Aspects of cardiac arrest in Sweden – studies based on the Swedish Registry for CPR

Fredrik Hessulf

UNIVERSITY OF GOTHENBURG

Department of Molecular and Clinical Medicine
Institute of Medicine, Sahlgrenska Academy
University of Gothenburg, Gothenburg

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SVANENMÄRKET

Trycksak
3041 0234

Till Frida, Fanny och Signe

ABSTRACT

Background: Since the introduction of modern cardiopulmonary resuscitation (CPR) by Peter Safar in the late 1950s, a tremendous amount of work and scientific discovery has expanded our knowledge of cardiac arrest (CA), made resuscitation a core skill of health care providers and improved survival substantially. Despite the many advances, the core elements of resuscitation have remained largely intact: immediate recognition and initiation of CPR and swift defibrillation. The importance of doing the basics well and evaluating the effect of guidelines and recommendations have only increased considering the rapid growth of cardiac arrest research.

Aims: The aims of the thesis were: to investigate factors associated with 30-day survival following IHCA (paper I); to evaluate the importance of adherence to resuscitation guidelines on survival following IHCA (paper II); to explore the impact of time day and day of week on 30-day survival following IHCA and investigate if hospital and ward characteristics modify the importance of time of CA (III); to build a prediction model for 30-day survival and neurological outcome following OHCA(IV), and to evaluate the impact of cardiovascular comorbidities on survival following OHCA (V).

Methods: Data from the Swedish Cardiopulmonary Resuscitation Registry (SCRR) was used through-out the thesis. IHCA data from the registry was used in papers I-III, and OHCA data was used in papers IV-V. In paper IV-V we merged the SCRR with the Swedish Patient Registry, the Swedish Prescribed Drug Registry and the Longitudinal Integrated Database for health insurance and labour market studies (LISA). Papers I-III and V were registry-based observational cohort studies. Paper IV was a registry-based machine learning study.

Results: Multiple factors (modifiable, partly modifiable and non-modifiable) were associated with 30-day survival following IHCA. Notably, several factors that relate to how resources are allocated (ECG-monitoring, ward type, witnessed status, time to treatment, time of day) were independently associated with the chance of 30-day survival (paper I). In paper II we show that adherence to resuscitation guidelines was high (70-80%) and increased marginally during the time period 2008-2017. Adherence to guidelines was associated with a higher odds ratio (OR) for 30-day survival for both shockable and non-shockable rhythms. Adherence was higher on high-resource wards including the ICU and CCU compared to general wards. In paper III we further evaluated the importance of time and location of IHCA and found that IHCAs that took place during the day had the highest rates of 30-day survival and that survival decreased during the evening and night. The decrease in survival from day to evening to night was associated with lower rates of witnessed CAs, lower rates of ventricular fibrillation or tachycardia as the initial recorded rhythm and greater delays from detection of a shockable rhythm to defibrillation. Survival decreased more from day to night in small hospitals, non-academic hospitals and on non-monitored wards.

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In paper IV we built a machine learning model (SCARS-1) to predict the chance of 30-day survival following OHCA in the emergency department. At a sensitivity level of 95%, the AUC-ROC was 0.97, with excellent calibration across survival probabilities. We developed a web application, the SCARS-1 app, that enabled a survival prediction to be made with readily available variables within 30 seconds in the emergency department.

In paper V we show that hypertension and associated cardiovascular conditions were prevalent in the population affected by OHCA and that hypertension and heart failure in combination had the lowest rates of survival. Early onset hypertension was associated with shorter time to OHCA compared to later onset hypertension.

Conclusions: The chance of survival following IHCA is dependent on rapid detection and treatment, and by selecting patients at high risk of CA and prioritizing these patients to wards with high resources (ICU, CCU) or ECG-monitoring, survival rates could potentially be improved. Adherence to current resuscitation guidelines is high and associated with increased survival rates in IHCA. Time of in-hospital cardiac arrest is associated with the chance of survival: IHCA during the day showed the highest survival rates followed by IHCA during the evening and during the night. Survival rates decreased disproportionally more from day to night in small hospitals, non-academic hospitals and on general wards indicating that IHCA care is not of equal quality around the clock. Prediction of OHCA survival is possible in the emergency department during ongoing CPR using the SCARS-1 prediction model and can be a valuable tool during ongoing resuscitation in adjunct to other sources of information. Finally, hypertension in combination with heart failure has the lowest survival rates of all cardiovascular conditions among patients with OHCA and should be considered a major risk factor. The earlier the onset of hypertension, the shorter the time from hypertension diagnosis to OHCA.

Keywords: Cardiac arrest, resuscitation, comorbidity, prediction

POPULÄRVETENSKAPLIG SAMMANFATTNING PÅ SVENSKA

Hjärtstopp innebär att hjärtats förmåga att pumpa blod upphört och leder inom några sekunder till medvetslöshet. Inom några minuter börjar hjärnans celler att dö och irreparabla skador uppstår. Det absolut viktigaste för att öka chansen till överlevnad är att återställa cirkulationen av syresatt blod i kroppen. Detta görs med hjälp av bröstkompressioner och inblåsning av luft i lungorna (hjärtlungräddning) samt med en elstöt med en defibrillator. Årligen drabbas uppskattningsvis 10000 svenskar av hjärtstopp där hjärtlungräddning (HLR) påbörjas, ca 1/3 drabbas på sjukhus och resterande 2/3 utanför sjukhus. Överlevnaden varierar beroende på en mängd faktorer, tack vare hjärtlungräddning räddas ca 1500 liv varje år. Vad som påverkar vem som överlever är syftet med denna avhandling.

I avhandlingens första studie visade vi att ett stort antal faktorer påverkar överlevnadschansen efter hjärtstopp på sjukhus, varav ett flertal faktorer inte har med patients hälsotillstånd innan insjuknandet att göra. Faktorer som i högsta grad är möjliga att påverka, exempelvis avdelningstyp, övervakningsgrad, hur snabbt vi larmar och påbörjar behandling, spelar väldigt stor roll för sannolikheten till överlevnad. Slutsatsen är att de val som görs när en patient vårdas på sjukhus delvis predestinerar till en bättre eller sämre chans till överlevnad vid ett eventuellt hjärtstopp, vilket väcker frågor om hur vi fördelar våra resurser.

I avhandlingens andra studie utvärderade vi vilken betydelse som följsamheten till HLR-riktlinjer hade för chansen att överleva ett hjärtstopp på sjukhus. Enligt gällande riktlinjer ska sjukvårdspersonal larma och påbörja HLR inom en minut från den tidpunkt som hjärtstoppet konstateras, samt genomföra så kallad defibrillering (strömstöt genom bröstkorgen) inom tre minuter (i de fall det är lämpligt). Dessa rekommendationer baserar sig på erfarenheten att tid är den kanske viktigaste faktorn för en lyckad återupplivning vid hjärtstopp. Vi kunde visa att även efter att vi tagit hänsyn till en mängd faktorer som vi vet påverkar överlevnadschansen (ålder, samsjuklighet, plats för hjärtstoppet mm) så var följsamhet till riktlinjer (larm och HLR inom 1 minut och defibrillering inom 3 minuter) självständigt och oberoende förknippat med en högre chans till överlevnad efter hjärtstopp på sjukhus jämfört med fall när man inte nådde upp till riktlinjerna. Således gav vår studie ytterligare stöd till att eftersträva följsamhet till gällande HLR-riktlinjer.

I arbete tre utforskade vi vilken betydelse som tid på dygnet och veckodag hade för sannolikheten att överleva ett hjärtstopp på sjukhus. Vi delade upp veckan i tre tidsperioder (dagtid (7-15 på vardagar), kvällstid (15-21 på vardagar) och nattetid (vardagar (21-07) samt helgtid 00-24)) för att spegla hur både bemanning och kompetens varierar över tid. Vi fann att både sannolikheten att återfå pulsbärande rytm (ROSC) samt att överleva 30 dagar påverkades av tidpunkten för hjärtstoppet; överlevnaden var bäst dagtid och minskade sedan successivt från dag till kväll till natt. Vi kunde även visa att skillnaden mellan dag och natt var större på små sjukhus, icke akademiska sjukhus och avdelningar utan EKG-övervakning. Dessa resultat

sätter frågan om jämlik vård i fokus då resultaten kan indikera att mindre sjukhus per definition behandlar hjärtstoppspatienter sämre nattetid jämfört med större sjukhus.

I arbete 4 byggde vi med hjälp av artificiell intelligens en modell för att förutsäga sannolikheten att överleva ett hjärtstopp utanför sjukhus. Vi utgick från över 55000 fall av hjärtstopp utanför sjukhus, och inkluderade nästan 400 olika faktorer (ålder, kön, sjukdomar, omständigheter vid hjärtstoppet, behandling, läkemedel). Vi utvärderade flera hundra prediktionsmodeller och ett stort antal olika typer av statistiska metoder. Den slutgiltiga modellen kunde med hög träffsäkerhet förutsäga överlevnaden efter hjärtstopp utanför sjukhus. Därefter förenklade vi modellen och kunde visa att dess träffsäkerhet var lika god med 10 faktorer som 393. Slutligen utvecklade vi en webbapplikation som möjliggjorde att en uppskattning av överlevnadschansen efter hjärtstopp kunde göras på akutmottagningen inom 30 sekunder.

I arbete 5 utforskade vi hur vanliga kardiovaskulära sjukdomar och riskfaktorer påverkade chansen att överleva ett hjärtstopp utanför sjukhus. Vi fann att kombinationen högt blodtryck och hjärtsvikt var förknippat med särskilt dyster prognos. Vi fann även att ålder vid tiden för diagnosticerat högt blodtryck spelar roll för när ett hjärtstopp sker - ju lägre ålder man drabbas av högt blodtryck, ju kortare tid från diagnos till hjärtstopp.

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications, which will be referred to by their roman numerals:

I.   **Factors of importance to 30-day survival following in-hospital cardiac arrest in Sweden – A population based study of more than 18000 cases.** Hessulf F, Karlsson T. Lundgren P, Aune S, Strömsöe A, Södersved-Källestedt ML, Djärv T, Herlitz J, Engdahl J. *Int J Cardiol. 2018 Mar 15;255:237-242*

II.   **Adherence to guidelines is associated with improved survival following in-hospital cardiac arrest.** Hessulf F, Herlitz J, Rawshani A, Aune S, Israelsson J, Södersved-Källestedt ML, Nordberg , Lundgren P, Engdahl J. *Resuscitation. 2020;155:13-21.*

III. **Temporal variation in survival following in-hospital cardiac arrest in Sweden.** Hessulf F, Herlitz J, Lundgren P, Aune S, Myredal A, Engdahl J, Rawshani A. *Submitted.*

IV.   **Predicting Survival and Neurological Outcome in Out-of-Hospital Cardiac Arrest Using Machine Learning: The SCARS Model.** Hessulf F, Bhatt DL, Engdahl J, Lundgren P, Omerovic E, Rawshani Ai, Helleryd E, Dworeck C, Friberg H, Nielsen N, Myredal A, Frigyesi A, Herlitz J, Rawshani A. *eBioMedicine. 2023 Feb 9;89*

V.   **Characteristics, survival and neurological outcome in out-of-hospital cardiac arrest: A nationwide study of 56,203 cases with emphasis on cardiovascular comorbidities.** Rawshani A, Hessulf F, Völz S, Dworeck C, Odenstedt J, Råmunddal T, Hirlekar G, Petursson P, Angerås O, Ioanes D, Myredal A. *Resuscitation Plus. 2022 Aug 24;11:100294.*

ABBREVIATIONS

ACLS	Advanced Cardiac Life Support
ADL	Activities of daily life
AED	Automated External Defibrillator
AF	Atrial fibrillation
AI	Artificial intelligence
AMI	Acute myocardial infarction
APACHE	Acute Physiology and Chronic Health Evaluation
AS	Asystole
AUC-ROC	Area under the receiver operating characteristic
BP	Blood pressure
BCLS	Basic cardiac life support
CA	Cardiac arrest
CAD	Coronary artery disease
CABG	Coronary artery by-pass grafting
CCU	Coronary care unit
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CPC	Cerebral performance category
CPR	Cardiopulmonary resuscitation
DNR	Do-not-resuscitate
DNAR	Do-not-attempt resuscitation
ECG	Electrocardiogram
ECMO	Extracorporal Membrane Oxygenation
EMS	Emergency Medical Services
ER	Emergency room
ERC	European Resuscitation Council
EWLT	Early Withdrawal of Life-sustaining Treatment
HR	Hazard ratio
HT	Hypertension
HTr	Hypothermia treatment
ICU	Intensive care unit
IGT	Impaired glucose tolerance
IHCA	In-hospital cardiac arrest
LUCAS	Lund University Cardiac Arrest System
LST	Life sustaining treatment
MI	Myocardial infarction
MPR	Multi patient occupancy room
NSTEMI	Non-ST elevation myocardial infarction
OHCA	Out-of-hospital cardiac arrest
OR	Odds ratio
PCI	Percutaneous coronary intervention

PEA	Pulseless electrical activity
POS	Probability of survival
PPG	Photoplethysmography
pVT	pulseless ventricular tachycardia
ROSC	Return of spontaneous circulation
RSSR	Risk Standardized Survival Rates
SCRR	Swedish Cardiopulmonary Resuscitation Registry
SCD	Sudden cardiac death
SD	Standard deviation
SFP	Self-fulfilling Prophecies
SPR	Single patient occupancy room
STEMI	ST-elevation myocardial infarction
STROBE	STrengthening the Reporting of Observational studies in Epidemiology
TOR	Termination of Resuscition
TRIPOD	Transparent reporting of a multivariable prediction model for individual prognosis of diagnosis
VF	Ventricular fibrillation
VT	Ventricular tachycardia
WLST	Withhold/Withdraw life sustaining treatment

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1. INTRODUCTION

The oldest accounts of attempts at resuscitation date back to the first book of Kings[1] published in the 7th century BD: the prophet Elijah calls upon God to let life return to a lifeless child, the child makes a miraculous recovery and wakes up. At the time it was thought that God had resuscitated the child through Elijah, although no account of how and by what technique. In the following centuries a growing number of accounts of resuscitation of lifeless babies and victims of drowning were published. Galen (129-210 AD) dominated the field of physiology and medicine for over a millennium and demonstrated that the lungs of animals could be ventilated by pushing air into the mouth with bellows. Galen introduced many revolutionary theories, amongst others, the anatomical concept of diseases[2]. However, he very much worked in the tradition of Hippocrates and Aristotle and was firmly convinced that much of medicine and anatomy could be explained with the theory of the four humours: black bile, yellow bile, blood and phlegm. It was not until the 16th century that Paracelsus challenged the classical Greek theories and modern medicine took its first steps[2]. Andreas Vesalius (1514-1564) pioneered the practice of human dissection (until then most anatomical and medical knowledge was based on dissections of animals) and demonstrated in experiments on dogs and pigs that the heart stopped beating if the lungs were not ventilated[3]. The interdependency of the heart and the lungs was demonstrated, a discovery that with time would prove essential for cardiopulmonary resuscitation.

The evolution of resuscitation took many turns: drowning was a common cause of death in the 16th century and in order to address this issue so called Humane Societies were founded in Holland in 1767 (the Amsterdam Rescue Society) followed by similar societies in Venice (1768), Paris (1771) and London (1774). The humane societies disseminated resuscitation recommendations through publications and guidelines and created public awareness of drowning. During the 17th-19th centuries numerous advances were made including mouth-to-mouth rescue breathing 1744[4], ventilation of the lungs with bellows(1782), open cardiac massage(1874) and closed cardiac massage(1858)[5]. By the end of the 19th century CPR was an established treatment involving different techniques of both cardiac massage and ventilation of the lungs[6]. The birth of modern CPR is credited Peter Safar (1924-2003) who in the 1950s published the first scientific studies demonstrating the effects of mouth-to-mouth breaths and ventilation[7, 8]. Safar is also credited for recommending mouth-to-mouth breaths in coordination with chest compressions (ratio of 1:5 or 2:15 depending on number of rescuers (one or two). The last step towards modern CPR was taken in the 1960s when Kouwenhofen, Knickerbocker and Jude combined manual chest compressions with defibrillation. After inducing VF in dogs, the scientists performed manual chest compressions and demonstrated that the compressions restored some level of circulation as measured by femoral arterial lines. After 20 minutes of manual chest compressions they could successfully defibrillate a dog with induced VF to SR and restored circulation[9]. The method was accepted at Johns Hopkins hospital in Baltimore, and in 1960 20 cases of CPR with external cardiac massage and three cases of defibrillation were published in JAMA[10]. Modern CPR

with a combination of cardiac compressions, ventilation of the lungs and defibrillation was born.

Since the introduction of modern cardiopulmonary resuscitation in the late 1950s and 1960s millions of health care workers and laypersons have been trained in basic and advanced life support and many thousands of lives are saved each year. More and more patients receive CPR and the last 30 years has seen survival increase substantially. Large resources have been invested in preclinical and clinical resuscitation research but the survival benefit of many treatments and interventions still remain questionable. Despite the many advances in cardiac arrest resuscitation, the core elements have remained largely intact: immediate recognition and initiation of CPR and swift defibrillation. The importance of doing the basics well and evaluating the effect of our guidelines and interventions we implement have only increased.

1.1 EPIDEMIOLOGY

1.2 DEFINITION
Multiple definitions of cardiac arrest exist but the definition established by the Utstein collaboration for uniform reporting of cardiac arrest is perhaps most widely used: "Cardiac arrest is the cessation of cardiac mechanical activity, confirmed by the absence of a detectable pulse, unresponsiveness, and apnoea (or agonal, gasping respirations)"[11]. In-hospital cardiac arrest requires the cardiac arrest to occur inside the hospital walls and includes all people in the hospital that had a pulse at the time of admission[12]. Other definitions include the question of time to the definition, the duration of the cardiac arrest and whether it can be considered as sudden/unexpected or not. Because a majority of patients suffering cardiac arrest have established coronary heart disease or other known risk factors, the relevance of whether a cardiac arrest ever really is unexpected or not sudden can be questioned. For that reason, the Utstein definition will henceforth be used to define CA.

1.3 INCIDENCE
In order to estimate the true incidence of CA, we need to identify all new cases during a given time period and divide by the total population at risk. But by applying this definition of CA and calculating incidence, the incidence will be close to the annual crude death rate since circulatory death by definition involves a cardiac arrest. To confuse matters even more, some registries include CAs with no attempt at resuscitation, some registries include only CAs with an attempt at resuscitation and some registries do not distinguish between the two groups. A study from Gothenburg, Sweden, compared the total number of in-hospital deaths during one year with the number of attempted resuscitation efforts and concluded that only 12% of cardiac arrests received an attempt at resuscitation[13]. Cultural and medicolegal differences as well as differences in DNAR practices exist between countries[14] and these differences are likely to explain some of the variation seen in incidence (and survival) following CA. In order to get as close to a true incidence as possible, one would have to combine as many national registries and observational studies as possible. There are also several ways of calculating CA incidence: CA per hospital bed, IHCA per hospital admission, IHCA or OHCA per country or city or state. As a result of the above, a substantial variation in reported

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incidence of CA exists in the literature. Table 1 summarize recently published IHCA and OHCA studies with incidence calculations.

Table 1 Incidence of IHCA/OHCA

Country	IHCA/1000 hospital admissions	IHCA/hospital beds and year	Year	Reference
Norway (Trondheim)	4		2000-2004	Skogvoll
USA	2.85 (0.86 – 6.31)		2003-2011	Kolte
USA	9-10		2008-2017	Holmberg
UK	1.9		2017	Hawkes
USA		0.175	2003	Peberdy
Country/ Region	OHCA/100´000 population and year		Year	Reference
Europe	56 (27-91)		2017	EuReCa-2[15]
North America	54.6		1990-2010	Berdowski et al[16]
Asia	28.3		1990-2010	Ibidem
Australia	44.0		1990-2010	Ibidem
Europe	35.0		1990-2010	Ibidem

Reports from national registries show large differences in reported incidence by region/county/city/state which is probably due to factors such as differences in definitions and the quality of registration. Kolte et al reported 0.86 CA/1000 hospital admissions in the Midwestern states and 6,31 IHCA/1000 hospital admissions in the Western states of the USA. Peberdy et al[17] reported an incidence rate (based on the GWTG-R) of 0,175 events/hospital bed and year.

The incidence of IHCA increase with age, and according to data from the SCRR the median age in Sweden at the time of IHCA is 75 years and women are on average slightly older at the time of CA[18]. However, male sex is a risk factor for suffering an IHCA, an incidence ratio of 1,4-1,6:1 has been reported based on Swedish[19] and North American[20] registry studies. It is only in the age group >90 years of age that women and men suffer IHCA to the same extent[21]. Because male sex correlates well with a higher prevalence and higher mortality rate of cardiovascular disease[22], the association is not surprising.

Paediatric IHCA is much more rare than adult IHCA, but probably not as uncommon as previously thought. Using the incidence calculation by Holmberg et al,[23] and admissions statistics from US,[24] an incidence of 2,9 IHCAs per 1000 pediatric hospital admissions can be calculated for the US. The corresponding incidence for the UK is 0.34 IHCA/1000 hospital

admissions[25]. Pediatric IHCA has a high incidence during the first year of life and a second incidence peak among adolescents[26].

1.4 RISK FACTORS

Cardiac arrest of cardiac origin is considered the leading cause of cardiac arrest and the most common underlying medical condition. Table 1 summarizes known risk factors categorized in three groups: pre-arrest factors (1), peri arrest factors (2) and post arrest factors (3). There are important differences between OHCA and IHCA when it comes to risk factors, especially regarding circumstances at resuscitation such as location of cardiac arrest, time to treatment, training of bystanders, level of monitoring. However, few studies have specifically compared the relative impact of known risk factors for OHCA and IHCA. For that reason, reported risk factors for both OHCA and IHCA are included.

Table 2 Predictors of survival

Risk Factor	Outcome	OR/RR	Reference
Pre arrest factors			
Age (>60)	30-d surv	OR 0.5	Al-dury et al[21], Fernando et al[27]
Sex (woman)	30-d surv	OR 1.27	Herlitz et al[28]
Ethnicity (black)	Survival rate	70% of caucasian	Becker et al[29]
Socioeconomic status	Survival to discharge	OR 1,96	Wells et al[30]
Comorbidity			
Circulatory system			
Ejection fraction	Sudden cardiac arrest	OR 11,2	Caruso et al [31, 32]
coronary heart disease			
prior acute myocardial infarction (AMI)			Vreede[19, 32]
ventricular premature beats	Death		Statters[33]
ventricular hypertrophy	Sudden death	OR 1,45	Haider[34]
atrial fibrillation	prevalence	1,76	Ryden et al[35]
hypertension	SCA (Sudden Cardiac Arrest)	OR 2,9	De Wreedeet al[32]
non-sust ventricular tackycardia (VT) in heart failure	2-year survival	RR 1,69	Doval et al[36]
Sepsis	In-hospital death	OR 1.2	Larkin et al[37]
Diabetes Mellitus	death	RR3,23	Jouven et al[38]
Obesity	death	RR 1,45	Jouven et al[38]
Smoking	death	RR 1,79	Jouven et al[38]
Hypercholesterolemia	death	RR 1,52	Jouven et at[38]

Respiratory system			
COPD (chronic obstructive pulmonary disease)	death	HR 1.25	Rusnak et al[39]
Respiratory insufficiency			
Medications			
Opioids/sedatives	incidence	OR 3.47	Overdyk et al[40]
QTc-prolonging drugs	incidence	OR 2.1	De Bruin et al[41]
Hereditary factors			
parental history of sudden cardiac death	death	RR 1.95	Jouven et al[38]
Peri arrest factors			
Etiology			
Cardiac etiology	survival	44% vs 23%	Wallmuller et al[42]
Sepsis	In-hospital death	OR 5,54	Campanile et al[43]
Treatment			
vasopressors	In-hospital death	OR 2.5	Larkin et al[37]
Vasodilators	In-hospital death	OR 07.	Larkin et al[37]
Arterial line	In-hospital death	OR 0.8	Larkin et al[37]
Invasive ventilation	In-hospital death	OR 0.8	Larkin et al[37]
Chest tube	In-hospital death	OR 0.7	Larkin et al[37]
Intubation	Survival to disch	RR 0,84	Andersen et al[44]
ECMO (Extracorporal Membrane Oxygenation)	Survival to disch	CI 1.6-30.2	Metzepoulos[45]
Intubation due to hypoxia	incidence	4,2%	Heffner[46]
Post arrest factors			
Hypothemia treatment(HTr)	CPC1-2	5,25	Bernard et al[47]
HTr: HACA			HACA-trial group[48]
HTr: TTM1 33 vs 36	Death/CPC3-5	NS	Nielsen[49]
HTr: TTM2 33 vs <37.5C	Death/CPC3-5	NS	Dankiewicz[50]

OR: Odds Ratio. RR = Relative Risk, CPC = Cerebral Performance Category, NS = non significant

1.4.1 Age
Increasing age is independently associated with higher risk of death following OHCA[21] and IHCA[27]. Concepts such as biological age have been suggested as better measures of risk compared to chronological age. Thus frailty, as measured by the clinical frailty scale[51], is also associated with a lower chance of survival[52].

1.4.2 Comorbidity
Multiple different comorbidities have been associated with modification of the chance of survival(table xx). The total burden of comorbidity, as measured by the Charlson Comorbidity

Index (CCI), is also associated with survival [53] with a near linear decline in survival rates with increasing CCI. The association seems to hold true for both IHCA[27] and OHCA[54]

1.4.3 Witnessed status
Witnessed CA are associated with higher odds of survival for both OHCA[55] and IHCA[56]. The association is highly likely to be correlated to shorter delays to CPR and defibrillation although this can be difficult to ascertain since the delay from unwitnessed CA to detection per se is impossible to know.

1.4.4 Bystander CPR
Hasselqvist-Ax[57] elegantly showed that CPR before EMS arrival was associated with better survival rates after OHCA. In the in-hospital setting CPR is routinely initiated immediately (within 1-2 minute among witnessed CAs) and the impact of bystander CPR[58] cannot be separated from the impact of the CA being witnessed.

1.4.5 Ranking of variables by degree of importance
Not all variables are of equal importance to survival. The relative importance plot is one way of illustrating the relative weight of different variables to an outcome measure. Al-Dury et al[21, 59] studied 45000 OHCAs in Sweden and found that the initial presenting rhythm was by far the most important factor tu survival, followed by age, time from CA to CPR, time from EMS dispatch, location of CA and bystander CPR. Figure 1 illustrated the importance of prearrest factors, peri-arreast factors and post-arrest factors to survival following OHCA (modified and adapted from Al-dury et al[59]) with permission from the senior author.
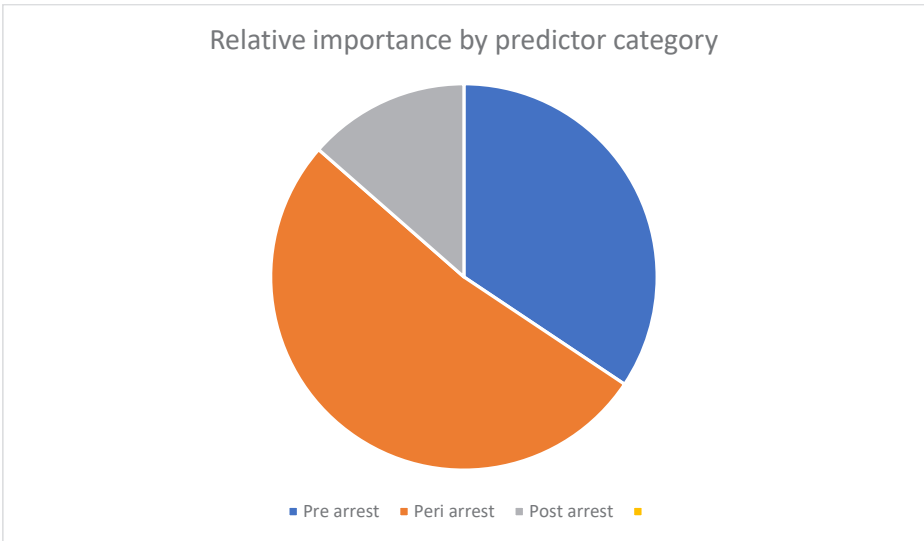

Figure 1 Pie Chart with the relative importance of pre arrest, peri arrest and post arrest factors to survival.

1.5 SURVIVAL

Survival following CA varies greatly depending on the study population and follow-up. IHCA have higher survival rates than OHCA. Survival to discharge of 3-25% following OHCA have been reported[53, 60, 61]. The corresponding figure for IHCA is 20-40%[58, 62, 63]. Survival following IHCA has increased gradually over time. A study based on the North American GWTG Registry reported an increase in survival to hospital discharge from 13,7% in 2000 to 22,3% in 2009. 30-day survival following IHCA in Sweden has increased from 26,8% in 2008 to 32,8% in 2017.[60]

The relatively modest increase in survival seen in Sweden could possibly be since early participation in the registry might reflect greater interest in CA care and better organizations (and possibly, better survival), with less interested hospitals (with lower survival rates) subsequently included in the registry. Table 3 summarizes recent publications reporting survival rates following IHCA.

Table 3 Survival following IHCA

ROSC (%)	30-day survival (%)	Survival to Discharge (%)	1-year survival (%)	year	Reference
54,1		18,6		2009	Girotra[20]
34		17	15	1990-1994	Skogvoll[64]
		41,7		1994-1995	Herlitz[63]
47,2	39,5			2004-2020	Sultanian[65]

1.6 LOCATION

In the in-hospital setting, the location of a cardiac arrest is important of several reasons. Ideally, the sickest patients with the highest risk of CA should be treated with the highest level of monitoring and cared for by the most experienced and best trained staff. In practice, patients are often cared for at the ward that handles the main medical condition (orthopaedic ward for hip fractures, surgical ward for appendicitis etc). Cardiology wards and the ICU are by definition well equipped to care for CAs: the staff is often specifically trained (ACLS) and, equally important, CAs occur with some regularity which means that the staff gains experience in treating the condition. Patients in cardiology wards and the ICU are often ECG-monitored and the wards are well-staffed leading to short delay times from CA to detection, call for the CAT and resuscitation. The opposite is also true: the staff at wards such as ortho, x-ray and psychiatry care for very sick patients but sometimes lack formal training and are seldom exposed to any large number of CAs during a given time period. To mitigate this Cardiac Arrest Teams (CAT) are commonplace: In case of sudden critical illness or suspected CA, the CAT is called upon and support or take over the management of the patient at hand. Some wards might be located far from the base of the CAT, and this could in theory impact the delay at which help can arrive. Not all hospitals and wards are equipped with the same equipment, AEDs (manual, semi-automatic, automatic) can sometimes be found in wards and corridors, but sometimes arrive with the CAT. Survival at different in-hospital locations differ substantially[19] with cardiac catheterization labs showing survival rates well >50-60% and general wards where survival is often <15%. After adjusting for covariates of importance such

as initial rhythm, aetiology and delay-times to treatment there still seems to exist residual factors that influence survival since the adjusted OR for survival in general wards is well below 1 and the OR for survival at the Cath lab and CCU is well above 1. The training of the attending nurse[66], the level of engagement and, possibly, the profession of the team leader[67] also influence survival, and the ward type often goes hand in hand with the attending nurses and physicians credentials and experience treating CA. The importance of physical distances in the hospital setting have not been well explored: however, time to call for the rescue team, time to CPR and time to defibrillation are all independently associated with survival. Thus, it´sa short leap of faith to assume that physical distances in-hospital can influence outcome. Leung et al[68] used 3-dimensional modelling to map actual and optimal AED placement and showed that optimization of AED placement could reduce the distance from an IHCA to AED substantially and reduce the number of AEDs needed to match existing AED performance.

In the out-of-hospital setting the location of the OHCA influences survival: OHCA in public locations is associated with more than three times the survival rate compared to residential locations[60] , shorter delay times to ambulance arrival and higher rates of bystander CPR. The geographic location (distance from EMS dispatch centre to OHCA) and the socioeconomic status (or level of deprivation - a composite of unemployment, social class, local authority housing and car ownership) of the area has also been showed to be associated with survival – the greater the distance from EMS dispatch centre to OHCA and the more underserved the community, the lower the survival rate[69]. The influence these factors have on survival are partly mediated by modification of the ambulance response time (Lyon et al[70]) showed that there is a linear relationship between the distance between EMS dispatch centre and time from call to arrival at the scene of the CA) and possibly also degree of bystander CPR will be of importance[71].

1.7 EDUCATINON AND TRAINING

Hundreds of thousands of laymen and health care professionals receive formal CPR training annually. The content of said training is adapted to the background and requirements of CPR skills that different student categories have and curated by professional organisations such as the European Resuscitation Council or the American Heart Association. B-CLS is adapted to suit most persons without formal health care training, advanced practitioners such as RNs in cardiology units and physicians that team lead cardiac arrest resuscitation require ACLS training. The optimal way of conducting CPR education is a matter of ongoing research and education material published by the dominating educational organisations (ERC/AHA) are updated every fifth year. The impact of education on cardiac arrest resuscitation quality and outcome has been studied: Dane et al[66] showed that the presence of a ACLS trained nurse at resuscitation was associated with an improved chance of survival and Moretti et al[72] showed that ACLS training was associated with improved rates of ROSC and 1-year survival. It has been difficult to prospectively show that education can improve survival (although it can improve retention, theoretical and practical skills[73-75]) but that is likely the case.

An integral part of CPR education is learning the treatment algorithms and adhering to them. The impact of adherence to guidelines has been evaluated and shown to be associated with increased chance of ROSC[76] and improved 30-day survival[77]. The number of deviations from guidelines have been shown to be associated with the degree of decreased chance of ROSC[76, 78]

1.8 TIME OF CARDIAC ARREST

Circadian factors likely impact survival following IHCA and OHCA differently. OHCA during the night compared to the day are less likely to be witnessed, less likely to receive bystander CPR and have lower rates of ROSC and survival to hospital discharge[79]. In the in-hospital setting, time of day and day of week correlates with the number of staff available, and also the competence of the physicians on call. Especially in smaller units and hospitals, during evenings and nights, the most experienced physician on call is often an intern or a junior resident. Regarding nurse staffing, the nurse to patient (NTP) ratio decreases when transitioning from day to night, and for every one patient increase in nurse workload there is a 7% increase in mortality. CA during the night compared to the day and weekday compared to weekend has repeatedly been shown to be associated with a decreased chance of survival[19, 80-83].

1.9 AETIOLOGY

Aetiology or assumed aetiology is essential to guide treatment of the underlying cause and is associated with prognosis. Many different classifications have been used historically, and no clear guidance exists in the Utstein template for reporting IHCA. Some classifications focus on the organ system (cardiac, pulmonary etc.), other classifications use physiological disturbances (hypotension, hypoxia), mechanism of injury (traumatic CA) or even symptoms (chest pain) The golden standard for deciding aetiology of CA should be a clinical autopsy, but that is rarely the case. Hospital autopsy rates have declined steadily since the 1960s and presently autopsy rates of about 10% at teaching hospitals and 5% at non-teaching hospitals are the norm[84]. The aetiology as reported in most registryss is based on the patient´s clinical presentation, past medical history, laboratory and radiological examinations, medical records and, in case of unsuccessful resuscitation, sometimes an autopsy report. Some degree of uncertainty often remains when the cause of CA is decided, and aetiology of CA should be interpreted with some caution. Kurkciyan et al[85] compared the initial diagnosis made by emergency room physicians following IHCA and OHCA with the definitive diagnosis established by autopsy or clinical evidence and concluded that the initial diagnosis was correct in 89% of cases. Validation of the assumed aetiology of CA based on clinical examination, patient charts etc. compared to autopsy reports indicate that non-cardiac causes of CA are underdiagnosed in favour of cardiac aetiologies and aetiologies such as pulmonary embolism, pneumonia, intoxication, intracranial bleeding and neurological conditions are sometimes overlooked[42, 64, 85, 86]. Patients presenting with a non-shockable rhythm (PEA/asystole) are more likely to have suffered a CA of non-cardiac aetiology[86]. Differences between the aetiology of OHCA and IHCA exist but have not been well explored in head to head comparisons in larger materials[87]. Patients suffering IHCA have been

reported to be older and have a larger burden of diseases compared to patients that suffered a OHCA[88].

The primary distinction is between CA of assumed cardiac or non-cardiac origin. As many as 59-69%[19, 42, 85] of cardiac arrests have been attributed to cardiac pathology. Cardiac aetiology can be further divided in subcategories: ischemic coronary disease (acute myocardial infarction), primary arrythmia, acute heart failure and valvular pathology are the most common cardiac aetiologies. Non-cardiac causes compromise all other causes. In order of falling prevalence, the most commonly reported non-cardiac aetiologies are pneumonia/respiratory insufficiency, pulmonary embolism, exsanguination (GI-bleed, vascular catastrophe), peritonitis, sepsis, trauma, malignancy, intoxication, intra/extracerebral bleeding, Sudden Unexpected Death in Epilepsy (SUDEP), metabolic[19, 42, 64, 85, 86, 89, 90].

Table 4 Aetiology or pathophysiology of CA modified from the Utstein definitions

Medical	Medical	Non-medical
Cardiac	Non-cardiac	Trauma
Primary arrythmia	Hypoxia	Drug overdose
Brugada syndrome	Respiratory insufficiency	Drowning
Long QT-syndrome	COPD	Asphyxia
	Pneumonia	Electrocution
	Pulmonary embolism	
Ischemic heart disease	Neurologic disorders	
	Hypovolemia	
Congenital heart disease	sepsis	
cardiomyopathy	bleeding	
Cardiogenic shock	malignancy	
Valvular heart disease	Electrolyte disturbances	

Table 4. The list presented in table 4 is non-exhaustive and not in order of frequency or importance.

1.10 INITIAL RHYTHM

The first recorded rhythm is of major prognostic importance and dictates the initial treatment according to current ACLS guidelines. The chance of survival decreases from pVT/VF (the best prognosis), to PEA, to Asystole, which has the worst prognosis[91, 92]. Rythm conversion from a non-shockable rhythm to a shockable rhythm is associated with an improved survival rate in OHCA[93, 94]. The first recorded rhythm is not always the first rhythm since only about 50% of IHCA are ECG monitored at the time of arrest[19]. Mainly

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animal studies but also human studies have shown that given time VT can degenerate into VF[95], VF can degenerate into PEA[96] and PEA can, naturally, degenerate into asystole. However, specific aetiologies and mechanisms of CA are associated with certain initial rhythms: VT/VF is often seen following CA due to cardiac causes[97], PEA is seen following a diverse list of conditions including hypovolemia(due to bleeding/distributive chock) or forward failure due to conditions such as cardiac tamponade, pulmonary embolism or tension pneumotorax[98]. During ACLS the patient can show transition between VT/VF/PEA/asystole and ROSC and this can bear specific prognostic importance[99]. Based on data from 2017 from the SCRR, 25% of IHCA had a shockable initial rhythm(VT/VF) and 75% had a non-shockable(PEA/Asystole) initial rhythm[100]. When and how rhythm transition occurs also bears importance to prognosis[91, 99, 101].

1.10.1 pVT/VF
VT occurs when depolarizations are generated repeatedly and rapidly from one or several foci in the ventricles. This results in atrioventricular dissociation and a rapid ventricular rate. VT may generate a normal (since the high ventricular rate may compensate for reduced stroke volume), reduced or unmeasurable blood pressure depending on hemodynamic conditions, systolic function and the ventricular rate. If the ventricular rate does not exceed 170 bpm, an adequate blood pressure is normally achieved. Ventricular rates higher than 170 bpm results in marked reductions in ventricular filling and thus stroke volumes, resulting in diminishing cardiac output and hypotension. Pulselessness occurs when the VT is incapable of maintaining palpable perfusion. VT often degenerates into VF, meaning that no organized electrical activity can be discerned. The ventriles fibrillate without generating meaningful contractions. No cardiac output is achieved. VF is by definition pulseless [102].

The majority of patients suffering cardiac arrest with VT/VF as initial rhythm have an underlying ischemic or structural heart disease in combination with a triggering factor[103]. Ischemia alters the excitability of myocardial cells. As a result, ischemic myocardium is particularly prone to developing VT or VF [102]. A large number of risk factors have been associated with ventricular arrythmias. Age, gender, smoking, cardiovascular disease, diabetes and hereditary factors and conditions such as channelopathies are some of the more common. One or several of these risk factors create a susceptibility to develop VT/VF. A high level of catecholamines, autonomic dysregulation or hemodynamic compromise contribute to this vulnerability of the heart. There is often a trigger factor that in combination with the above risk factors cause the initial arrhythmia. Premature ventricular contractions (PVC), re-entry mechanisms or ventricular tachycardia are thought to be common immediate triggers of VF[104]. Bayes de Luna[105] showed that among 157 patients wearing a Holter device at the time of CA, VF developed from VT in 62% of cases. Depending on patient population and selection, as many as 60-80% of IHCA are thought to be of cardiac causes, primarily coronary heart disease causing ischemia[42, 106]. This, however, is not supported by the low proportion of patients with a shockable initial rhythm in the SCRR [107]. It is possible and even likely that the low frequency of autopsy verification of the cause of CA leads to an overestimation of assumed cardiac CAs and an underestimation of CAs of other aetiologies[85]

Once VF has occurred, CO and BP drop very quickly below critical levels causing a very low or no -flow of blood through the circulation or, by definition, a cardiac arrest.

Patients suffering a CA and found in pVT/VF have by far the best chance of survival compared to all other CA rhythms. Survival rates as high as 60 % have been reported[108]. The reason for the high survival rate is likely to be the existence of an effective treatment: defibrillation by electrical counter shock often restores a pulse bearing rhythm and defibrillation within the first minutes of CA is associated with very high survival rates[109]. In addition, the underlying cause of the CA is often treatable (coronary artery diseases) and is therefore associated with a better prognosis. According to Weisfeldt and Becker[110] there are three phases of ventricular arrhythmias. Phase one is called the electrical phase and takes place within 0-4 minutes, phase two is the circulatory phase (4-10 minutes) and after more than 10 minutes of VF the third stage, the metabolic phase, occurs. The clinical importance of the three phases is thought to be related to the chance of restoring normal circulation. During the first two phases (<10 minutes) the chance of restoring circulation following defibrillation is relatively high. After 10 minutes, the success rate of defibrillation decreases quickly and it is likely that the metabolic alterations at this stage are so profound (acidosis, deranged electrolyte concentrations) that a better circulation (for example, CPR) is needed to increase the chance of a successful defibrillation.

1.10.2 PEA

PEA is defined as a syndrome characterized by the absence of a palpable pulse in an unconscious patient with organized electric activity other than ventricular tachyarrhythmia on ECG[111]. PEA, previously called electromechanical dissociation (EMD), is found in a heterogenous group patients of many different aetiologies. A useful sub classification is to distinguish between PEA and pseudo-PEA. Pseudo-PEA is basically a severe chock state and can be distinguished from PEA by 1) the presence of a blood pressure following insertion of an arterial line 2) high end tidal carbon dioxide in intubated patients reflecting some level of circulation or 3) cardiac activity as seen on cardiac ultrasound. This carries clinical significance since pseudo-PEA is associated with a significantly better prognosis than true PEA (ROSC 70.4 vs 20.0 and survival to hospital discharge 22% vs 0% for Pseudo-PEA and PEA respectively[112]. Many different kinds of electrical activity have been described (organized wide or narrow QRS complexes, regular or irregular rhythms). What clinical importance this carries is not well understood[113]. Weiser et al[114] showed that the initial PEA frequency predicts survival; PEA with a frequency >60 bpm had significantly better survival rates than PEA with frequencies 10-24/min, 25-40/min and 40-59/min and showed survival rates comparable to shockable rhythms – 22% 30-days survival. The cause of PEA can vary greatly. PEA has historically been categorized as either cardiac or non-cardiac. Non-cardiac causes include hypovolemia (trauma/exsanguination), obstruction (pulmonary embolism, cardiac tamponade, tension pneumothorax). PEA due to cardiac causes can be either primary (the first rhythm following CA, requires ECG monitoring at the time of arrest) or secondary (other primary rhythm that subsequently develops into PEA). Current ACLS guidelines recommend looking for reversible causes when faced with a CA due to PEA. The

T´s (Toxins, tamponade, tension pneumothorax, thrombosis and trauma) and the H´s(hypovolemia, hypoxia, hydrogen ions, hypo/hyperkalaemia and hypothermia) but there is no high-quality data to support this recommendation. Survival is generally lower compared to shockable rhythms, 30-day survival rates around 8-15% following IHCA have been reported.

1.10.3 Asystole

Asystole constitutes about 80-90 % of non-shockable rhythm and is defined as no electrical activity detectable on ECG[91]. As described above, asystole can be the last step in a dying process and it is not unusual to see a transition from VT/VF to PEA and finally asystole. However, asystole can be the initial CA rhythm. Asystole can either be primary (failure of the electric conduction system of the heart) or secondary (hypoxia)[115]Among children, asystole is the dominant presenting rhythm, most commonly caused by asphyxia[116]. Survival is low, 10-15% following IHCA among adults[117] and 15-20% among paediatric IHCA[116].

1.11 TREATMENT OF CARDIAC ARREST

As outlined in the introduction, how we treat cardiac arrest has evolved over the years, but the core elements that were established in the 1960s have remained intact: chest compressions, ventilation and defibrillation. The next crucial step was the launching of the concept of the "chain of survival" that was approved by the AHA in 1990 and first published in Circulation in 1991[118]. The concept was inspired by the "Rescue Chain" introduced in German prehospital care by Professor Ahnefeld [119, 120] in 1970. The authors introduced the concept by stating that more people survive a cardiac arrest when a particular sequence of events follows: 1) recognition of early warning sings 2) activation of the emergency medical system 3) basic cardiopulmonary resuscitation 4) defibrillation 5) intubation 6) intravenous administrations of medications. They also emphasized the importance of each link in the chain and stressed that weaknesses in one link lessened the chance of survival. The concept was originally designed with OHCA in mind but was later adapted to IHCAs as-well. In 2000 Spearpoint et al[121] applied the concept in the in-hospital setting and showed that when all links of the chain were connected (witnessed IHCA with initial rhythm of VT/VF and rapid defibrillation) survival was substantially increased).

The chain of survival (figure 2) has since then evolved and in the 2021 ERC/AHA guidelines the concept was applied to both OHCA and IHCA[122]: 1) Early recognition and call for help 2) Early CPR 3) Early Defibrillation and 4) (good) Post resuscitation care. The first three links in the chain have been shown to increase survival[80]. The fourth link is more heterogenous and involves diverse interventions such as vascular access, airway interventions, ventilator treatment, hypothermia treatment and percutaneous coronary intervention. The evidence base for the fourth chain is not as robust as the first three chains and partially based on expert opinions[123].

Figure 2 The chain of survival

Chain of survival

BASIC LIFE SUPPORT

Figure 3 Basic Life Support

Basic life support is aimed at the wide majority of the public and focuses on recognition of a CA, call for help and 2(3) basic skills: CPR (30:2) 30 chest compressions and, if trained and comfortable, 2 rescue breaths performed continuously with minimal interruptions, and use of an automated defibrillator when available.

1.11.1 Recognizing a cardiac arrest

The initial step, to recognize a cardiac arrest, is not always evident for the untrained eye, and some effort has been put into simplifying this process. Current guidelines[124] recommend that after ensuring the safety of the victim and yourself, you check for response by loudly speaking to the patient and gently shaking the victim´s shoulders. If no response, a basic airway manoeuvre to open the airway (chin lift, head backwards) is performed and 10 seconds to look, listen and feel for normal breathing. If no normal breathing, you call for the rescue team, send for an AED and initiate CPR (30:2). The evidence for these recommendations is sound, delays in recognition of CA, call for the rescue team, initiation of CPR and defibrillation are associated with a decreased chance of survival[19, 80, 122, 124].

1.11.2 Chest compressions

Following recognition of a CA, chest compressions is the second link in the chain of survival. The time from CA to chest compressions is inversely associated with survival – increasing delays are independently associated with a decreased chance of survival[87, 125, 126]. Numerous animal models have investigated the physiology of why chest compressions are beneficial in CA: Kouwenhoven et al induced VF in a dog model of CA and suggested that the compression of the heart per se generated a forward flow of blood (and thereby increased or even restored blood pressure[10]. Halperin et al[127] suggested that it was also the rhythmic change in intrathoracic pressure (i.e. compression of the thorax) that created the forward flow of blood. The optimal rate, force and compression depth have been studied extensively, currently the ERC/AHA recommend 30 compressions and 2 ventilations for adults(), a depth of compressions of x-y cm and a frequency of 100-120 compressions per minute[128]. The rate of bystander CPR for OHCA has increased nationally[57] and internationally[15] and is associated with double the survival rate[57, 129].

1.11.3 Airway management

Basic airway manoeuvres such as the chin lift and extension of the neck aim to establish a patent airway. If no or insufficient breathing is seen, chest compressions followed by ventilation should follow. According to the BLS guidelines rescue breaths are recommended at a rate of 30 compressions to 2 breaths. The value of ventilation during BLS has been questioned, Nichol et al compared uninterrupted chest compressions vs the traditional 30 compressions and 2 ventilations with a bag valve mask (BVM) performed by EMT in a very well designed RCT and found no difference in survival or neurological function. Both ILCOR and ERC recommend ventilation during BLS if the providers is comfortable doing the ventilation: If not compression only CPR is considered an acceptable second line[124].

1.11.4 AED

Early vs late defibrillation is associated with better outcome[19, 124] and there seems to exist a graded association; for every one-minute delay in defibrillation a decreased chance of survival has been observed[130]. Defibrillation before EMS arrival has been shown to be independently associated with a higher likelihood of survival[131].

1.12 ADVANCED LIFE SUPPORT

In addition to the components of BLS mentioned above (securing a patent airway, chest compressions, ventilation and defibrillation) ALS can encompass many other treatment that can be offered prehospitally or in-hospital: advanced airway management, vascular access(iv/io), medications, specific treatments and diagnostic procedures including angiography and ECMO[132]. The benefits of ACLS could potentially involve specific treatments and procedures, some of which would be feasible prehospitally (ultrasound imaging, intubation etc), some that are not likely to be practical prehospitally (cardiac catheterization) On the other hand, more time consuming and elaborate treatment with ACLS carries the potential risk of delaying transport to the hospital where more resources for definitive treatment are available, highlighting the old debate of whether to "scoop and run" or "stay and play". To date published studies comparing ACLS vs BCLS in the prehospital setting have showed conflicting results: increased rates of ROSC with ACLS vs BLS but no difference in survival to discharge [133-135], increased rate of ROSC and survival to discharge with epinephrine vs placebo also more patients with unfavourable neurologic function in the epinephrine group[136]. The airways-2 study compared more advanced airway management (endotracheal intubation) with a supraglottic airway device, and showed similar neurologic outcome at 30 days[137] where-as Wang et al showed improved 72-hour outcome with a less advanced airway management (supraglottic airway device) vs endotracheal intubation[138]. In traumatic CA a 2021 meta-analysis and systematic review of BLS vs ACLS showed no difference in ROSC or survival but increased on-scene time with ACLS. Some interventions in resuscitation are likely to be time dependent (airway management) and the longer delay times seen in OHCA possibly make beneficial effects of said interventions difficult to prove.

1.12.1 Airway management
The optimal way to handle the airway in cardiac arrest is a matter of ongoing debate, and there is no definitive answer presently. The international Liason Committee on Resuscitation (ILCOR) has identified the method of airway management during IHCA as a specific knowledge gap[139]. Airway management can schematically be described in a step-wise fashion from basic to advanced: the most basic of interventions being compression-only CPR and no airway manoeuvre and on the other end of the scale we find endotracheal intubation.

Figure 4 Airway management during CA
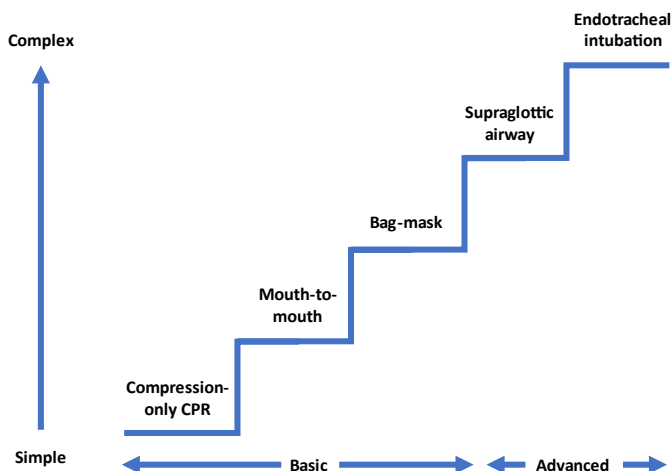
The patient´s airway is often managed in a step-wise fashion as more experienced help arrives. Current guidelines recommend that the airway should be managed by the technique the rescuer is proficient in, as there is currently a lack of data to suggest one technique over another[128, 140]. In the post ROSC period, the patient is often unconscious, aspiration is common and circulatory compromise is not unusual. By the very same reason, tracheal intubation is often performed and probably the most reasonable option[123, 128]. There is a lack of data to support what values (fraction of inspired oxygen(fiO2), positive end-expiratory pressure (peep), partial pressure of carbon dioxide/oxygen (pco2/pO2), mean arterial pressure (MAP), driving pressure) should be targeted in the post ROSC period. Jakkula et al targeted two different levels of both arterial carbon dioxide and oxygen[141] as well as two levels of mean arterial pressure[142] and found no clinically relevant differences in outcome.

1.12.2 The skill of the provider

Especially in the prehospital setting, but to a certain degree in-hospital as well, the skill and experience of the provider needs to be taken into account. Insertion of a laryngeal airway device (LMA) such as a laryngeal tube(LT) requires fewer steps and is significantly faster compared to endotracheal intubation[143]. Wang et al showed that EMS providers in the US on average required two endotracheal intubation-associated CPR interruptions with a total interruption time of 109,5 seconds to successfully intubate an OHCA patient. The Airways-2 trial[144] in the UK reported intubation success rate of 69,4% within two attempts when performed by EMT (emergency medical technician)-providers and the PART trial reported an intubation success rate of 53%[145].

Whether the potential benefits or harms associated with ET vs LMA is due to longer delays and interruptions associated with ET intubation (in the hands of unskilled practitioners) or inherent drawbacks with a certain technique when performed optimally is not known.

Hyperventilation is common and can cause significant increases in intrathoracic pressure and a decreased coronary perfusion pressure[146]

1.12.3 The duration of resuscitation
Depending on the duration of the cardiac arrest, the importance of oxygenation is likely to change. Following apnoea the oxygen saturation and partial pressure starts to decrease and within a couple of minutes clinically relevant desaturation will occur. How long the oxygen reservoir is adequate to prevent desaturation depends on oxygen delivery and demand, theoretical models and clinical experience indicate that most people desaturate below 90% Sa02 after about one minute but desaturation within the range of 25 seconds to 8 minutes can be calculated[147, 148]. The so called safe apnoea time/ ortime to desaturation can be prolonged significantly by preoxygenation and denitrogenation[149]. Neuronal damage occurs within a matter of minutes following complete apnoea and circulatory arrest. During the first few minutes following CA the oxygen content in the body is adequate to oxygenate the blood and deliver oxygen to the cells as long as there is some degree of circulation, ie chest compressions. After depletion of the available oxygen reservoir in the body, new oxygen is needed and the importance of ventilation increases.

1.12.4 The aetiology of the CA
If the cause of the cardiac arrest is related to hypoxemia in contrast to arrhythmias, the patient will already be located on the steep part of the oxygen dissociation curve and the time to clinically relevant desaturation will be very short. It is therefore physiologically sound to assume that establishing ventilation and oxygenation of the blood has the potential to reverse the CA and establish ROSC quicker than increasing the CO.

1.13 PHARMACOLOGICAL TREATMENT
A large number of drugs have been studied for their effect during resuscitation[150, 151] but only two drugs are included in the most commonly used treatment algorithms: Adrenaline and Amiodarone. The effect of Adrenaline and Amiodarone has been extensively studied, with some-what disappointing results.

1.13.1 Adrenaline
The best available evidence comes from two randomized controlled studies (RCTs) that compared adrenalin and placebo in OHCA. Jacobs et al[152] studied 500 patients and showed that adrenaline was associated with an increased rate of ROSC and survival to hospital admission compared to placebo, but no benefit in the rate of survival to discharge was found. The PARAMEDIC-2 study[136] randomized 8000 patients with OHCA to adrenaline of placebo and found an increased survival rate at 30 days (3,2% vs 2,4 % p=0,02) but severe neurological impairment occurred in more of the survivors in the adrenaline group compared to the placebo group (31,0% vs 17.8%). Subsequent meta-analysis[153] of the two aforementioned RCTs showed that adrenaline was associated with increased ROSC and survival to discharge, with no increased rate of unfavourable neurological outcome. Support for the use of adrenaline in IHCA comes primarily from extrapolation of the results of the two adrenaline vs placebo RCTs in the OHCA setting, and two observational

studies[154, 155] that evaluated the impact of time to adrenaline administration on IHCA outcome and showed and association between earlier treatment and a more favourable outcome in the adrenaline group.

1.13.2 Amiodarone
Amiodarone is an antiarrhythmic drug and recommended to patients with a shockable rhythm after three defibrillations[132]. Amiodarone has been shown to be superior to Lidocaine and placebo in terminating VF and increase survival to hospital admission for OHCA[156-158]

1.13.3 Other medications
A large number of drugs have been evaluated in the context of cardiac arrest[159], and a few should be mentioned. The combination of vasopressin and hydrocortisone was tested in two RCTs published 2009 and 2013[160, 161]: the studies evaluated 20 international units (iu) of vasopressin for each dose of adrenaline and 1 dose of the glucocorticoid Methylprednisolone 40mg in addition to standard ACLS vs placebo and standard ACLS, and found significant improvements in survival with a favourable neurologic outcome (14 vs 5 %) in the vasopressin/corticosteroid group. However, European and US guidelines do not recommend the use of vasopressin/corticosteroids due to a lack of studies replicating the findings of Mentzepoulos et al. Recently Andersson et al[162] randomized 512 patients with OHCA to vasopressin and hydrocortisone vs placebo, and found that a greater proportion of patients in the active treatment group achieved ROSC (42 vs 33%) p=0.03 but no difference in 30-day survival or favourable neurologic outcome. Other compounds that have failed to improve outcome are calcium([163]), atropine[164], sodium bicarbonate[165]beta-blockers[166] and magnesium[167].

1.14 CAUSE SPECIFIC TREATMENT: 4T, 4H AND BEYOND
CA treatment beyond ACLS is aimed at identifying possible underlying conditions and correcting them. The 4 Ts and the 4 Hs summarize 8 possible, reversible causes of CA: hypoxeimia, hypovolemia, hypo/hyperkalemia (and other electrolyte disorders), thrombosis (coronary and pulmonary), tamponade(cardiac), tension pneumothorax and toxins(poisoning)[168]. Ultrasound (both trans thoracic and trans oesophageal) has become increasingly popular but is not uncontroversial: the use of ultrasound has been shown to increase the duration of pulse checks during CA resuscitation[169] although dedicated CA ultrasound protocols can reduce the duration of pulse checks[170]. The definitive verdict is probably not out on ultrasound in CA but it seems reasonable to think that ultrasound in one way or another will be a part of more advanced CA algorithms in the future.

1.15 POST RESUSCITATION CARE
Post-resuscitation care encompasses everything following ROSC from acute and sub-acute to prognostication and rehabilitation. The most important aspects have been summarized in the 2021 post-resuscitation guidelines published by the ERC/AHA[123]:
1) Use of the ABC approach post ROSC

a. intubation, titration of oxygen to a SpO2 of 94-98% and lung-protective ventilation (tidal volume of 6ml/kg) and normocapnia. Reliable venous access, normovolemia and MAP>65/systolic BP>100mmHg.
2) Rapid cardiac catherization if ST-elevation on ECG
3) Target temperature management for adults following IHCA/OHCA if patient isunresponsive after ROSC: Hypothermia(34-36C) or avoiding fever(<37,5C) is probably equally effective[50]
4) Multimodal prognostication

1.15.1 Hypothermia
Mild therapeutic hypothermia (32-36 degrees) following brain hypoxia/ischemia has been shown to affect many pathways to neurological cell injury and improve outcomes in experimentally induced hypoxia in animals. In 2002, two RCTs[47, 48] showed higher survival rates and improved neurological function (CPC 1-2) when treated with mild hypothermia(32-34 degrees C for 12-24h for OHCA patients with shockable rhythms and 33 degrees C(+/-0.5) for patients with either OHCA/IHCA with shockable rhythms). Subsequently the TTM1 study randomized patients to 32-34 degrees C vs 36 degrees C and found no difference in outcome. In 2021 the TTM2 study compared 33 degrees C vs normothermia (<37.5 degrees C) and also didn't show any benefit of MTH. As of 2021 ERC/AHA guidelines it is still recommended to maintain comatose post cardiac arrest patients at 32-36 degrees Celsius for 24 hours[123].

1.15.2 ECMO
Extracorporeal membrane oxygenation is intuitively very appealing as a bridge to definitive treatment of the underlying cause of CA. ECMO has been shown to improve short term survival in various animal models including pigs[171]. Several challenges such as the logistics, patient selection and resource allocation, remained. In 2020[45] Yannopoulos studied OHCA and conducted a RCT comparing conventional ACLS with ECMO-facilitated CPR in shock-resistant VF without ROSC. The authors could demonstrate that survival to discharge was 7% among the standard ACLS group and 43% in the ECMO-facilitated group (posterior probability of ECMO superiority 0.9861 as quantified by Bayes factors). To balance the impressive results of Yannopoulos, neither Hsu[172] nor Belohlavek[173] nor Suverein[174] found any significant difference in outcome. ECMO has the potential to revolutionize CA treatment but there are still many challenges before it can be implemented on a grand scale. The logistics of having a functional ECMO service require large resources and a well knit together EMS to in-hospital health care system. Which patients and when to choose ECMO is still a matter of discussion.

1.16 PREDICTION OF SURVIVAL
Prediction is said to be difficult, especially about the future. A large number of studies have evaluated associations with outcome and we now know a lot about risk factors for CA and risk factors for a favourable vs unfavourable outcome[19]. Some researchers have combined known risk factors and constructed decision tools, for example regarding termination of resuscitation (ToR). Morrison et al[175] developed a termination of resuscitation rule for

OHCA treated by EMS staff with basic life support (BLS). They prospectively evaluated whether a combination of no ROSC, no defibrillation and if the arrest was unwitnessed by EMS staff could be used to terminate resuscitation following OHCA. The rule had a specificity of 90.2 % for recommending transport to hospital for survivors, and a positive predictive value of 99.5% for death when termination was recommended.

There can be several purposes for a decision algorithm for CA.

- Identify patients with a poor chance of survival

Some combinations of risk factors have been shown to be associated with very poor short and long term chance of survival (advance age, cancer, unwitnessed CA, no bystander CPR) and in these cases further CPR is unlikely to benefit the patient, but rather, lead unnecessary patient harm. Apart from being unethical, futile CPR increases costs and puts a strain on health care resources(transport of CA patient to the ED, further ICU-treatment). Identifying patients with a minimal chance of survival in the prehospital setting or in the ED/hospital could reduce suffering and costs.

- Identify and triage patients to a specific treatment or hospital

It is a matter of debate which patients should go to the cath lab, which patients would benefit from ECMO and which patients should go to a specific hospital (for example; high volume cardiac arrest centers with advanced resources such as 24/7 interventional cardiology, ECMO, cardiothoracic surgery service). A prediction model could be useful by identifying these patients and help the EMS service/physician in charge in the decision process.
One purpose is to identify patients that likely benefit further CPR, and perhaps select the patients for more advanced treatment such as ECMO-facilitated CPR.

1.17 ETHICAL ASPECTS OF CPR
The purpose of CPR is to restore circulation/breathing and, in the best of cases, enable the patient to resume activities at the same level as before the CA. Unfortunately, this is seldom the case. If you step back and consider all deaths in a single (western) country, in this case Sweden, approximately 100000 persons die/year. Of these, 20000 die at home, 40000 die in elder care/institutions and the remaining 40000 die in-hospital[176]. Out of the 40000 that die in the hospital/suffer a cardiac arrest, CPR is initiated in 5-15% of cases[13] (4000 patients) and 1/3 or 1300 patients survive the IHCA and are alive at 30 day follow up. To rephrase it, out of 40000 patients that suffer an IHCA, 1300 survive. Most of the patients that suffer an IHCA where resuscitation is not initiated are in the end-stages of their life and therefore CPR cannot be considered an appropriate treatment. Bertilsson et al[177] studied all patients that died in a Swedish county hospital during one year, and found that, after excluding patients that were admitted to the ED after OHCA (and were declared dead the ED), approximately 90% of patients that died had a prior valid decision to not attempt resuscitation (DNAR).

1.17.1 Reasons to not attempt resuscitation

Schematically, there are three reasons to no attempt resuscitation

1) The patient does not want CPR

As is the case with all treatments, the patient has the right to decline CPR. Unfortunately, many patients are not given the chance to discuss/express their preferences regarding life sustaining treatment[178, 179].

2) CPR is medically futile

For a treatment to be considered futile, the chance of success (response) needs to be small. What is "small" or futile is context specific and a matter of debate. Schneiderman and colleagues suggest two definitions; one quantitative defined as less than a 1 % chance of success/survival [180] and one qualitative that states that medical futility can be defined as "the unacceptable likelihood of achieving an effect that the patient has the capacity to appreciate as a benefit"[181, 182]. Rephrased in a clinical context; based on clinical presentation/comorbidities/circumstances at resuscitation, the clinician responsible for the care of the patient does not believe that CPR will restore circulation, and might advocate for a DNAR order on the basis of medical futility.

3) CPR is unlikely to be of value/benefit to the patient

What is of value and benefit for the patient is very individual and takes into consideration the patient's own beliefs of quality of life, and what constitutes a life worth living. A patient with a advanced chronic diseases with low QoL might very well survive a CA if treated with CPR, but the chances are that if ROSC is not achieved quickly (10 minutes?) the ability of the patient to be rehabilitated to a physical/cognitive level acceptable to the patient might be low. Based on discussions regarding what constitutes a life worth living, one might argue against CPR on the basis of no/low benefit for the patient (a prerequisite is of course the involvement of the patient)

1.18 NEUROPROGNOSTICTION FOLLOWING ROSC

Identifying patients with a good or a bad neurological outcome following cardiac arrest is one of the goals of care following ROSC. How we define good vs bad neurological outcome is crucial, according to current guidelines[183, 184] good neurological outcome is defined as CPC-score 1-2[185] or a modified Rankin Scale Score (mRS)[186] of 0-3. Poor outcome is defined as CPC-score 3-5 or mRS of 4-6[183, 184]. The minimum time from CA to determination of neurological outcome is at 30 days or hospital discharge.

Now that we have defined neurological outcome, why is it important? We want to identify patients with a potentially good neurological outcome so as not to terminate life-sustaining treatment prematurely. At the same time we want to identify patients that are likely to have a bad neurological outcome to avoid futile resuscitation efforts.

Schematically, how neuroprognostication can be performed is categorized in four categories
- Clinical examination
- Biomarkers
- Electrophysiology

- Imaging

Each method has its advantages and disadvantages…

1.18.1 When should neuroprognostication be performed?

Current guidelines[123] suggest we wait at least 72 hours before we prognosticate for a poor neurological outcome. Different tests have different performance at different times post ROSC and it is always important to relate a specific test to the time of testing. There is no "wait at least 72-hours"-limit for prognostication of good neurological outcome – if there are positive signs (signs and symptoms associated with a good outcome, normal EEG, low NSE..) at 24 hours they are likely to be present at 48 and 72 hours. However, most patients that are unconscious following CA are treated with MTH and thus remain sedated at least 24 hours from ICU admission and then a few more hours of weaning. It therefor makes sense to wait at least 24-26 hours before prognostication (for good neurological outcome) to allow for the effect of sedatives/relaxants/other medications to taper.

As with the timing of testing, there is a balance to be struck regarding which and how many tests to use to prognosticate. Current guidelines[123] recommend combining several different tests (multimodal testing) and have strict inclusion/exclusion criteria for entering a patient in the prognostication strategy algorithm.
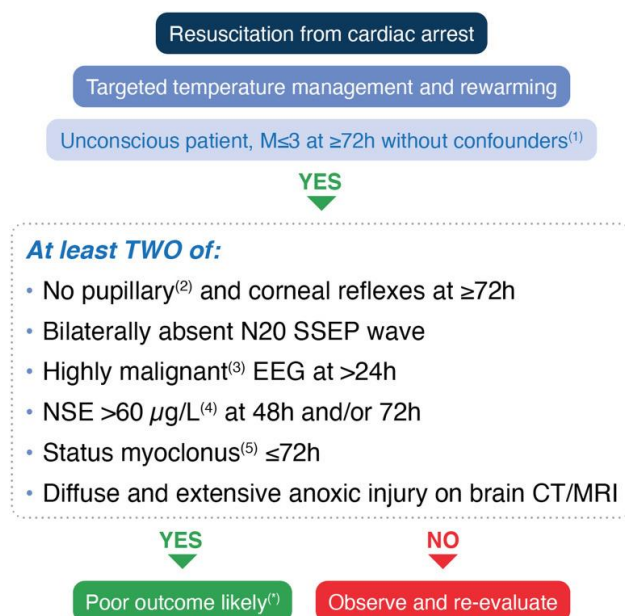
Figure 5. Prognostication strategy algorithm

Figure reprinted from Nolan et al[123] via the PMC Open Access Subset. Copyright European Resuscitation Council 2021. M3 = motor response 3 on the Glasgow Coma Scale. N20 SSEP = Somatosensory Evoked Potential of 20 milliseconds duration. NSE = Neuron-Specific Enolase. CT/MRI = Cat Scan/ Magnetic Resonance Imaging.

1.18.2 When and why do patients that achieve ROSC die?

Somewhere between 50-89% of patients that have ROSC following OHCA die in the hospital[187, 188]. The most common cause of death following resuscitation and ROSC after OHCA is withdrawal of life-sustaining treatment (WLST)[189, 190]. Treatment is withdrawn because of perceived poor prognosis and fear of survival with severe brain injury. The decision to withdraw treatment is often based on different combinations of tests for neuroprognostication (as outlined above in the section on post cardiac arrest care, any combination of clinical examination, biomarkers, electrophysiology and imaging). Data is collected continuously from the CA but WLST should not be considered <72 hours because a substantial number of patients who remain comatose on day 3 have a reasonable chance of survival with a good clinical outcome. Elmer et al[191] investigated the mortality associated with the premature (<72 hours) establishment of WLST orders. They concluded that WLST occurred in about 1/3 of subjects that died in-hospital. After calculating the chance of survival and good neurological outcome in this patient group and extrapolating the results to a national (US) level, the authors concluded that WLST < 72 hours could have contributed to 2300 additional OHCA deaths of whom 2/3 might have had a good neurological outcome. The timing of deescalating treatment is crucial since the establishment of treatment limitations and WLST is ultimately self-fulfilling.

1.19 THESIS BACKGROUND

Paper I

IHCA is both common and associated with a poor outcome. Relative to OHCA, less attention has been paid to investigating the factors that are associated with a favorable versus a poor outcome in the in-hospital setting. It has become common practice to extrapolate OHCA results and apply to the IHCA population, as is the case with hypothermia treatment[49]. Recent, large and representative studies of IHCA have focused on incidence and overall survival[192]. There is a lack of studies exploring factors of importance to survival, especially in a Swedish population.

Paper II

Core elements of CA treatment are summarized in the chain of survival[193]: early recognition and call for help, early and efficient CPR, swift defibrillation and effective post resuscitation care. Most national and international resuscitation guidelines have recommendations regarding these initial steps. The Swedish Resuscitation council has issued guidelines for the treatment of IHCA based on the ERC/AHA guidelines[194]. In addition to the ERC/AHA recommendation that patients found in a shockable rhythm should be defibrillated within three minutes, the Swedish resuscitation council recommend that the delay from CA to call for the rescue team and to starting of CPR should not exceed one minute. However, the impact of adhering to the guidelines regarding delay times to 1) call for the CAT 2) starting CPR and 3) defibrillation have not been evaluated.

Paper III

Outcomes for multiple conditions such as upper GI-bleed[195], ruptured abdominal aneurysm and acute epiglottitis[196] are worse during the night compared to the day, a phenomenon known as the week-end effect. Reasons such as understaffing[197], less experienced staff[196] and a lack of diagnostic and therapeutic resources[198] have been suggested causes for the difference in outcome. OHCA and IHCA also show similar patterns, lower survival rates have been demonstrated during the night vs the day for both IHCA[19] and OHCA[199] but there is a lack of studies exploring why there are differences in outcome.

Paper IV
OHCA is common and survival is only 5-10%. Most resuscitation efforts are terminated in the prehospital setting or upon admission to the hospital, often due to assumed medical futility. However, it has been shown that estimating survival periarrest is difficult and clinician´s estimates of survival can differ widely. There is a lack of good predictive tools to assist clinicians estimation of the chance of survival and neurological function.

Paper V
The importance of cardiovascular comorbidities in OHCA remains sparsely studied[200]. We cross-linked several national Swedish registries with the aim of studying how pre-existing cardiovascular conditions including HT, heart failure, DM and ischemic heart disease, etc, affected the likelihood of survival following OHCA.

2. AIMS OF THE THESIS

To study epidemiological aspects of cardiac arrest in Sweden based on the Swedish Registry for Cardiopulmonary Resuscitation (SCRR)

- To study incidence and survival following IHCA (I)
- To investigate the importance of multiple factors (modifiable, partly modifiable and non-modifiable) and their association with 30-days survival following IHCA (I).
- To assess the trend in adherence to current Swedish resuscitation guidelines and the importance of adherence in relation to 30-days survival (II).
- To study the importance of time of IHCA with special emphasis on a comparison between resource limited wards off-hours and high resource wards on-hours (III).
- To develop a periarrest prediction model that is simple to use and can estimated 30-day survival and neurological function at 30 days following out-of-hospital cardiac arrest (IV)
- To study the impact of cardiovascular risk factors and comorbidities on the survival of OHCA (V)

3. PATIENTS AND METHODS

3.1 PAPER I

Paper 1 is a retrospective observational study based on the Swedish Cardiopulmonary Resuscitation Registry (SCRR). All patients 18 years and older that suffered a IHCA where resuscitation was initiated were included. The inclusion period was 1 January 2006 to 31 December 2015. The primary outcome variable was 30-day survival, secondary outcome variables were 1-year survival, ROSC, survival to hospital discharge and neurological function as measured by the Cerebral Performance Category (CPC) score. Multiple variables (baseline variables and circumstances at resuscitation) were evaluated for an association with 30-day survival. For the univariable analysis we used logistic regression to calculate ORs with corresponding CIs. Due to missing data multiple imputations were performed for the multivariable analysis. Multiple logistic regressions were performed in each of the 50 imputed data sets and the variable with the highest p-value in the pooled results was excluded from the model until all remaining variables had $p<0.01$ in the pooled results. We also tested for interactions. Two-sided tests were used and p-values below 0,01 were considered statistically significant.

3.2 PAPER II

Paper II is a retrospective observational study based on the Swedish Cardiopulmonary Resuscitation Registry (SCRR). All patients 18 years and older that suffered a witnessed IHCA where resuscitation was initiated were included. Complete data on initial rhythm, time to call for the CAT and time to defibrillation was mandatory for inclusion. The inclusion period was 1 January 2008 to 31 December 2017. Patients were stratified according to initial rhythm, shockable (VT/VF) or non-shockable (PEA/asystole). We assessed trends in adherence to guidelines (defined as follows: time from CA to call for the rescue team and start of CPR within one minute and time from CA to defibrillation within three minutes). The last criterion only applied to patients who presented with a shockable rhythm. Baseline characteristics were presented using means, medians, and proportions with appropriate measurements of dispersion.

Hypothesis tests were not computed for baseline features[201] We studied trends in adherence to guidelines by examining the proportion of patients treated according to guidelines from 2008 to 2017. We also assessed the proportion of patients surviving to 30-days (2008-2017) in relation to adherence to guidelines. Logistic regression was performed for each group to evaluate annual changes in 30-day survival. Differences in survival trends, in relation to adherence to guidelines, were evaluated using an interaction term between calendar year and adherence to guidelines.

The association between guideline adherence and 30-day survival was ultimately evaluated using logistic regression, with adjustment for covariates of clinical importance or displaying varying distributions between the groups at baseline.

We built gradient boosting models to estimate the most important predictors or 30-day survival among patients suffering an IHCA with a shockable and non-shockable initial rhythm. The measurements of strength of an association in gradient boosting is denoted as relative influence. Gradient boosting is a machine learning technique that can be used for regression analysis. It uses machine learning techniques and overcomes some of the limitations of conventional logistic regression models (such as linearity) and can discover nonlinear associations and high-order interactions[202].

We also computed odds ratios (ORs) in the entire population by imputing missing data using Multiple Imputation by Chained Equations (MICE) algorithm[203]. One data set was imputed and we compared the obtained ORs with those obtained in the complete case set. P-values<0.05 were considered statistically significant.

3.3 PAPER III

In paper III we used the Swedish Registry for Cardiopulmonary Resuscitation to study 26595 patients from January 1 2008 to December 31 2019. Adult patients 18 years and older were included and only cases where resuscitation was attempted. Patients were stratified in three groups: "day" = Monday to Friday 7am-3pm, "evening" = Monday to Friday 3pm-9pm and "night" Monday-Friday 9pm-7am and Saturday-Sunday am-pm. Baseline characteristics were compared between groups using chi-square test and ANOVA. Standard Mean Difference (SMD) was calculated for baseline characteristics and outcome variables. The association between time of cardiac arrest by category (day vs evening vs night) and 30-day survival was ultimately evaluated using logistic regression, with adjustment for covariates of clinical importance or displaying varying distributions between the groups at baseline. P-values<0.05 were considered statistically significant.

3.4 PAPER IV

In Paper IV we merged five Swedish registries (the Swedish Cardiopulmonary Resuscitation Registry (SCRR), the Swedish Inpatient and Outpatient registries, the Swedish Prescribed Drug Registry and the Integrated Longitudinal database for health insurance and labor market studies) and ultimately ended up with 55,615 cases of OHCA and 393 variables. Data was collected retrospectively, inclusion criteria were patients that suffered a OHCA where resuscitation was initiated. The inclusion period was 1 January 2010 to 31 December 2020. The primary outcome was 30-day survival. Secondary outcome was neurological function as measured by the Cerebral performance category score. To develop, evaluate and test multiple prediction models, we stratified our data in three sets: a training data set (60% of data), an evaluation data set (20% of data) and a test data set (20% of data). To develop the best possible prediction model, we used multiple machine learning frameworks (support vector

machines, neural networks, gradient boosting, extreme gradient boosting, random forest) as well as conventional logistic regression to develop multiple prediction models. The models were compared for performance by comparing the ROC curves.

3.5 PAPER V

Paper V is a retrospective observational study based on the Swedish Cardiopulmonary Resuscitation Registry (SCRR). All patients 18 years and older that suffered a OHCA where resuscitation was initiated were included. The inclusion period was 1 January 2010 to 31 December 2020. We merged the SCRR with the Swedish in and outpatient Registry, the Swedish Prescribed Drug Registry and the LISA (integrated longitudinal database for health insurance and labor market studies) registry. The primary outcome was 30-day survival. Secondary outcome was neurological function as measured by the Cerebral performance category score. We divided the study cohort based on the presence of 4 common cardiovascular risk factors: hypertension, heart failure, hypertension + heart failure, heart failure + ischemic heart disease, acute myocardial infarction and diabetes mellitus. Baseline characteristics were presenter using means and medians with SDs and IQRs. Time from HT diagnosis to OHCA was evaluated using the Kaplan Meier method. We evaluated an association with 30-day survival and CPC-score using multivariate logistic regression analysis. Cox adjusted survival curves were calculated. An association between initial rhythm and time to initiation of CPR (no flow time) was evaluated using cubic splines(3 knots) due to suspicion of non-linearity of associations.

3.6 THE SWEDISH REGISTRY OF CARDIOPULMONARY RESUSCITATION

The SCRR is a national quality registry that contains information on patients that suffer a cardiac arrest who received CPR. The registry contains information on OHCA (since 1990) and IHCA (2006). In 2021 all EMS systems and all hospitals with emergency services reported to the registry. Following OHCA and IHCA, a report is filed electronically by the EMS-crew or the nurse in charge. At 30 days following the CA, follow-up is carried out by a designated nurse to record 30-day survival and estimate CPC-score at admission and 30 days. Information about the CA is recorded in accordance with the Utstein guidelines for recording of CA data. Variables include patient characteristics, circumstances at resuscitation, interarrest circumstances and post arrest care.
Data from the registry was used in paper 1-3 (IHCA-data) and paper 4-5 (OHCA data).

3.7 STATISTICAL METHODS
Table xx Summary of statistical methods

	paper I	paper II	paper III	paper IV	paper V
Group comparisons					

Categorical variables					
student´s t-test		x	x		
ANOVA (one way)		x	x		
ANOVA (factorial)			x		
Log-rank test			x		
Dichotomous variables					
Chi-square test		x	x		
Fischer exact test					
Categ./Cont. variables					
SMD		x	x		x
Regression					
Linear regression		x			
Logistic regression	x		x	x	
Cox regression					
Trend analyses					
Mann-Whitney U test		x			
Machine learning					
Supervised learning					
Gradient Boosting		x		x	
Support Vector Machines				x	x
Extreme Gradient Boosting				x	
Neural Networks				x	
Random Forest				x	
Imputation method					
Marcov Chain Monte Carlo	x				
MICE[203]	x	x			
Random Forest / Predictive mean matching[204, 205]				x	

Descriptive statistics

The distribution of baseline characteristics is given as means (standard deviations) and medians (interquartile range).

Univariate statistics

Chi-square and Fischers exact test were used to test for difference between dichotomous variables (paper III). ANOVA was used to test for difference between continuous variables (paper III). Univariate logistic regression was used to calculate OR with corresponding 95% confidence intervals in paper 1. Standardized mean difference (SMD) was calculated for baseline characteristics and outcome variables (paper III-V). SMD is the difference between the means for two groups divided by their standard deviation. Values below 0.1 (10%) were considered inconsequential.

The Kaplan-Meier method was used (paper V) to calculate the time from HT diagnosis to OHCA. Cox adjusted survival curves were calculated to estimate survival with adjustment for age, sex and no-flow time.

Multivariate statistics

Logistic regression with multiple covariates was used to investigate associations with 30-day survival (paper I-V). Feature selection was performed based on clinical relevance and differing distribution (paper II-V) and backwards selection (paper I)

To account for missing data, multiple imputations were used after checking for the pattern of missingness (data was assumed to be missing at random). In paper 1, data (50 data sets) was imputed using the Markov Chain Monte Carlo method. The pooled results from the 50 imputed data sets were used. In manuscript II-V, data was imputed using the MICE (multiple imputations by chained equations) algorithm. In paper I, several multivariable logistic regressions were performed with imputation of missing data and selection of included variables was made using a stepwise approach starting with all variables from the univariate model. In paper II-III variables that were included in the multivariate model were chosen based on clinical relevance. In paper II difference in survival trends was assessed by comparing the slopes and the hypothesis test was carried out with the students t-test.

3.8 MACHINE LEARNING

In paper II and IV-V machine learning methods were used to analyze the data.

Machine learning has the ability to handle very large amounts of data, model complex interactions and capture highly non-linear associations. When compared to conventional statistical methods (e.g ordinary least squares), machine learning techniques (gradient boosted machines, support vector machines, random forest and neural networks) outperform logistic regression in predicting outcome following IHCA[206].

Machine learning (ML) methods can schematically be divided in four categories: supervised, unsupervised, semi-supervised and reinforcement learning[207].

Supervised ML: Supervised ML uses labeled outcome data for regression and classification. Common types include random forest, boosted trees (boosting), support vector machines and regularized regression.

Unsupervised ML: Unsupervised ML uses unlabeled data to find new associations and hidden patterns in complex data. Examples include K-mean clustering and principal component analysis.

Semi-supervised ML: Semi-supervised ML uses both labeled and unlabeled data.

Reinforcement learning: Reinforcement learning (RL) is a technique designed to maximize a specific long- or short-term outcome by optimizing a chain of decisions. One example is the patient with sepsis; a large number of decisions has to be made: Fluids? Pressors? Mechanical ventilation? Dialysis? Antibiotics? Each decision is likely to influence the patients outcome (resolution of infection? ICU survival? 1-year survival?) but each decision also likely influences the downstream options[208]. In such scenarios, reinforcement learning may be suitable.

Random Forest
Random forest (RF) is a supervised ML method used in papers II, IV. The method is an ensemble algorithm that uses many weak learners (individual trees). RF works by creating multiple decision trees, each tree being a weak prediction model, and then combining (by averaging) the results (predictions) of all trees to obtain a final prediction. Trees are built by sampling observations and predictors randomly. Each tree will use the available predictors to partition the observations into subgroups that, based on their predictors values, maximize the heterogeneity in the outcome being studied. Thus, the outcome supervises the algorithm to create a decision tree. Because all trees are built using random samples of observations and predictors, all trees will be decorrelated.

Extreme gradient boosting (XGBoost)
Extreme gradient boosting is a supervised ML method that is considered one of the most powerful methods for any prediction task on structured data. The method is a highly optimized and parallelizable decision tree that utilizes boosting, which means that weaknesses of each tree is improved by building subsequent trees using the residuals of the previous trees.

Support Vector Machines (SVM)
SVMs Separates data in a high-dimensional space into two or more categories.

Neural networks (NN)
Neural networks are loosely inspired by the neurons of the human brain. Schematically, the network starts with an input vector (input layer) which feeds data forward to a hidden layer, in which all inputs are multiplied by weights, and then summed before passing it through a non-linear activation function (e.g rectified linear unit, ReLU). The number of hidden layers, neurons in the hidden layer, the use of weights and the number of connections between the neurons are the hallmarks that define different NN architectures.

3.9 ETHICAL APPROVALS

All papers were approved by a regional or the national ethics committee of Sweden.

Paper I: Ethical Approval No: 2014/ 371-14.
Paper II: Ethical Approval No: 2016:349-16
Paper III: Ethical Approval No: 2018/018-18
Paper IV: Ethical Approval No: 2019-01094
Paper V: Ethical Approval No: 2019-01094

4. RESULTS

4.1 PAPER I

In all, 18069 patients were included, 39% of whom were women. The median age was 75 years. 61% of patients had ROSC, 50% of patients were alive after the initial resuscitation attempt and 30-day survival was 28.3%, 93% with a CPC score of 1-2. One-year survival was 25.0 %. IHCA incidence in 2015 was 1.7 IHCAs per 1000 hospital admissions Survivors were younger, had fewer comorbidities but more often an ongoing AMI, more often suffered a CA during the daytime on working days, more often had a primary arrythmia or AMI as aetiology, were more often witnessed and ECG-monitored and had shorter delays to call for the CAT, start of CPR, defibrillation and arrival of the CAT. The location of the CA was strongly associated with the odds of survival in the univariate analysis, IHCA in the ICU/CCU/cath lab/OR had a prevalence of 34% and an OR of 2.81(95% CI 2.63-3.01) for survival. We observed very strong associations between the location of the CA and whether the CA was both witnessed and ECG-monitored – almost all CA in the ICU/CCU/cath lab/OR were both witnessed and ECG-monitored. Several factors were found to be associated with 30-day survival in the multivariate analysis. They included cardiac arrest (CA) at working days during the daytime (08-20) compared with weekends and night-time (20-08) (OR 1.51 95% CI 1.39-1.64), ECG-monitored (OR 2.18 95% CI 1.99-2.38) and witnessed CAs (OR 2.87 95% CI 2.48-3.32) and if the first recorded rhythm was ventricular fibrillation/tachycardia, especially in combination with myocardial ischemia/infarction as the assumed aetiology of the CA (OR for interaction 4.40 95% CI 3.54-5.46).

Table 4 Independent predictors of 30-day survival

Table 4

Independent predictors of 30-day survival ($n = 18,069$).

	Survival at 30 days	
	OR[a]	95% CI
Background variables		
Age > 75 years	0.68	0.62–0.74
Co-morbidity		
Heart failure	0.62	0.56–0.68
Respiratory insufficiency	0.65	0.58–0.72
Malignancy	0.64	0.57–0.72
Renal dysfunction	0.48	0.44–0.53
Ongoing disease		
Stroke	0.66	0.51–0.84
Time of IHCA		
Working day 08–20	1.51	1.39–1.64
Clinical signs before arrest/assumed aetiology		
Arrhythmia	3.05	2.74–3.39
Myocardial ischemia/infarction	0.44	0.37–0.51
Pulmonary oedema	0.39	0.29–0.53
ECG monitored	2.18	1.99–2.38
Witnessed	2.87	2.48–3.32
VT/VF as initial rhythm	3.05	2.69–3.45
Interaction		
VT/VF as initial rhythm myocardial ischemia/infarction as aetiology	4.40	3.54–5.64
Delay		
CA to call > 1 min	0.77	0.68–0.87
Treatment		
Intubation	0.63	0.57–0.70
Adrenalin	0.20	0.18–0.22

[a] The ORs and corresponding 95% confidence interval for factor present in relation to factor absent regarding 30-day survival.

Table 4 Independent predictors of 30-day survival following IHCA. Multiple factors including baseline characteristics of the patients, time of day, circumstances at the time of the CA, level of monitoring and treatment were associated with 30-day survival. Abbreviations: IHCA=in-hospital cardiac arrest ECG= electrocardiogram VF/pVT=ventricular fibrillation/pulseless ventricular tackycardia. Reproduced with permission from the publisher.

4.2 PAPER II

23460 IHCA patients suffered a IHCA with an attempt at resuscitation and were included in the SCRR 1st of January 2008- 31st of December 2017. 12325 patients met the study criteria, 3212 had a shockable rhythm and 9113 a non-shockable rhythm. There were several differences between patients treated according to guidelines and patients not treated according to guidelines: patients on general wards and/or without continuous ECG monitoring at the time of CA were less likely to be treated according to guidelines – delay times to call for the rescue team, initiation of CPR and, when appropriate, defibrillation, were significantly longer irrespective of rhythm. Patients with a shockable initial rhythm that were treated according to guidelines had a lower burden of disease compared to patients with a shockable rhythm who were not treated according to guidelines. Fig 2 shows how adherence and survival changed in the study period – there were small increases in adherence for both rhythm categories where-as survival increased substantially for both rhythm categories but especially for non-shockable rhythms.

Figure 2 Adherence to guidelines and survival trends for shockable and non-shockable rhythms 2008-2017

Figure 2 – Adherence to guidelines and survival. (A and C) The proportion of patients treated according to guidelines over time (2008–2017) for shockable (A) and non-shockable (C) rhythms. (B and D) The survival rate over time (2008 –2017) for shockable and non-shockable rhythms comparing patients treated according to guidelines with those not treated according to guidelines.
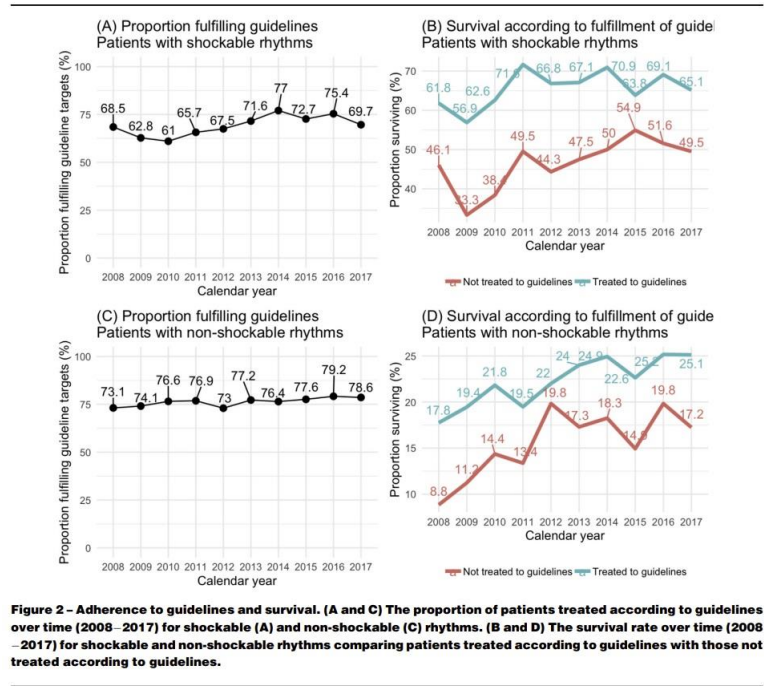
Figure 2. Reproduced with permission from the publisher.

Independent predictors of survival

Figure 1A: Forest plot of odds ratios for 30-day survival following in-hospital cardiac arrest among patients with a shockable rhythm

Odds ratios (95% CI) for survival
Patients with shockable rhythm

	Odds ratio (95% CI)
Treated to guidelines	1.84 (1.52–2.22)
Not treated to guidelines	Reference
Age	0.96 (0.95–0.97)
Women	1.09 (0.91–1.31)
Men	Reference
Regular ward	Reference
Outpatient ward, lab, radiology	2.05 (1.27–3.35)
Other ward	1.46 (0.86–2.51)
OR	0.72 (0.33–1.57)
ICU	0.69 (0.5–0.96)
ER	1.18 (0.89–1.57)
Catheterization laboratory	1.74 (1.24–2.44)
CCU	1.4 (1.09–1.79)
Not ECG monitored	Reference
ECG monitored	1.72 (1.37–2.16)
Non-Academic	0.87 (0.73–1.04)
Academic	Reference
No heart failure	Reference
Heart failure	0.55 (0.46–0.65)
No diabetes	Reference
Diabetes	0.76 (0.63–0.92)
Respiratory insufficiency	0.57 (0.45–0.73)
No respiratory insufficiency	Reference
No myocardial infarction	Reference
Myocardial infarction	1.1 (0.91–1.33)
No cancer	Reference
Cancer	0.77 (0.61–0.99)
Stroke	0.81 (0.61–1.07)
No stroke	Reference

Odds ratio (95% CI)

Fig. 1A Forrest plot with the adjusted ORs for 30-day survival among patients with a shockable rhythm for multiple variables including age, sex, ward type, monitoring, academic vs non-academic hospital and multiple comorbidities. Abbreviations: OR = operating room ICU = intensive care unit ER = emergency room CCU = cardiac care unir ECG= electrocardiogram. Reproduced with permission from the publisher.

Figure 1B: Forest plot of odds ratios for 30-day survival following in-hospital cardiac arrest among patients with a non-shockable rhythm

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Odds ratios (95% CI) for survival
Patients with non-shockable rhythms

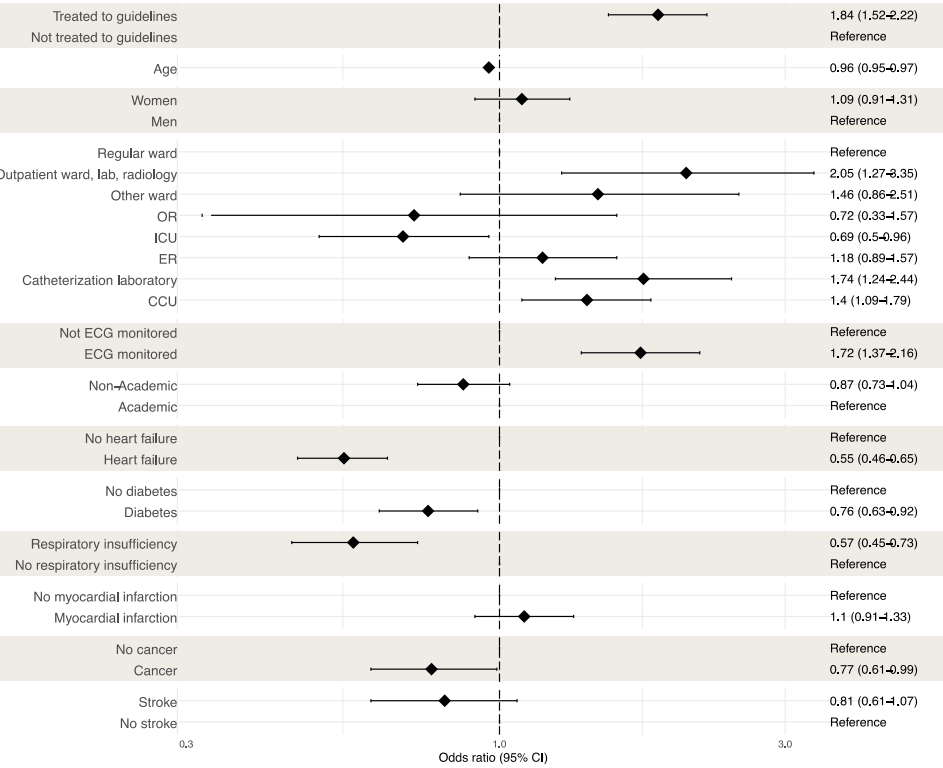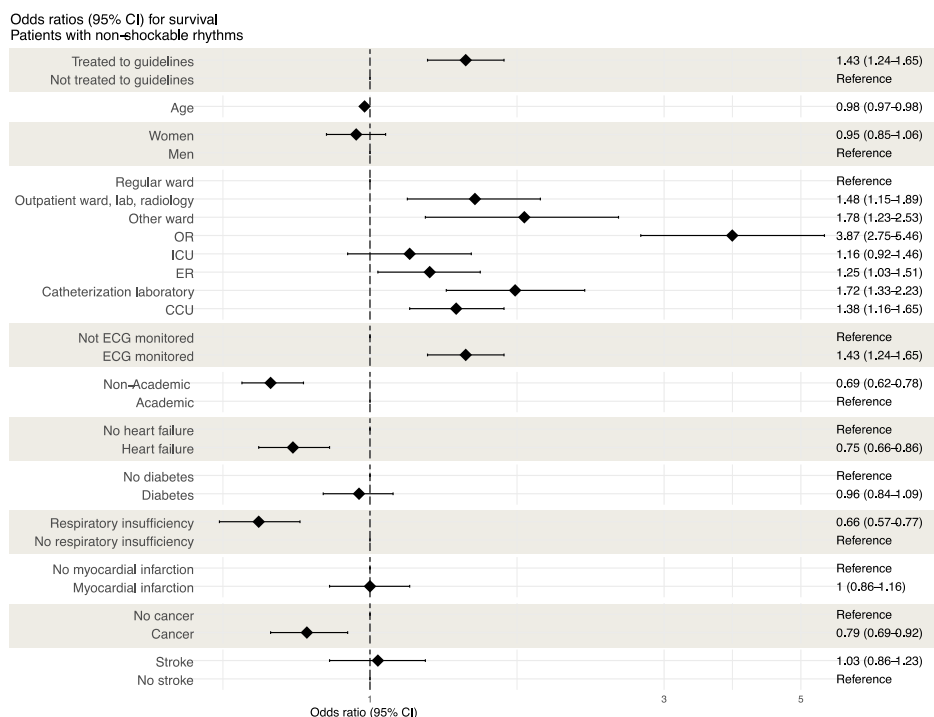|	
Treated to guidelines	1.43 (1.24–1.65)
Not treated to guidelines	Reference
Age	0.98 (0.97–0.98)
Women	0.95 (0.85–1.06)
Men	Reference
Regular ward	Reference
Outpatient ward, lab, radiology	1.48 (1.15–1.89)
Other ward	1.78 (1.23–2.53)
OR	3.87 (2.75–5.46)
ICU	1.16 (0.92–1.46)
ER	1.25 (1.03–1.51)
Catheterization laboratory	1.72 (1.33–2.23)
CCU	1.38 (1.16–1.65)
Not ECG monitored	Reference
ECG monitored	1.43 (1.24–1.65)
Non-Academic	0.69 (0.62–0.78)
Academic	Reference
No heart failure	Reference
Heart failure	0.75 (0.66–0.86)
No diabetes	Reference
Diabetes	0.96 (0.84–1.09)
Respiratory insufficiency	0.66 (0.57–0.77)
No respiratory insufficiency	Reference
No myocardial infarction	Reference
Myocardial infarction	1 (0.86–1.16)
No cancer	Reference
Cancer	0.79 (0.69–0.92)
Stroke	1.03 (0.86–1.23)
No stroke	Reference

Odds ratio (95% CI)

Fig. 1B Forrest plot with the adjusted ORs for 30-day survival among patients with a non-shockable rhythm for multiple variables including age, sex, ward type, monitoring, academic vs non-academic hospital and multiple comorbidities. Abbreviations: OR = operating room ICU = intensive care unit ER = emergency room CCU = cardiac care unit ECG= electrocardiogram VF/pVT=ventricular fibrillation/pulseless ventricular tackycardia. Reproduced with permission from the publisher.

Figure 2a-b Strength of association with 30-day survival and various risk factors for patients with a shockable and non-shockable rhythm
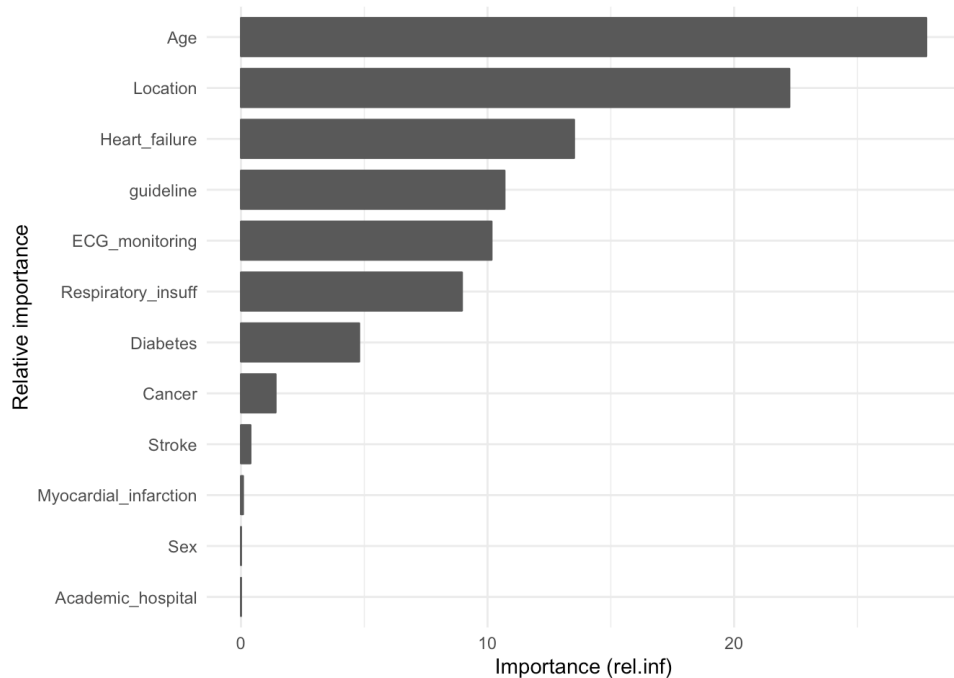
Figure 2a. Relative variable importance plot for patients with a shockable rhythm. Adherence to guidelines was the most important modifiable factor to 30-day survival. Abbreviations: ECG= electrocardiogram. Reproduced with permission from the publisher.
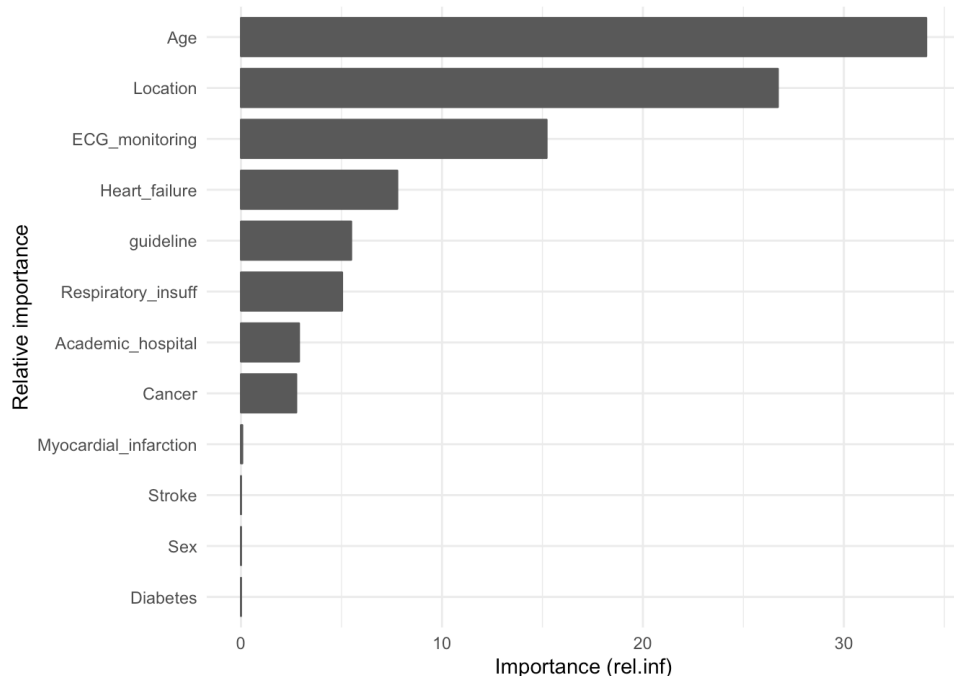
Figure 2b. Relative variable importance plot for patients with a non-shockable rhythm. Abbreviations ECG= electrocardiogram. Reproduced with permission from the publisher.

After adjusting for covariates, multiple factors including age (OR 0.96 CI 0.95-0.97), ECG-monitoring (OR 1.72 CI 1.37-2.16) hospital type (OR 0.69 CI 0.62-0.78 for shockable rhythms) and adherence to guidelines (OR 1.84 CI 1.52-2.22 for non-shockable and OR 1.43 CI 1.24-1.65 for shockable rhythms) were associated with survival (fig 1a-b) The relative influence of the most important predictors of survival are shown in figure 2 A-B (supplemental fig S8a-b in paper II). Adherence to guidelines was the most important modifiable factor among patients with a shockable rhythm and the second most important modifiable factor among patients with non-shockable rhythms.

4.3 PAPER III

In paper III 26595 patients were initially included in the study of which 24794 patients met inclusion criteria. There were small differences in baseline characteristics between the three time categories, for example IHCAs that took place during the week-ends/night compared to the weekdays/daytime were less often witnessed, more often had asystole as the initial rhythm and time to defibrillation was slightly longer. Both ROSC and 30-day survival were highest during the daytime on weekdays and decreased from daytime→evening→night (67.9% →66.3% →60.2% for ROSC and 36.8%→32.0%→26.2% for 30-day survival p<0.001 and p=0.028 respectively). The proportion of patients with good neurological outcome at 30 days also decreased (80.5%→79.1%→76.6%). To understand how time of day and day of week

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were influenced by other factors known to have an impact on survival, we compared wards with high minimum staffing(ICU, CCU, cath lab) to wards with lower minimum staffing(general wards), ECG-monitored patients vs non ECG-monitored patients, small hospitals vs larger hospitals and academic vs non-academic hospitals and consistently show that there were smaller decreases in 30-day survival on wards and hospitals with a higher minimum staffing (CCU/ICU, larger hospitals and academic hospitals) and among ECG-monitored patients. After adjusting for covariates of known importance to the outcome or with varying distribution in the multivariate analysis, time category (day vs evening vs night), hospital size (larger vs smaller) and hospital type (academic vs non-academic) were independently associated with an increased chance of 30-day survival.

Figure 1a-c Witnessed status, initial rhythm and time from CA to defibrillation by time of IHCA
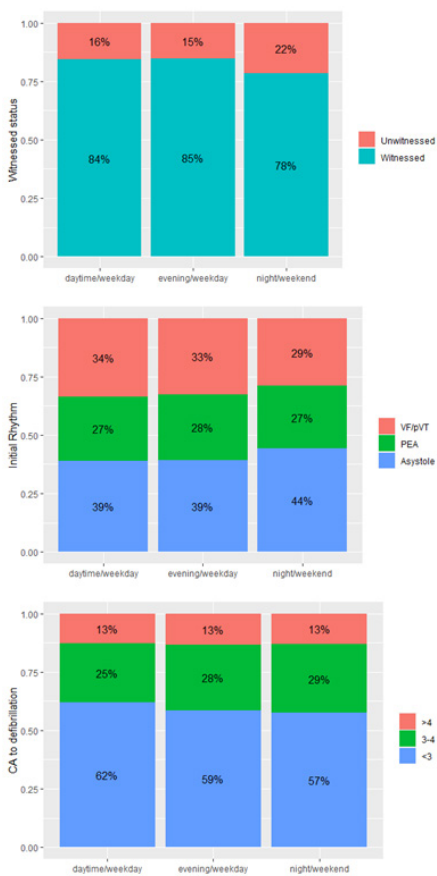

Figure 1a-c: Cumulative bar plots of witnessed status, initial rhythm and time to defibrillation by time category. Abbreviations: ECG= electrocardiogram VF/pVT=ventricular fibrillation/pulseless ventricular tackycardia PEA: Pulseless Electrical Activity; pVT/VF: pulseless Ventricular tachycardia/Ventricular Fibrillation.

Figure 2 Forrest plot of adjusted OR for 30-day survival

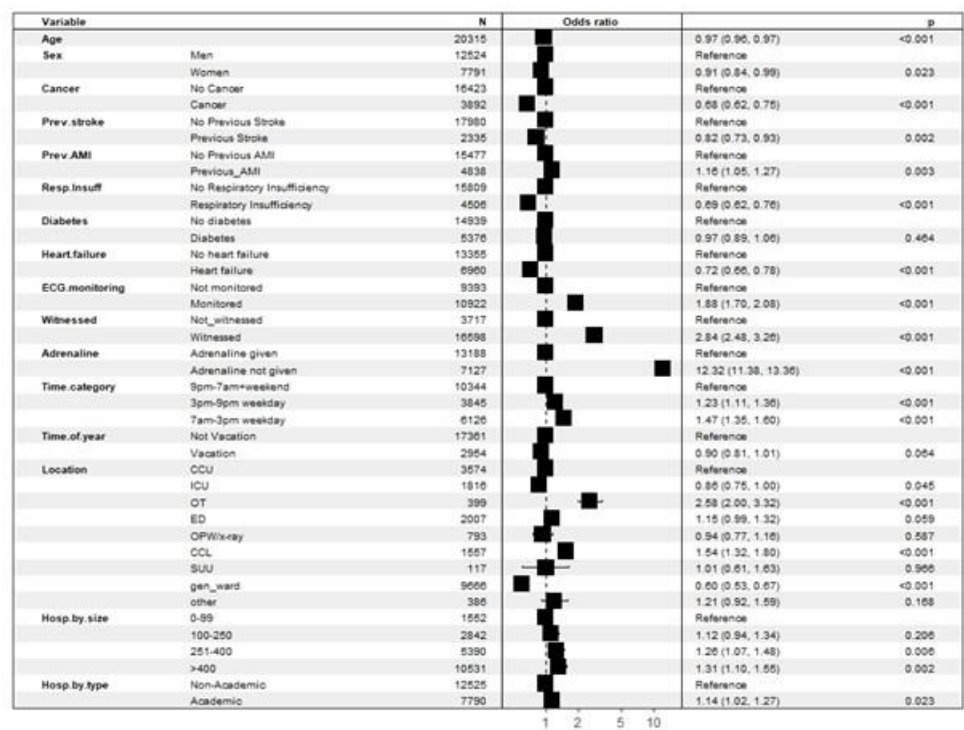| Variable		N	Odds ratio	p
Age		20315	0.97 (0.96, 0.97)	<0.001
Sex	Men	12524	Reference	
	Women	7791	0.91 (0.84, 0.99)	0.023
Cancer	No Cancer	16423	Reference	
	Cancer	3892	0.68 (0.62, 0.75)	<0.001
Prev.stroke	No Previous Stroke	17980	Reference	
	Previous Stroke	2335	0.82 (0.73, 0.93)	0.002
Prev.AMI	No Previous AMI	15477	Reference	
	Previous_AMI	4838	1.16 (1.05, 1.27)	0.003
Resp.Insuff	No Respiratory Insufficiency	15809	Reference	
	Respiratory Insufficiency	4506	0.69 (0.62, 0.76)	<0.001
Diabetes	No diabetes	14939	Reference	
	Diabetes	5376	0.97 (0.89, 1.06)	0.464
Heart.failure	No heart failure	13355	Reference	
	Heart failure	6960	0.72 (0.66, 0.78)	<0.001
ECG.monitoring	Not monitored	9393	Reference	
	Monitored	10922	1.88 (1.70, 2.08)	<0.001
Witnessed	Not_witnessed	3717	Reference	
	Witnessed	16598	2.84 (2.48, 3.26)	<0.001
Adrenaline	Adrenaline given	13188	Reference	
	Adrenaline not given	7127	12.32 (11.38, 13.36)	<0.001
Time.category	9pm-7am+weekend	10344	Reference	
	3pm-9pm weekday	3845	1.23 (1.11, 1.36)	<0.001
	7am-3pm weekday	6126	1.47 (1.35, 1.60)	<0.001
Time.of.year	Not Vacation	17361	Reference	
	Vacation	2954	0.90 (0.81, 1.01)	0.064
Location	CCU	3574	Reference	
	ICU	1816	0.86 (0.75, 1.00)	0.045
	OT	399	2.58 (2.00, 3.32)	<0.001
	ED	2007	1.15 (0.99, 1.32)	0.059
	OPW/x-ray	793	0.94 (0.77, 1.16)	0.587
	CCL	1557	1.54 (1.32, 1.80)	<0.001
	SUU	117	1.01 (0.61, 1.63)	0.966
	gen_ward	9666	0.60 (0.53, 0.67)	<0.001
	other	386	1.21 (0.92, 1.59)	0.168
Hosp.by.size	0-99	1552	Reference	
	100-250	2842	1.12 (0.94, 1.34)	0.206
	251-400	5390	1.26 (1.07, 1.48)	0.006
	>400	10531	1.31 (1.10, 1.55)	0.002
Hosp.by.type	Non-Academic	12525	Reference	
	Academic	7790	1.14 (1.02, 1.27)	0.023

Figure 2: Forest plot with the adjusted ORs for 30-day survival for multiple variables. CPR: cardiopulmonary resuscitation; CCU: Cardiac Care Unit; ICU: Intensive Care Unit;OT: Operating Theatre; ED: Emergency Department; OPW/x-ray: Out-patient Ward/Radiology Department; CCL: Cardiac Catherization Lab SUU: Step Up Unit; Gen Ward: General Ward: CAT: cardiac arrest team.

4.4 PAPER IV

Paper IV included a total of 55 615 cases of OHCA identified in the SCRR database from 2010-2020. After cross-linking five registries we obtained 393 candidate predictors. The mean age was 69 years, 34% were women. 34% of patients achieved ROSC, 30-day survival was 12%, 91% of survivors had a CPC-score at discharge of 1-2. We divided the data in 3, a training data set with 60% of the data (33 370 patients), a test data set with 20% of the data (11122 patients) and an evaluation data set (11123 patients). We evaluated multiple machine learning frameworks: Extreme gradient boosting outperformed all other methods. We optimized the model until we could not observe any improvements in AUC. We next tuned the decision threshold of the model to maximize sensitivity for survival using the Youden index.

Relative predictor importance

To visually illustrate the relative importance of different predictors and predictor groups, we created relative importance plots for the top 50 predictors (figure 1A) and the predictors by group (figure 1B). The 5 most important predictors to 30-day survival were ROSC and independent breathing at the time of arrival in the ED, prehospital administration of adrenaline, initial rhythm and age. Figure 1B shows that the patients presentation in the ED, prehospital interventions and critical time intervals (time to call for the ambulance, time to CPR..) where as information regarding location of CA, comorbidity and medications were of less importance.

Tuning of prediction model
At a sensitivity of 95%, specificity was 89%, PPV 52%, NPV 99% on test data to predict 30-day survival. The UAC-ROC was 0.97% in the test data using all 393 predictors or only 10 predictors.

Best Predictors
To evaluate the added value of each predictor, we refitted the model with the 10 most important predictors, starting with the most important. After 10 predictors were added, little improvement was observed regarding model performance (figure 2).

Model performance and calibration
Figure 3 illustrates the ROC curves of the model on evaluation and test data.
Figure 4 shows the calibration curve of the final model across different survival probabilities.

Web application
To illustrate how the model and web application can be used, we created a step-by-step tutorial (see supplement S4 for example patients).

Figure 1A Relative variable importance plot: Top 50 out of 393 predictors
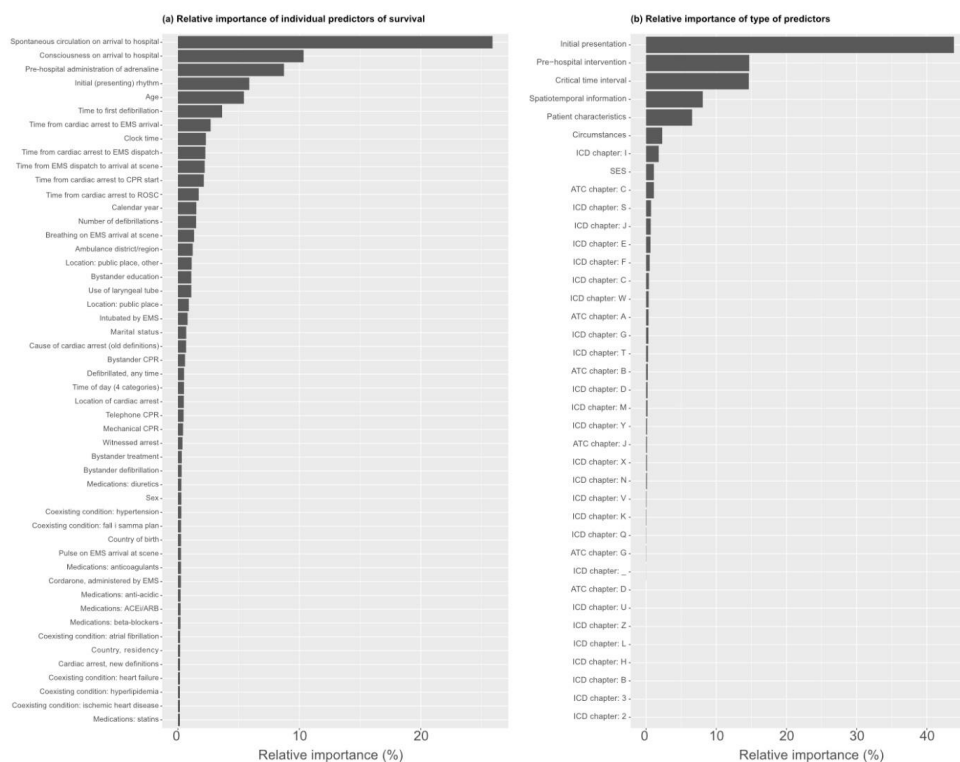Figure 1B Relative variable importance plot: Top predictors by category

Figure legend Fig. 1A: Relative variable importance plot: Top 50 predictors ranked by relative importance to 30-day survival. Abbreviations: CPR= cardiopulmonary resuscitation ACE = Angiotensin converting enzyme inhibitor ARB = Angiotensin receptor-II blocker EMS = emergency medical system

Figure legend Fig. 1B: Relative variable importance plot: 39 predictor categories ranked by relative importance to 30-day survival. Abbreviations: SOS= socioeconomic status, ICD= International classification of diseases, ATC= Anatomical, Therapeutic, Chemical classification SES = socioeconomic status. Reproduced with permission from the publisher.

Figure 2. AUC-ROC for 20 models including the top 1 to top 20 predictors of survival
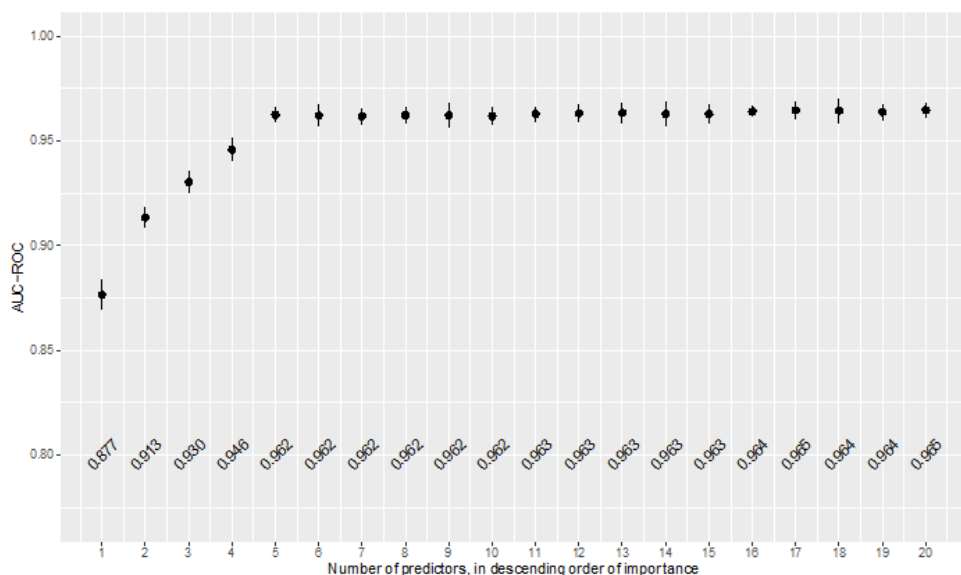
Figure legend Fig. 2: AUC-ROC with corresponding 95% confidence intervals for prediction of 30-day survival for 20 models including the top 1 to top 20 predictors of survival. Abbreviations: AUC-ROC = area under the curve receiver operating characteristic. Reproduced with permission from the publisher.

Figure 3. AUC-ROC on evaluation and test data
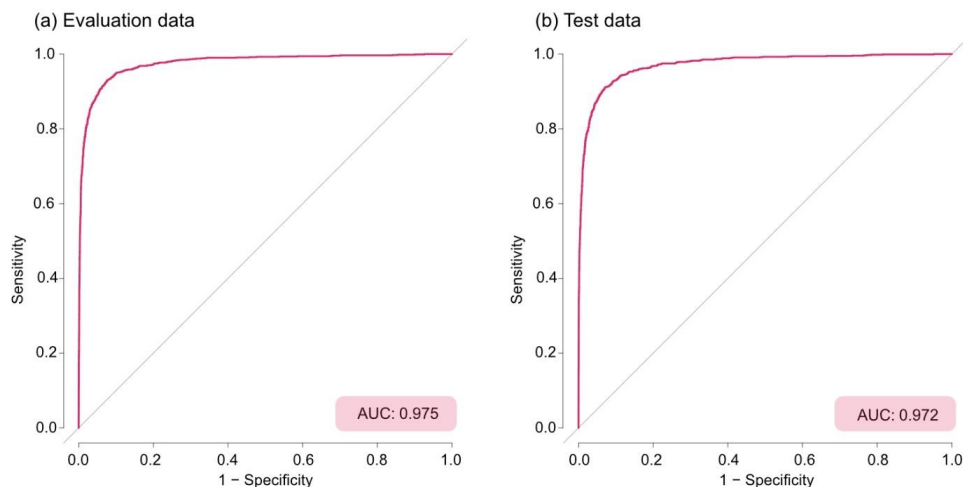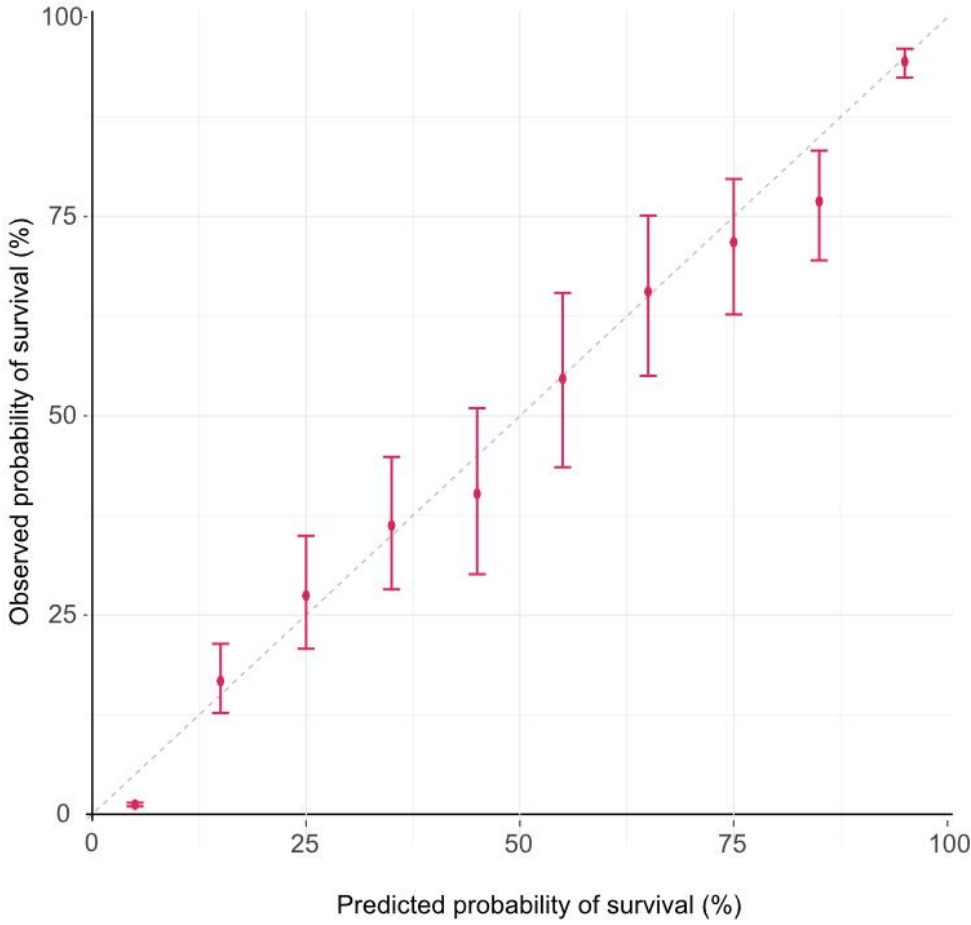

Figure legend Fig. 3: Receiver operating characteristic (ROC) curve for prediction of 30-day survival based in (a) evaluation data and (b) test data. Abbreviations: AUC-ROC = area under the curve receiver operating characteristic Reproduced with permission from the publisher.

Figure 4. Calibration curve for test data

Figure legend fig 4. The calibration plot illustrates the agreement between predicted probabilities and observed probabilities of survival with 95% CI. Reproduced with permission from the publisher.
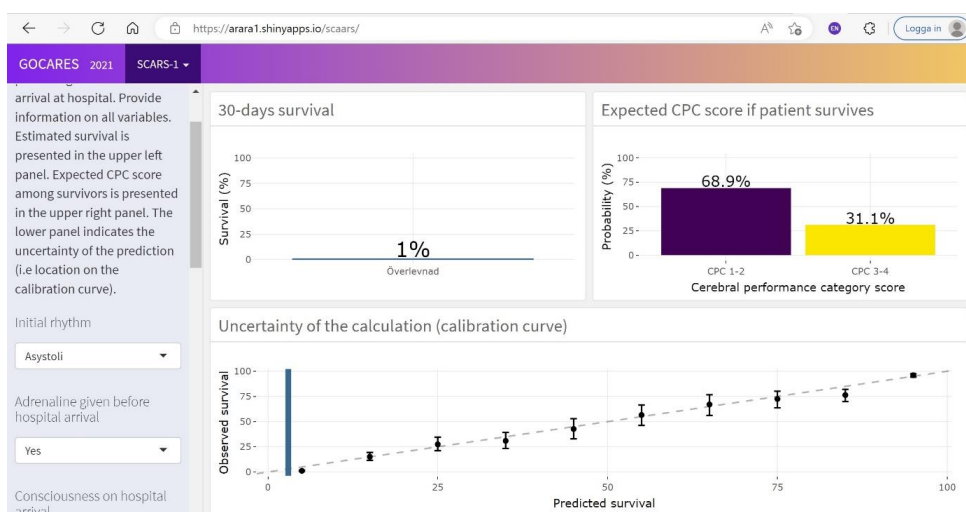
Supplemental figure S4. SCARS-1 web application

Figure S4. The screen shot shows the web application SCARS-1. By entering 8 variables regarding circumstances at resuscitation on the left of the screen, an estimation of 30-day survival and CPC-score can be generated with a corresponding calibration plot for the 30-day survival prediction. The figure is a truncated version of supplemental figure S4. Reproduced with permission from the publisher.

4.5 PAPER V

In paper V 56 203 OHCAs were included, 59% of patients had at least on cardiovascular condition and the prevalence of HT was 45%. Patients were categorized into separate groups (14.1% of patients had hypertension only, 3.9% HT and HF, 2.6% HF+IHD, 8.8% IHD, 1.7% AMI and 2.7% Diabetes and the remaining 63.1% were categorized as "other") There were small differences in-between groups, most notably were patients with any of the cardiovascular conditions older (mean age 69-79 years) than patients categorized as other (mean age 65 years) and the distribution of patients initial rhythm varied across groups with the largest proportion of patients found with pVT/VF among cases with HF and IHD (37%). The proportion of patients that survived to 30 days varied from 6.5% among patients with a HT diagnosis up to 13% among patients with IHD. Figure 1A shows that among patients with HT that experienced an OHCA, the lower the age at which time that the HT diagnosis was established, the shorter the time until OHCA. Patients that received a HT diagnosis < 41 years of age and did experience a CA did so within a median of two years where-as patients in the oldest cohort, aged >81 years, experienced a CA after on average six years. Supplementary figure 3 shows that there were no differences in adjusted ORs for 30-day survival when stratifying patients with hypertension compared to patients without HT – age, location of OHCA, initial rhythm, witnessed status, ECG-monitoring and cardiac causes of the CA were all associated with survival although ORs were consistent for patients without HT vs patients with HT. Supplemental figure 4 illustrates the importance of immediate CPR on the proportion of patients found with an initial shockable rhythm - irrespective of comorbidity group the proportion of patients with a shockable initial rhythm decreased rapidly.

Figure 1A. Time from HT diagnosis to OHCA
Fig. 1

(A) Time to cardiac arrest in hypertension

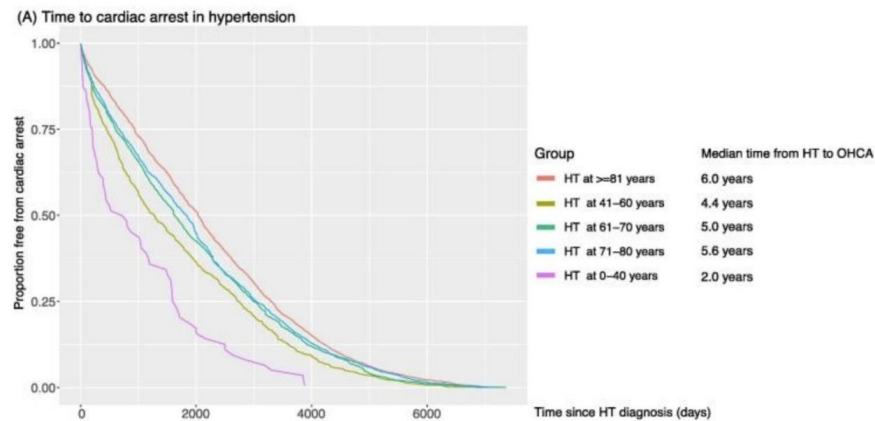| Group	Median time from HT to OHCA
HT at >=81 years	6.0 years
HT at 41–60 years	4.4 years
HT at 61–70 years	5.0 years
HT at 71–80 years	5.6 years
HT at 0–40 years	2.0 years

Figure 1A shows a Kaplan-Meier survival curve comparing the time from HT diagnosis to the time of OHCA. The lower the age at the time for HT diagnosis, the shorter the time to OHCA. The graph includes only cases with HT and OHCA. Abbreviations: HF=heart failure HT: hypertension IHD= Ischemic heart disease AMI= acute myocardial infarction CPR= cardiopulmonary resuscitation OHCA = out-of-hospital cardiac arrest. Reproduced with permission from the publisher.

Supplementary figure 3 Independent predictors of 30-day survival among patients with hypertension(red) and patients without hypertension(blue)
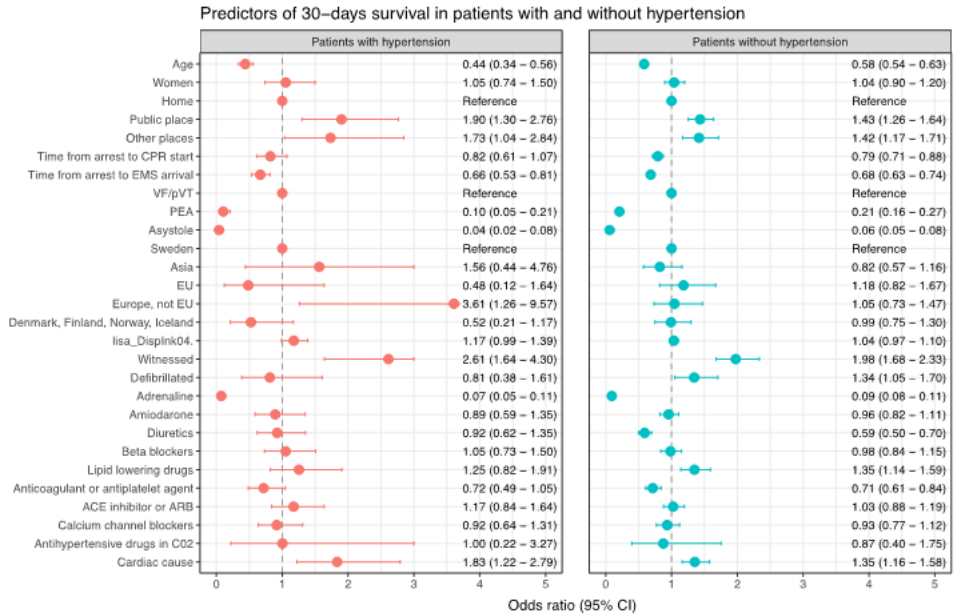

Predictors of 30-days survival in patients with and without hypertension

Figure 3. Forest Plot of adjusted ORs for 30-day survival categorized by the presence(red) or absence (blue) of a HT diagnosis. There were no significant differences regarding what variables predicted 30-day survival following OHCA depending on whether the patients had hypertension or not. Abbreviations: VF/pVT = ventricular fibrillation/pulseless ventricular tachycardia PEA= pulseless electrical activity CPR= cardiopulmonary resuscitation EU= European union lisa_Dispink = disposable income ACE = Angiotensin converting enzyme inhibitor ARB = Angiotensin receptor-II blocker. Reproduced with permission from the publisher.

Supplemental figure 4 Rates of shockable rhythm in relation to time to CPR
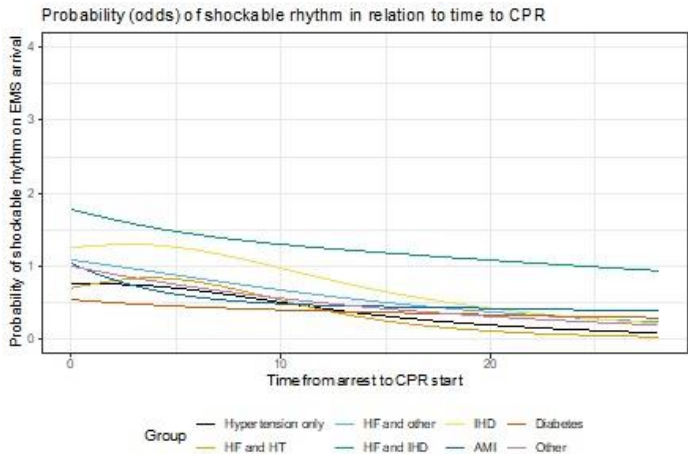
Supplemental figure 4 shows that for all groups the likelihood of a shockable initial rhythm decreased rapidly with increasing time from collapse to CPR. Abbreviations: HF=heart failure HT: hypertension IHD= Ischemic heart disease AMI= acute myocardial infarction CPR= cardiopulmonary resuscitation. Reproduced with permission from the publisher.

5. DISCUSSION

5.1 CAN WE IMPROVE SURVIVAL BY UNDERSTANDING WHICH VARIABLES ARE ASSOCIATED WITH SURVIVAL IN IHCA AND OHCA?

When discussing what can be done to improve survival, one starting point is to establish what can and can´t be modified. Some factors such as age and gender can´t be modified, but age does modify the likelihood of survival. As much as 30% of the variation in survival seen following IHCA can be explained by age (paper II), with very low survival rate among the very young (<1) and very old (>90)[80]. Survival follows a bimodal distribution as shown by Herlitz et al with peak survival rates at 10-30 years of age[209]. The results of paper I and V show that age is a marker of a worse prognosis for both IHCA and OHCA, adjusted OR for 30 day survival following IHCA 0.68 (95% CI 0.62-0.74) and 0.44 (95% CI 0.34-0.56) (patients with hypertension) - 0.58 (95% CI 0.54-0.63) (patients without hypertension) for OHCA. Whether age alone should be used as a marker of poor prognosis can be questioned – higher age is accompanied by higher prevalence of known risk factors for CA (HT, AF, stroke, AMI[210]) but also, one can speculate, with higher prevalence of residual confounders (unknown risk factors or risk factors not included in multivariable analysis). A more modern concept than chronological age is biological age – the only problem being how to define and stratify such a variable. Different frailty scales have been suggested as a method of quantifying biological age. Frailty can be described as a measure of physiological reserve but has been defined in many ways using different criteria such as cognition, grip strength, gait speed and level of independence[211]. Increasing frailty has been associated with increased OR for death or poor outcome in a number of different circumstances – in the general population[211], in the ICU[212], following surgery (coronary artery bypass grafting[213]) among patients with sars-covid-2 infection[214] and following IHCA[52]. Chronological age does no correspond to frailty[211] and age should not be used in isolation when prognosticating for CA. Although age >80 has been shown to be associated with decreased chances of survival following OHCA, among survivors the majority were discharged with a favourable neurological outcome (CPC 1-2) suggesting age does not negate resuscitation[215].

5.2 WHAT IS THE INFLUENCE OF COMORBIDITIES?

How different comorbidities interact with the chance of survival following CA is multifactorial – different conditions confer different risks and interact in different ways with other factors of importance to survival. As shown in papers I-V multiple comorbidities including heart failure, diabetes, respiratory insufficiency, malignancy, renal dysfunction and stroke are associated with decreased chance of survival following IHCA and OHCA. It's likely that different comorbidities interact with the risk of CA and chance of survival following CA in different ways. HT (often an early manifestation of cardiovascular diseases) is an established risk factor for death[216] but CA due to cardiac origin is often associated with an increased chance of survival (paper 1) an association often attributed in part to a high

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degree of shockable initial rhythm. In theory we sometimes make a clear distinction between past medical history/comorbid conditions (a history of previous AMI, current HT), ongoing disease processes at the time of the cardiac arrest and assumed aetiology of CA. In practice, what we decide is the assumed aetiology of a CA is often an educated guess – only a very small proportion of CAs (indeed of all deaths) undergo autopsy[84].

Hierlekar[53] et al and others have shown that with an increasing burden of comorbidity as measured by the Charlston comorbidity index the chance of survival after OHCA decreased in a linear fashion. Comorbidity confers an increased risk but how much is likely dependent on disease stage (level of kidney failure, level of heart failure) and how the disease process interacts with the cause of the CA. Kidney failure has been shown to increase the risk of sudden cardiac death exponentially and in a somewhat dose dependent fashion – with declining kidney function (as measured by Glomerular Filtration Rate and kidney failure stage) the risk of SCD increases[217]. There have been several studies expressing fear that patients with kidney failure receive less aggressive treatment compared to patients without kidney-failure ("renalism"[218]) and that this could explain why kidney failure patients might have lower survival rates following CA. Interestingly, Starks et al[219] showed that although patients with kidney failure received slightly less aggressive treatment compared to a matched cohort of IHCA patients without kidney failure, survival to discharge was not statistically different and their rates of ROSC and survival with favourable neurological function was better. These findings are somewhat in contrast to prior studies that indicated that as many as 17% of all IHCA occur among dialysis patients, that dialysis patients have 20 times higher risk of IHCA and that survival is lower compared to the general population[220, 221]. Perhaps the "truth" lies somewhere in-between, but the example illustrates the complex interactions between comorbidity on a population level and the influence of aetiology of cardiac arrest and outcome.

In paper 5 we investigate the influence of different manifestations of cardiovascular disease on survival following OHCA. We show that HT, DM, HF and IHD were prevalent in the OHCA population (59%) and strong predictors of mortality. As is the case with kidney failure – different manifestations of cardiovascular conditions such as HT and DM are associated with lower rates of survival but can be associated with relatively high rates of ROSC and comparable neurological outcome in cases of survival to hospital discharge. With increasing time from CA to start of CPR (no flow time) the chance of ROSC and/or return of a shockable rhythm decreased. The initial rhythm modified the chance of ROSC/survival among all comorbidity combinations – after 10 minutes of low-flow time among patients with a non-shockable initial rhythm, very few survivors were found. However, among patients with a shockable initial rhythm a significant number of survivors were noted after more than 10 minutes of low-flow time.

5.3 IS AGE AT ONSET OF COMORBID CONDITIONS ASSOCIATED WITH A MODIFIED RISK OF CA?

Early onset of a variety of conditions and habits including hypertension[222], diabetes mellitus[223, 224], Alzheimer's disease[225] and smoking[226] is associated with increased mortality and morbidity. In paper V we show that there is a graded association between the age of HT diagnosis and the time to OHCA – the lower the age at the time of HT diagnosis, the shorter the time from HT diagnosis until the event of OHCA. We know that incidence of CA increase with age with a mean age of onset of IHCA of 73 years (paper III) and 69 years for OHCA (paper IV). Receiving a diagnosis of HT at a young age is a marker of high risk and risk factors for HT should be addressed immediately. Several of the known risk factors for HT have a common denominator – they can be lumped together as lifestyle factors including smoking, exercise, obesity, diet quality and alcohol consumption[227]. Life-style factors can be addressed but numerous studies have shown that on average only 5% of US adult citizens follow all recommendations for optimal cardiovascular health[228]. Interventions to change life-style behaviours are recommended by most national and international guidelines as part of the non-pharmacological management of cardiovascular risk[229]. The evidence from association studies is overwhelming in support of life-style factors as mediators of cardiovascular health, unfortunately it´s proven difficult to show sustained effect on cardiovascular outcomes of specific life-style interventions. An RCT on life-style interventions among individuals with obesity and impaired glucose tolerance showed decreased risk of developing DM by 58% in a finish cohort with a mean duration of follow-up of 3.2 years. However, the longer the follow up, the more difficult it´s been shown to demonstrate a sustained effect even on surrogate markers of risk such as BP. A recent review[230] showed that structured life-style interventions could reduce BP, cholesterol levels and triglycerides but fell short on showing improvements in cardiovascular complications. In the case of preventing complications secondary to obesity and IGT (Impaired Glucose Tolerance), it seems that in order for an intervention such as weight loss to be effective in terms of reduced risk of DM, the reduction in weight has to be substantial AND the window of opportunity is primarily in the initial stages of diabetes development when there is still some function left to save in the β-cells of the pancreas[231]. It is likely that for interventions to reduce the risk of subsequent cardiovascular events in patients with early-onset HT, aggressive interventions should begin immediately following diagnosis. As is often the case, prevention is the best treatment.

Family and twin studies have evaluated the impact of genes on the development of HT and on a group level as much as 30-50% of the risk can be attributed to genes [232, 233]..

5.4 WHAT CAN THE PATIENT DO?

The patient can under some circumstances contribute to the early detection of deterioration by alarming the ward staff. How wards are organized (number of beds per room, no of patients per nurse, how the patient gets the attention of the ward nurse) is likely to affect how this information is transmitted from patient to nurse to physician in charge. The nurse-to-patient ratio has been shown to be associated with the over-all in-hospital survival: for every additional patient a nurse needs to attend to there is a 7 % increase in mortality[234]

5.5 CAN TRACK AND TRIGGER SYSTEMS IMPACT SURVIVAL?

Track and trigger systems usually rely on two so called limbs, one recognition (afferent) limb or early warning score (EWS) and one response (efferent) limb associated with escalation and intervention[235]. These systems have shown promising results including associations with decreased mortality[236] and lower rates of IHCA[237] but there results remain to be reproduced prospectively.

5.6 CAN INCREASES IN ADHERENCE TO RESUSCITATION GUIDELINES IMPROVE OUTCOME FOLLOWING IHCA?

In paper II we show that adherence to Swedish resuscitation guidelines was independently associated with higher survival rates for both shockable (1.84 (95% CI 1.52–2.22)) and non-shockable (1.84 (95% CI 1.52–2.22)) IHCAs. Survival increased substantially for all patients in the study 2008-2017 but adherence increased only slightly (0.73% / year for shockable rhythms and 0.81% for non-shockable rhythms). As can be seen in the relative importance plot in the supplements and figure 2A-B adherence to guidelines was important to survival (the most important modifiable factor to survival among patients with a shockable rhythm and the second most important modifiable factor among patients with a non-shockable rhythm). Adherence to guidelines did not improve much in the study period and the question is therefore if it is worthwhile striving for improvements in adherence or if we have reached a plateau or ceiling regarding adherence.

Paper II was not designed to evaluate differences in resuscitation quality metrics between hospitals. However, there is evidence to suggest that there are important inter-hospital differences in adherence to resuscitation guidelines and risk adjusted survival. Khera et al[238] studied the GWTG-registry and categorized hospitals as award-hospitals or non-award hospitals based on >85% compliance to four resuscitation quality metrics (time to chest compressions ≤1 minute; time to defibrillation ≤2 minutes; device confirmation of endotracheal tube placement; and a monitored/witnessed arrest – for at least 12 consecutive months). They found that adherence to guidelines varied between hospitals, 40% of hospitals were categorized as award-hospitals and 60% as non-award hospitals. However, after calculating Risk Standardized Survival Rates (RSSR) for each hospital they found no association between award status and survival to discharge and only a weak association with rate of ROSC. Their results raised the question whether adherence to guidelines was a valuable quality indicator or perhaps only an indicator of the performance of the hospital in the acute phase of the CA. To further understand how hospital performance impacts survival to discharge[239] Girotra et al calculated RSSR for 290 hospitals and 86426 IHCA from the GWTG-registry and evaluated if risk-standardized survival rate correlated with acute(rates of ROSC) and/or post-resuscitation (survival to discharge among patients with ROSC) survival. What they found was that hospitals with a high overall survival to discharge either had high rates of acute resuscitation survival (ROSC) or high levels of post-resuscitation survival but seldom both. There were no associations between risk-adjusted acute resuscitation and post-resuscitation survival indicating that they are two separate entities or two distinct phases of

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care. At the bottom line, there are differences in risk-adjusted survival[240] and over the course of time as many as half of hospitals in the GWTG-registry either substantially improved their performance as measured by RSSR or saw substantial decreases in RSSR[241]. Although adherence to guidelines, as defined in paper II, is only reflective of quality in the acute phase of resuscitation, there is value in measuring adherence across hospitals and over time to track progress and identify opportunities for improvement. Ideally, relevant quality metrics for the post-resuscitation phase should be investigated but this remains to be elucidated since much of post-resuscitation care is based on expert opinion rather than high-level evidence. Interventions once thought to be standard of care (targeted hypothermia) have now been shown not to improve survival following OHCA compared to targeted normothermia[50] making evidence-based quality indicators in the post-resuscitation phase more difficult to establish. There are studies that have evaluated what characterizes resuscitation teams at top performing hospitals for IHCA[242] (dedicated IHCA teams, pre-established team composition and roles, closed loop communication and regular training including mock codes) – but these factors remain difficult to measure quantitatively and therefore difficult to use as quality metrics.

5.7 HOW CAN ADHERENCE TO GUIDELINES BE IMPROVED?

Barriers to adherence to guidelines and the chain of survival
The first three links in the chain of survival: 1) Early recognition and call for help 2) Early CPR and 3) Early Defibrillation are all associated with a higher chance of survival. These factors are to a large degree modifiable and, in theory, there´s room for improvement. Guidelines state that time from CA to call for the rescue team and initiation of CPR should be within one minute and time from CA to defibrillation (when shockable rhythm) should be within three minutes. In paper II we illustrate the difference in outcome between cases where there was adherence to guidelines (ie call for the rescue team and CPR within one minute for non-shockable rhythms and ibidem in addition to defibrillation within three minutes for shockable rhythms) and cases of non-adherence to guidelines. Both 30-day survival, rates of ROSC and adjusted ORs for 30-day survival were higheramong patients treated according to guidelines. Trends over time indicated that adherence to guidelines increased slightly but the proportion of patients that were treated according to guidelines remained in the range of 70-80%. It´s difficult to tease out how many additional lives could be saved if delay times were in the recommended maximum range for all patients. One way is to simplify the association and compare the survival rate among patients treated according to guidelines vs patients not treated to guidelines, and subtract the difference for each variable (time to call for the rescue team, time to CPR and time to defibrillation) during one year. Such an estimate, although imperfect and probably an overoptimistic estimate, suggests that an additional 100(132) lives could have been saved in Sweden 2015 corresponding to a 10% increase in survival (32 vs 29% 30-day survival)[243].

Circumstances at the time of the CA
Since time to detection and treatment is crucial for outcome, factors that influence detection and treatment are key, and often modifiable. Witnessed and ECG-monitored IHCAs are

associated with short delay times and an independent association with higher odds for 30-day survival. The location of the CA is also of importance: after adjusting for covariates CA in the cardiac care unit and the cath lab are associated with increased chance of survival, where as CA in regular wards are associated with decreased survival. To a certain degree this association is explained by long delay times to detection and treatment on general wards, and very short delay times in the CCU and cath lab. ECG-monitoring all hospitalized patients would in theory lead to decreases in delay times to detection of CA, but it would on the other end require a lot of resources in terms of monitoring equipment, education of staff and more staff to attend to monitors. Not to mention the number of "false" alarms due to technical errors and the potential for patient harm due to screening of unselected patients.

Should all patients have continuous in-hospital ECG-monitoring?
According to current guidelines from the American heart association[244, 245] patients can be categorized depending on the likelihood that they will benefit from ECG-monitoring: will likely benefit, may benefit and unlikely to benefit. Based on these guidelines' patients with a primary cardiac diagnosis including acute coronary syndrome, arrhythmia and post cardiothoracic surgery were considered most likely to benefit. However, several other factors influence the decision to ECG-monitor a patient: availability, non-cardiac diagnosis, fear of haemodynamic instability or general deterioration etc. A US study[246] evaluated the use of continuous ECG-monitoring in a community hospital non-ICU setting and found that almost 50% of continuous ECG-monitoring was not indicated according to guidelines. They also found that the number of arrhythmic events among hospitalized patients where telemetry was "indicated" was 15-fold higher compared to patients where telemetry use was "not indicated". The study conclusion was that telemetry use probably wasn't optimal.

Ultimately the decision comes down to the trade-off between benefit and harm: ECG-monitoring can detect arrhythmias and survey ischemia but it also leads to alarm fatigue, it is costly and lacks specificity[247]. Patients in the ICU are routinely monitored with continuous ECG, as is the case in the post operative unit. Certain conditions are known to carry a higher risk of both less malign (atrial flutter/fibrillation) and very malign arrhythmias(pVT/VF) such as sepsis, but ECG-monitoring this specific patient population was not associated with a survival benefit[248].

There is robust evidence to suggest that in case of IHCA, patients under continuous ECG-monitoring fare better than patients without ECG-monitoring[249, 250]. How we select which patients to monitor should primarily be influenced by how likely they are to benefit, but other factors such as availability and physician preference likely also contribute[251]. Increased use of telemetry could potentially decreased IHCA mortality, but at a prize that society currently is not willing to pay. It is possible that alternative solutions such as photoplethysmography (PPG) could offer an alternative: Continuous measurement of variables such as oxygen saturation, heart rate, blood pressure and cardiac output can be derived from a PPG[252]. PPG is less costly and intrusive than conventional continuous ECG-monitoring and is currently being evaluated for screening of heart conditions, mainly atrial fibrillation[253]. It is possible

that future advances will combine the detection of arrhythmias with a PPG with an external automatic defibrillator and thus minimize the time to detection of CA and defibrillation.

5.8 SHOULD ALL PATIENTS BE ADMITTED TO HIGH-RESOURCE WARDS?

Patients that suffer an IHCA in high-resource wards such as the CCU, cath lab, ICU and post op unit have shorter delay times from CA to CPR and defibrillation, and also higher chances of survival when adjusting for covariates of importance (CCU and cath lab)[19, 80]. It is likely that time to detection and treatment can explain some of the difference in survival between general wards and high-recourse wards. ECG-monitoring is also more common in high-resource wards. Witnessed IHCAs have better outcomes than unwitnessed IHCAs and it is likely that factors such as staff density can have an influence. Staffing is generally higher in high-resource wards and the nurse-to-patient ratio has been shown to be associated with mortality – for every additional patient added to the work load of one nurse above 1:8 an additional 7% increase in mortality can be observed[234]. It is also often the case that high-resource wards have more single-bed units and multi-bed units generally have fewer beds per unit compared to general wards. If this has an impact on detection of patient deterioration is not known. It´s likely that the higher degree of patient monitoring in high resource wards (telemetry, continuous photoplethysmography) and the higher staff density mitigates any negative effect that single bedrooms might have. Whether single vs multi- occupancy patient rooms (SPR vs MPR) have any substantial effect on patient outcomes is not known. Since 2006 there´s a requirement in US-hospitals for SPRs, in part based on a review article by Chaudhury et al[254] that had a high impact. Since then, another influential review has been written[255]. Pros and Cons are listed; the level of evidence was mixed but there seemed to be more advantages (less infections, less noise, preferred by patients) than disadvantages(isolation) and no robust evidence of patient harm. However, the impact single-occupancy bedrooms might have on detection of very sudden deterioration of the unmonitored patient is not addressed and it is possible that there could be disadvantage inherent when isolating patients. For every hour of delay for the transfer of a patient from a general ward to the ICU there´s a 1.5% increase in ICU-mortality and 1% increase in hospital mortality[256]. It is likely that improved remote monitoring can balance the risks of intermittent observations and checks of vital signs.

5.9 DOES TIME OF CA MATTER?

The circadian rhythm is known to influence both physiological and pathological functions of several organ systems including the cardiovascular[257], respiratory[258] and GI-system[259]. The central clock of the body is thought to be located in the suprachiasmatic nucleus in the hypothalamus. The central clock interacts with peripheral clocks in many different organ systems of the body and regulate gene expression and induce changes in the autonomic nervous system and endocrine systems. The interactions are complex and have not been fully elucidated: different systems seem to be at work since different physiological processes vary differently over the course of the day (blood pressure, heart rate, respiratory

rate) and different pathological conditions have different peaks and nadirs. Acute myocardial infarctions and pulmonary embolisms incidence peaks in the early morning.

As presented in the supplemental fig 2 of paper III, both incidence and survival following IHCA varied by time of day, day of the week and month of the year. We chose to divide the week in three time categories to reflect the variation in staffing and experience of staff on call . As could be expected, we found a graded association between the time of IHCA and 30-day survival with IHCA during the "daytime" showing the highest rates of survival. We hypothesized that the "time factor" would be more pronounced with less staff, lower levels of ECG-monitoring and in hospitals with, presumably, greater decreases in staff competence from the daytime to the evening (smaller hospitals and non-academic centres) and our results were consistent with our hypothesis.IHCA during the day vs the evening vs the night were also associated with lower degrees of witnessed Cas, more asystole as the initial rhythm and longer delay times to defibrillation.

The results of paper III clearly demonstrate what experience might suggest – with smaller staff and less expertise comes worse outcomes following CA. The question comes down to deciding how many lives not saved are acceptable while balancing a workforce that is already both too small and, in some cases, lacking competence. How large declines in survival from day to evening to night can be considered acceptable – 10%? 20%? 30%? And at what cost? Forcing nurses and physicians to work double shifts would on paper increase both staff and competence during the night, but with the added risk of burn-out and even worse staffing problems at the end of the line.

How organizational factors affect the chance of surviving a critical condition is of course a question of resources and resource allocation. We know a priori that unmonitored patients will fare worse than monitored patients, but we choose to accept it. Our gut feeling might suggest that one nurse/24 geriatric patients on an orthogeriatric ward might not quiet be what we are aiming at when we discuss the virtues of patient safety, but we accept it. Where we draw the line (90 year old with DM2 and HF too sick and old to benefit from ECG-monitoring in NSTEMI?) is a question of priorities (and politics). As this is not a sociology thesis, digressing into politics is out of the scope of this discussion. But we can state the facts- Sweden has fewer ICU beds per 100000 inhabitants than almost all comparable western countries (5 ICU beds/100000 inhabitants according to a 2019 report[260]). It is difficult to see why Sweden needs 2-3 fewer ICU-beds/100000 compared to neighbouring Denmark and Norway, well below the OECD average of 12 and far behind Germany at 34 ICU beds/10000 inhabitants[261]. The same goes for the chronic lack of nurses and nurse assistants in the Swedish health care system – study after study show that when the nurse to patient ratio passes a certain threshold, [234] some studies suggesting <1 nurse per 8 patients, mortality starts to increase. A higher nurse work burden per patient was associated with longer length of stay, higher rates of urinary tract infections and pneumonia, higher rates of shock/cardiac arrest and "failure to rescue" in 799 hospitals in the US[262]. Considering what we have known since the 1990s – that many critical conditions including CA are preceded by

alterations in vital parameters,[263] it is only a short leap of faith into believing that better monitoring and more staff in the in-hospital setting could improve CA outcome.

5.10 CAN AND SHOULD WE PREDICT SURVIVAL DURING ONGOING CPR?

As we show in paper IV, the SCARS-1 model showed remarkable performance with an AUC-ROC of 0.97 with an excellent calibration curve indicating that survival at 30 days following OHCA can be predicted in the ED during ongoing CPR. Before the prediction model is ready for prime time, a few questions remain to be answered.

5.11 IS IT POSSIBLE TO USE THE WEB APPLICATION DURING ONGOING CPR IN THE ED?

The web application requires 10 items of which 2 are entered automatically (time of day and calendar year). The remaining 8 variables can be divided in 2 categories: 6 that are routinely collected prehospitally (initial rhythm, adrenaline, age, time to start of CPR, time to EMS arrival, number of defibrillations) and 2 (ROSC or consciousness at arrival in the ED) that can quickly be entered upon arrival in the ED. The physician can open the SCARS-1 app and enter what data is available before admission to the ED, or instruct a colleague (scribe, nurse assistant) to do it. When the ED is notified by the EMS that there is an incoming OHCA, a few pieces of information are often included regarding the circumstances of the OHCA – witnessed status, bystander CPR, initial rhythm. During handover in the ER the EMS nurse reiterates what is known and relevant regarding the resuscitation, and the final pieces of information can be recorded. The resuscitation efforts in the initial stages following arrival in the ER should be focused on the patient and not adjuncts such as the SCARS-1 app. When the code is progressing as planned and the basics of ACLS are functioning, the physicians in charge of the patient can focus on reversible causes, next steps, calling for certain expertise or considering alternative treatments. The team can, with the help of the SCARS-1 app, within 30 seconds get an estimation of the chance of 30-day survival and CPC-score the patient had upon admission.

5.12 WHEN CAN THE APPLICATION BE USED?

The application includes data that needs to be collected upon admission to the ED and therefore cannot be used before hospital admission. Patients that have had ROSC and/or have regained consciousness should not be considered for the application since these patients, with very few exceptions, should be triaged to the appropriate level of care (ICU, CCU, medical ward, OR, CCL).

5.13 HOW CAN THE APPLICATION BE USED?

The SCARS-1 prediction model was developed and optimized to detect survivors. As can be seen on the calibration curve, the predictions have the smallest deviations between expected and observed survival probabilities in the very low and very high probabilities. During

ongoing CPR the treatment of the patient progresses in tandem with thoughts regarding the prognosis of the patient – what was the patients status before CA, what had happened up to admission to the ED and what happened in the ED? Information of different sources (and reliability) are consciously or subconsciously integrated with personal experiences of the resuscitation team. It has been shown in different settings that estimation of prognosis is difficult – estimates are often inaccurate, vary between observers and have been known to deviate up to a factor of 3-5. To test how well physicians could predict survival following OHCA, we presented 17 colleagues with four OHCA scenarios and gave them the same information as was entered in the SCARS-1 web application. Estimates varied up to a factor of three from both the SCARS-1 estimate and in-between individual physicians. A calibration of survival probabilities did seem to be of value. Survival probabilities (very high or very low) and predictions of especially poor neurological outcome can be of value when considering pros and cons of continued resuscitation.

5.14 ARE THE RESULTS RELIABLE?

As reported in paper IV, a large number of different models and research methods were evaluated to find the best possible model to predict survival. Data from 10 years covering a entire nation was aggregated and more than 55´000 patients and almost 400 candidate predictors included. Data was divided in three chunks, 60% of data was used to train the model, 20% of data was used to evaluate the performance of the model and optimize it and the remaining 20 % of data was used to test the performance of the model. As measured by the ROC-AUC a performance of 0.97 is unusually high and indicates that the model can be trusted to classify survival vs death.

5.15 REGISTRY DATA AS A SOURCE OF INFORMATION?

If we establish that we can trust the model to describe and predict the data it has been built with, the next question would be: can we trust the underlying data? The SCRR is a national quality registry and has worked as a role model for many CA registries since the first CA was included. The first scientific publication based in the registry was published in 1994 and the first doctoral thesis published in the year 2000. Several of the publications based on the SCRR have ended up in international guidelines including the importance of bystander CPR([57]), comparisons of chest compressions only CPR vs standard CPR for OHCA[264] and the impact of mobile phone dispatch of laypersons in OHCA[265]. As of 2021 the registry covers all EMS-systems and hospitals in Sweden, so the internal validity of the data is out of the question. Some of the variables reported in the registry are notoriously prone to error: variables of the nature "time to" are imprecise and especially in the prehospital setting when we must rely on laypersons to approximate, for example, the time from CA to CPR. To not include "time to"-variables would mean losing many opportunities since these very variables have been shown to be of great importance to survival[109, 266], repeatedly and from different regions and settings. We should strive to improve the precision and reliability of all variables especially those that might be prone to error. As imperfect as the current state of affairs is, it's the best we have got.

5.16 HOW SHOULD THE RESULTS OF THE MODEL BE INTERPRETED?

The prediction can calibrate the beliefs of the treating clinicians with a calculated historical survival probability. In cases where the benefits of resuscitation can be questioned, survival rates higher than expected could tilt the physicians in favour of prolonged resuscitation efforts where-as very low survival probabilities could encourage the clinician to consider medical futility. Even without prediction models, we integrate and weigh a myriad of variables against each other to inform and guide in the decision to continue or terminate resuscitation. A well-built prediction model can possibly be of value in the same way as some guidelines – offering some valuable information to be taken into account with all other available sources of information.

5.17 WHAT ARE THE DANGERS OF "ABUSING" A PREDICTION MODEL?

There are obvious risks with overreliance on guidelines and prediction models. As expressed in the BMJ in 1999[267], guidelines have the potential of optimizing treatment by promoting evidence-based treatment and discouraging ineffective treatments. For society, the benefits can be great especially on a macro level – by focusing resources on treatments founded on a solid base and avoiding treatment that don't work, scarce resources can be saved. The flip side of the coin is that guidelines need to be relatively broad in scope and therefor need to be interpreted and individualized – they cannot cover all aspects of care and may not fit every patient. What evidence base guidelines are based on may also vary, thus the need to regularly check the quality and validity of guidelines.

Prediction models run the risk of creating self-fulfilling prophecies (SFPs) – if our guidelines or models predict a bad outcome, we are less likely to offer all treatments available and more likely to establish treatment limitations and thus the outcome becomes worse. The perils of SFPs were elegantly summarized by De Arteaga and Elmer[268]. The authors reviewed the existing literature and summarized and synthetized four key mechanisms by which ML-derived prediction models may produce SFPs. Firstly, we as humans have often made up our minds about a specific patient's prognosis and more or less subconsciously treat patients we believe unlikely to survive less aggressively (for example, transfer to ICU following CA, less intensive nursing etc.) Prediction models trained to predict outcomes based on available data (that was influenced by our beliefs about prognosis) will identify and predict that the decisions not to transfer a patient will be associated with a worse outcome. A large portion of humility regarding our abilities both as clinicians and the performance of prediction models could possible balance some of the negative effects of this firsts mechanism of generating SFPs.

Secondly, how we as humans interact with the prediction of ML algorithms (or any prediction tool) risk reinforcing and augmenting the impact of the prediction tool. PM that are affected by past decisions run the risk of reinforcing associations if followed to the letter. The authors exemplify this by simulating how many excess deaths would happen if we blindly follow

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TOR rules when the probability of survival is < 5 %. If we terminate resuscitation when the probability of survival (POS) is < 5%, each year when the model is updated with the previous years CA cases, the time to <5% survival will decrease and the TOR rule will thus recommend termination of resuscitation earlier for each update of the model.

Thirdly, errors in prediction models risk affecting survival negatively for certain patient categories, and following recalibration run the risk of increasing the error. If the model erroneously predicts that patients with no ROSC in the ED will have a poor outcome, some clinicians will be tempted to terminate resuscitation if the patients with OHCA is admitted to the ED without ROSC. When we recalibrate the model, the outcome will be even worse for patients with no ROSC in the ED and the algorithmic association between a poor outcome and no ROSC will be even greater. A typical example of a SFP!

Lastly, prediction models that are not updated in the face of medical progress risk underestimating the chance of a positive outcome. The authors exemplify with the case of ischaemic stroke: 20 years ago treatment options were limited and thrombolysis was only offered to a few patients within a limited time frame. With time, the time window increased and additional treatments such as endovascular minimally invasive thrombectomy can now be offered to many patients. The prognosis has improved. The model needs to be retrained but we also need to update and deviate from existing guidelines – otherwise the SFP will prevail.

5.18 CAN WE TRUST AI?

As outlined above, AI holds the promise of revolutionizing medicine as we know it. By handling enormous amounts of data and complex interactions no human could handle, possibly automatically as the data is recorded, we might be on the brink of a second industrial revolution, the AI revolution. That being said, predictions about the future are known to be wrong: we still don't have flying cars and humanity still exists despite the fact that the end of the world has been predicted and postponed many times. ML-derived predictions should be used and interpreted critically as should all other sources of information. It's natural to be sceptical of new technologies, however its also the case that "traditional" statistics is no panacea to correct predictions. Standardization is probably a good thing; complying with guidelines such as STROBE (STrengthening the Reporting of Observational studies in Epidemiology) is mandated by many journals. Likewise, guidelines are emerging regarding prediction studies (Transparent reporting of a multivariable prediction model for individual prognosis of diagnosis (TRIPOD)) and on the way regarding ML-derived prediction studies (AI-TRIPOD). As famously stated by statistician George E. P. Box "Essentially, all models are wrong, but some are useful"[269]. Meta-research investigating interactions between ML-derived prediction models and clinicians is an emerging area of research that will be crucial if we are to understand how we should build and use prediction models and how prediction models change the outcome they are built to predict[268].

6. CONCLUSIONS

I)   The patient's comorbidity, the aetiology of the CA and the degree of monitoring are factors that are associated with the chance of survival following IHCA.

II)   Adherence to resuscitation guidelines is associated with increased odds of 30-day survival following IHCA.

III)   Patients suffering an IHCA have the highest chance of survival during the day, and the chance of survival decreases from day to evening to night.

IV)   IHCA survival decreases more when comparing the day vs the night in small hospitals, non-academic hospitals and on wards with no ECG-monitoring suggesting inequality of CA care.

V)   The SCARS-1 prediction model and web application can predict survival following OHCA in the ED rapidly and with high accuracy.

VI)   Hypertension is common among patients that suffer an OHCA and hypertension in combination with heart failure or a young age at the onset of hypertension is especially unfavourable.

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9. ORIGINAL PUBLICATIONS