand what a valuable asset and endless source of information a registry of this kind signifies for cardiac arrest research and the persistent effort of improving survival for cardiac arrest victims.

WHAT ARE THE WEAKNESSES OF THE MEDICAL EMERGENCY TEAM REGISTRY?

Due to the disadvantages of retrospective registry studies mentioned above, some issues must be considered with regard to the MET patient study in Paper IV as well. The study population was recruited from a specific period of time with relevant inclusion criteria, without the enforcement of a power analysis. However, with reference to similar studies, the assumption was that the disposable number of study participants would be regarded as more than sufficient for good statistical precision. After all, the sample size was considerable, with a relatively large proportion of study participants reaching the endpoint, i.e. death at 30 days. Moreover, due to very few individual exclusions and minor loss to follow-up, the risk of selection bias was small.

In spite of this, the results are limited to the retrospective and observational nature of the study, deriving from the completion of MET protocols and depending entirely on the additional documentation in the medical records. For this reason, the number of cases with missing information for various variables was substantial. Furthermore, there were systematic errors such as misclassification, due to approximations and interpretations of medical record data compiled in the registry. As in all retrospective studies, there are most likely numerous confounders. However, by adjusting for age and supplementing the analyses with multivariable logistic regressions, the scale of the problem should have been reduced.

HOW TO DIFFERENTIATE CLINICAL RELEVANCE FROM STATISTICAL SIGNIFICANCE?

Statistical tests and p-values are a way of quantifying chance and help to decide whether an apparent difference in results is random or real. Statistical significance indicates how unlikely it is that a null hypothesis is true. When

$p < 0.05$, there is a less than 5% chance that the observed difference is caused by chance [264].

P-VALUES: Several factors affect whether or not an effect difference in a clinical study is statistically significant. One important factor is the size of the cohort. Extensive studies with larger study populations generally generate more credible results than studies with smaller study populations [264]. An effect difference in a large study cohort means that there is a smaller probability that the observed difference is caused by chance; many study participants therefore generally generate lower p-values. However, a small p-value does not necessarily mean that the effect difference is large. It may just mean that the result is based on a very large number of study participants. In extensive registry-based studies, it is therefore crucial to recognise that statistical significance, with reference to the p-value, does not necessarily equal clinical relevance in the observed results.

SMD: Due to a large study population and many p-values indicating statistically significant changes, the standardised mean difference (SMD) was applied in Paper III. The SMD measures the effect sizes of associations between variables or the size of differences between group means [265]. It is a way of quantifying the difference between two groups and may thereby facilitate the identification of effect size differences of clinical relevance. An SMD of 0 means that there is an equivalent effect in both groups, i.e. no measurable difference in effect size, whereas an SMD of 1 means that the effect size between the two groups differs by one standard deviation. The SMD can be interpreted as small, medium, or large, although the exact effect size for the individual level may vary depending on context and definition. According to Cohen's guidelines for interpreting the magnitude of the SMD, the cut-off levels of 0.2 (small), 0.5 (medium) and 0.8 (large) were suggested in the social sciences [266]. However, others have argued that the practical importance of an effect strongly depends on the relative cost and benefits. As a result, smaller effect size changes in the SMD equalling 0.1 may also be of relevance, in certain circumstances [267].

A significant p-value indicates that there is an effect difference, whereas an increase in the SMD indicates the size of the effect difference. As the effect size is independent of sample size, it has been suggested that this reveals greater scientific quality compared with significance tests. Consequently, effect size analyses might be preferable in extensive studies with large study populations, in order to better demonstrate the clinical relevance.

HOW CAN THE PROBLEM WITH MISSING DATA BE HANDLED?

One common occurrence in all research, which is nevertheless an aggravating problem, is the issue of missing data and its impact on research results. In epidemiological and clinical research, missing data are unavoidable, as data collection is generally completed before the study start. If this is not dealt with in a careful manner, missing data may create considerable challenges in the analyses and cause misleading results, weakening the validity of the research and its conclusions. The main problem with missing data is that it reduces the representativeness of the sample and possibly affects the conclusions that are drawn and further extrapolated to the population.

Missing data can occur at two levels; 1) at unit level (a whole study person) and 2) at item level (partially missing data in a study person). In addition, different types of missing data impact the validity of the research differently. Being aware of why data are missing is crucial to the correct handling of the remaining data. Missing data are commonly classified into three groups; 1) missing completely at random (MCAR), 2) missing at random (MAR) and 3) missing not at random (MNAR) [268]. If data are missing completely at random, the available data are probably representative of the population, whereas if the data are missing at random or missing not at random, the reason for the missing data is more systematic. In these cases, when analyses are based on complete cases, the results may be biased. However, by using statistical methods that allow for the inclusion of individuals with incomplete data in the analyses, these biases can be controlled [269, 270].

There are several approaches to managing the problem of missing values, depending on the type and reason for missing. In what follows, only the techniques for handling missing data relevant to this thesis will be further elaborated, i.e. complete cases in Paper III and multiple imputations in the multivariable analysis in Paper IV.

COMPLETE CASES: Accordingly, complete cases can be used to estimate incomplete cases. Complete cases refer to cases with complete observations with no missing values, the information about which can be used to estimate the values of incomplete cases, i.e. cases with missing values in parts of the observation. In certain circumstances, analyses of complete cases will not lead to bias, such as when the proportion of missing data is considered small or under the assumption that the data are missing completely at random and, moreover, in cases where the missing data in predictor variables are unrelated to the outcome. By avoiding the exclusion of individuals with

incomplete predictor variables, the loss of precision and power will be reduced [269, 271].

IMPUTATIONS: If data are assumed to be missing at random, unbiased and statistically more powerful analyses, in comparison with complete case analyses, can be performed by including individuals with incomplete data in multiple imputation analyses, for example. Imputation implies that an imputation model based on the missing mechanisms is used to replace the missing values with estimates of the actual values. Through simple imputation methods, a complete data set may be obtained. In the case of multiple imputation methods, missing values are instead replaced by estimated values generated from repeated analyses of the available data. The estimated values are extracted by random sampling from their predictive distribution based on the observed data. Multiple imputations generally obtain more reliable estimates of missing values than simple imputations, as they comprise an average of all data. Multiple imputations have the potential to improve the validity of clinical, epidemiological research, provided that the procedure is performed in an appropriate manner [269, 270].

6 CONCLUSIONS

In four retrospective registry-based studies with large study populations, several important findings were identified, including significant changes over time and various factors associated with outcome.

Firstly, the survival after shockable out-of-hospital cardiac arrest of presumed cardiac aetiology nearly doubled. Females and persons collapsing outside the home had a significantly higher survival rate. Other factors associated with survival were bystander CPR and early defibrillation.

Secondly, from a nationwide perspective, the overall survival after in-hospital cardiac arrest increased over time, regardless of the initial rhythm and monitoring level of the ward and also despite the fact that the proportion of initial shockable rhythms decreased significantly. Among patients found in a shockable rhythm, the relative number who were defibrillated before the arrival of the cardiac arrest team increased.

Thirdly, at Sahlgrenska University Hospital specifically, similar findings with regard to a decreasing proportion of initial shockable rhythms were made, although this was only observed on the non-monitoring wards. In overall terms, there was a trend towards shorter delays from collapse to treatment, resulting in a significant increase in survival among patients on monitoring wards.

Finally, as for MET-assessed patients, the overall mortality was high and associated with numerous factors. The patient's age, type of ward, vital parameters, routine biomarkers, previous medical history and acute medical condition all contributed to the prediction of death. A particularly ominous prognosis was identified in patients with hypoglycaemia, hypernatraemia, hypoxia, haematological disease, liver disease or renal failure. In conclusion, the risk of dying was significantly higher for medical ward patients and distressed respiratory patients.

7 FUTURE PERSPECTIVES

For natural reasons, it is easier to say what has been rather than what is to come. In the absence of fundamental data in support of any claim, it is presumably better to refrain from commenting on future perspectives with any kind of scientific certainty. As a result, the thoughts expressed in this section should be regarded as speculative beliefs rather than well-founded predictions.

Based on the reported results and conclusions in this thesis, it can be stated that cardiac arrest care in Sweden has improved substantially over time and, satisfactorily enough, this has led to a significant increase in survival rate. In spite of this, and this needs to be stressed, despite reported advances, the vast majority who suffer a sudden cardiac arrest still die, regardless of whether they are in or out of hospital. The high mortality rate cannot be interpreted in any other way than that sudden cardiac arrest is an extremely severe condition with an extremely poor prognosis. Consequently, the rescue efforts in most cardiac arrest victims are literally a fight for life against the odds. However, as has been shown, several factors are associated with increased survival which may improve the generally unfavourable condition and possibly enhance the odds, albeit only moderately.

What should be sought in the future are therefore new opportunities and further improvements in already identified variables with strong predictive value for survival. Resuscitation in the acute phase of sudden cardiac arrest is highly dependent on basic qualities such as time, ability and knowledge. The obvious way forward is therefore the continuous re-invention and development of these very aspects, in order to shorten the delay from collapse to the initiation of life-saving actions.

Other areas of interest for future improvements in cardiac arrest care may include enhanced measures in the post-resuscitation phase in terms of optimising cardio- and neuroprotective interventions, such as more advanced revascularisation techniques, therapeutic hypothermia and pharmacological treatments. The post-cardiac arrest aspect has admittedly not been covered extensively in this thesis, but it is nonetheless an active research field with many promising ongoing studies. Having said this, it must be understood that the most crucial phase for survival and maintaining neurological function after a cardiac arrest is within the first 5-10 minutes after the collapse. Analogously, the critical opening minutes are the period during which the most significant achievements for increased survival can be accomplished by

creating new opportunities for immediate resuscitation efforts. Interestingly enough, the greatest medical skills and competence have so far been invested further down the chain of survival, where the benefits are demonstrably less. In order to bring about a change in resource allocation, a complete change of attitude will be required.

With regard to the in-hospital environment, conditions are different and, in some respects, more advantageous. In other words, even if the majority of patients are still cared for without continuous surveillance, medical help is more readily available when the collapse occurs. However, it is important to highlight that the cardiac arrests with the absolutely highest survival are those in which the heart never arrests. In other words, prevention is the area in which future resources should be invested in order to reduce sudden cardiac arrest mortality most efficiently.

In a way, it may seem startling that, in this high-tech-developed era, we still allow the majority of our in-patients to be cared for without proper surveillance. It can be argued that the most impaired patients with the highest risk of dying are commonly continuously monitored at a higher level of care, provided that they are found quickly and the level of care is escalated. In spite of this, judging from the number of serious adverse events and sudden cardiac arrests occurring on a daily basis inside our hospitals, it is not difficult to conclude that far too many patients become victims of unforeseen in-hospital mortality, possibly needlessly. As evolution progresses and more advanced equipment, such as wireless monitoring, becomes more accessible, the demand for extended hospital safety will reasonably increase.

By improving the chances of the early detection of clinically deteriorating patients, the adverse course of events may be reversed in time and a deleterious cardiac arrest avoided. In spite of this, the prevention of further clinical decline and possible death requires not only that the actual deterioration is detected but also that adequate measures are taken. From this perspective, there is significant developmental potential. Instead of relying on the competence of an individual doctor under lottery-like forms, hoping that appropriate action will be taken, the clinical assessment pre-conditions could be expanded and increasingly refined. By acquiring and analysing a number of variables, both laboratory and clinically related, at an early stage, the assessment process could be significantly facilitated. Moreover, further handling and a preliminary position on the appropriate level of care could also be suggested based on an assessed standardised risk score, including feasible treatment plans linked to prevailing physiological deviations.

In order to guarantee safety, the in-hospital environment in relation to the level of care would need to be more aligned, monitored and automated. At this moment, the thought of making such extensive structural changes may be unfamiliar. Nevertheless, current healthcare relies for the most part on the human factor, potentially at the expense of the sickest patients. As a result, one presumption is that in-hospital safety could significantly improve if healthcare management had the ambition and funding to approach the aviation industry's safety levels with regard to prevention, as opposed to now, when the aviation safety strategies and crisis management are only applied after serious incidents, injuries and deaths have already occurred.

In aviation, safety is maintained with the aid of monitoring instruments, computerised analyses of registered variables and autopilots acting on the data, subsequently controlling the aircraft with the highest precision, while the human pilots supervise the process and, if needed, interfere to re-adjust any erroneous course. If a similar automated system were to be implemented within the hospital environment, it would potentially guarantee the patients a minimum level of safety through continuous monitoring, instant alerts of deterioration and the activation of programmed intervention plans, in contrast to the current nurse- or doctor-related event outcome.

At the same time, it must be acknowledged that, sooner or later and regardless of advanced innovations, eminent surveillance, proficient medical professionals and progressive safety systems, there will inevitably come a day when the heart stops beating. The fact that, just because resuscitation is possible, this does not mean that it is always reasonable. After all, survival is only a temporary state and we shall all eventually face the same outcome. It may therefore be that, when the time comes and the future is indecisive, the right thing to do is put an end to it.

The end!

"One should die proudly
when it is no longer possible to live proudly."

– Friedrich Nietzsche

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