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SURVIVAL AFTER DIFFERENT FORMS OF BYSTANDER CARDIOPULMONARY RESUSCITATION IN OUT-OF-HOSPITAL CARDIAC ARREST

“TO BREATHE OR NOT TO BREATHE?”

Gabriel Riva



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Survival after different forms of bystander cardiopulmonary resuscitation in out-of-hospital cardiac arrest

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“Absence of evidence is not evidence of absence”

Carl Sagan

ABSTRACT

Background: Out-of-hospital cardiac arrest (OHCA) affects more than 6000 people per year in Sweden and only one in ten survive. One of the most important modifiable factors determining survival is early cardiopulmonary resuscitation (CPR), but different forms of CPR and their association with survival remain inadequately studied. The overall aim of this thesis was to assess the association between different forms of CPR prior to Emergency Medical Services (EMS) arrival and survival in OHCA.

Methods: All patients were EMS treated OHCA reported to the Swedish register for cardiopulmonary resuscitation. Study I-III are register based observational cohort studies. Study IV is a feasibility study of a national, investigator-initiated, multicentre, randomized clinical trial (RCT) comparing survival after dispatcher instructions of standard CPR (S-CPR) with compressions and rescue breaths vs of compressions only (CO-CPR) to trained bystanders in OHCA (TANGO2),

Specific study Aims and Results: In *Study I* we assessed survival after CPR prior to EMS arrival compared to no CPR prior to EMS arrival. Witnessed OHCA in 1990-2011 were included (N = 30 381). CPR prior to EMS arrival was performed in 51 % of all cases. Survival to 30 days was 10.5 % for patients receiving CPR and 4.0 % when CPR was not performed, odds ratio (OR) 2.80 (95 % CI, 2.47 – 3.18), adjusted OR 2.15 (95 % CI, 1.88 – 2.45). The association with survival was greater when the time to the initiation of CPR was short.

In *Study II* we aimed to describe temporal changes in CPR rates and type of CPR prior to EMS arrival and survival in relation to three time periods of different CPR guidelines in Sweden. Witnessed OHCA in 2000 – 2017 (N = 30 455) were divided into groups reflecting guideline periods (2000 – 2005, 2006 – 2010, 2011 – 2017). Exposure was no CPR, S-CPR or CO-CPR. The proportions of patients receiving CPR prior to EMS arrival changed from 40.8 % to 68.2 % and CO-CPR changed from 5.4 % to 30.1 % between the first and the last guideline period. Adjusted OR for 30-day survival was 2.6 (95 % CI, 2.4–2.9) for S-CPR and 2.0 (95 % CI, 1.8–2.3) for CO-CPR, in comparison with no CPR. S-CPR was superior to CO-CPR (adjusted OR, 1.2; 95 % CI, 1.1–1.4).

In *Study III* we aimed to assess survival after CPR with dispatcher instructions compared with no CPR and spontaneously initiated CPR. Lay-bystander witnessed OHCA in 2011 – 2017 were included (N = 15 471). Propensity score matched cohort were used for comparison. Using dispatcher assisted-CPR as reference, spontaneously initiated CPR was associated with higher survival, OR 1.21 (95 % CI, 1.05–1.39) and no CPR with lower survival, OR 0.61 (95 % CI, 0.52–0.72).

In *Study IV* we aimed to assess feasibility and intermediate clinical outcomes in the TANGO2 trial. From Jan 1st to Dec 31st, 2017, a total of 729 emergency calls of suspected OHCA were randomized and 381 (51.4 %) of these were EMS treated OHCA, 185 (48.6%) were assigned to S-CPR and 196 (51.4%) to CO-CPR. CPR instructions were provided in 89.3 % of all calls

and CPR was initiated in 93.4 % of all calls. Median time to CPR instructions was 210 s in the S-CPR group (IQR 140 – 301) and 180 s in the CO-CPR group (IQR 135 – 275), this time difference was not significant (NS). Cross-over from the S-CPR group to CO-CPR instructions was found in 22.3 % (40 calls), and from the CO-CPR group to S-CPR instructions in 16.1 % (30 calls). The number of patients surviving to hospital admission were 17.3% (n = 32) versus 20.4% (n = 40) for S-CPR and CO-CPR respectively (NS).

Conclusions: The current studies confirm the independent association between CPR prior to EMS arrival and survival in OHCA, irrespectively if CPR was performed with compressions and ventilation, compressions only or with dispatcher assistance. There was an almost doubled rate of CPR prior to EMS arrival in Sweden between 1990 – 2017 and a concomitant 6-fold increase in the rate of CO-CPR between 2000 – 2017. The pilot study of the TANGO2 trial was found to be feasible and safe. However, cross-over was found as a limitation.

PRELUDE

Out-of-hospital cardiac arrests is sudden and for the majority of victims difficult to prevent and predict. It affects more than 6 000 people every year in Sweden and only one in ten survive. It is a condition with heterogenous etiology, but underlying cardiac disease is the most common cause.

Once it has occurred the chance of survival is dependent on swift and efficient interventions by witnesses and a coordinated emergency medical response.

Cardiopulmonary resuscitation (CPR) performed before arrival of the ambulance is one of the strongest predictors of survival. This treatment is commonly performed by witnesses to the event, often a relative, partner, friend, colleague or a stranger. Many people might have limited training and little experience of this kind of situation. Nevertheless, their interventions can be lifesaving.

In 1983 the Swedish Society of Cardiology proposed their first standardized CPR training program. This was done under the supervision of Dr Stig Holmberg.¹ The aim was to disseminate CPR knowledge to the general population. Since then, an estimated 5 million attendees have been registered at basic CPR courses in Sweden.²

This work is a tribute to that movement and to the more than 20 000 bystanders, hidden behind the numbers, saving lives.

LIST OF SCIENTIFIC PAPERS

This thesis is based on the following studies which will be referred to by their roman numerals

- I. Hasselqvist-Ax I, Riva G, Herlitz J, Rosenqvist M, Hollenberg J, Nordberg P, Ringh M, Jonsson M, Axelsson C, Lindqvist J, Karlsson T, Svensson L.

Early Cardiopulmonary Resuscitation in out-of-hospital cardiac arrest

New England Journal of Medicine. 2015; 372: 2307–2315

- II. Riva G, Ringh M, Jonsson M, Svensson L, Herlitz J, Claesson A, Djärv T, Nordberg P, Forsberg S, Rubertsson S, Nord A, Rosenqvist M, Hollenberg J.

Survival in out-of-hospital cardiac arrest after standard cardiopulmonary resuscitation or chest compression-only before arrival of emergency medical services

Circulation. 2019;139:2600–2609

- III. Riva G, Jonsson M, Ringh M, Claesson A, Djärv T, Forsberg S, Nordberg P, Rubertsson S, Rawshani A, Nord A, Hollenberg J.

Survival after dispatcher-assisted cardiopulmonary resuscitation in out-of-hospital cardiac arrest – a nationwide observational study

Submitted

- IV. Riva G, Ringh M, Jonsson M, Claesson A, Nord A, Rubertsson S, Blomberg H, Nordberg P, Forsberg S, Hollenberg J.

Compression-only or Standard Cardiopulmonary Resuscitation for Trained Bystanders in Out-of-Hospital Cardiac Arrest – A Nationwide Randomized PILOT study

Manuscript

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LIST OF ABBREVIATIONS

AED	Automated External Defibrillator
AHA	American Heart Association
ALS	Advanced Life Support
BLS	Basic Life Support
CI	Confidence Interval
CO-CPR	Compression-only Cardiopulmonary Resuscitation
CPC	Cerebral Performance Category
CPP	Coronary Perfusion Pressure
CPR	Cardiopulmonary Resuscitation
DA-CPR	Dispatcher assisted CPR
ECG	Electrocardiography
EMS	Emergency Medical Services
ERC	European Resuscitation Council
ETI	Endotracheal Intubation
ICD	Implantable Cardioverter Defibrillator
ILCOR	International Liaison Committee on Resuscitation
ITT	Intention To Treat
IQR	Interquartile Range
mRS	modified Ranking Scale
NS	Not Significant
OHCA	Out-of-Hospital Cardiac Arrest
OR	Odds Ratio
PEA	Pulseless Electrical Activity
PP	Per Protocol
PPV	Positive Pressure Ventilation
PROM	Patient Reported Outcome Measurements
RCT	Randomized Controlled Trial
ROSC	Return Of Spontaneous Circulation
S-CPR	Standard CPR

SCD	Sudden Cardiac Death
SRCR	Swedish Register for Cardiopulmonary Resuscitation
TEE	Transesophageal Ecography
TTM	Targeted Temperature Management
VF	Ventricular Fibrillation
VT	Ventricular Tachycardia

1 BACKGROUND

1.1 HISTORICAL GLANCE

One of the first reports of chest compressions as a way of supporting circulation was “Resuscitation technique following cardiac death after inhalation of chloroform” by Dr Friedrich Maas in 1892.³ Dr Maas was a student of the famous surgeon Dr Franz Koenig at the University Hospital of Göttingen, Germany, who in 1883 developed a technique for treating the dreaded “chloroform syncope”. The technique consisted of compressing the xiphoid and costal margins at the rate of respiration, as a form of assisted ventilation.

Dr Maas described a nine-year old boy who became unresponsive with no pulse or breathing after chloroform anesthesia. Dr Koenig’s technique was started, but as the boy did not show any sign of improvement Dr Maas started to compress faster. He then noticed that the compressions produced a palpable carotid pulse. Dr Maas suggested that fast chest compressions could support circulation.³ However, this discovery appears not to have spread outside Germany.⁴ In 1901 the first open chest “cardiac massage” was performed in Tromsø, Norway, and attention shifted to open cardiac massage for nearly 70 years.

In 1958 Kouwenhoven, Knickerbocker and Jude made an accidental discovery while performing experimental studies on defibrillation in anesthetized dogs. They found that firm application of the defibrillation pads on the thorax could produce a femoral pulse. After further experiments they concluded that manual compressions over the sternum could induce a circulation and prolong the time window for successful defibrillation. Shortly afterwards, Jude successfully applied this technique in a patient with cardiac arrest following anesthesia. In 1960 they reported 20 in-hospital cardiac arrest treated by means of closed cardiac chest massage, of whom 14 survived. They stated: “Anyone, anywhere, can initiate cardiac resuscitative procedures. All that is needed is two hands”.^{5,6}

Successful resuscitation by means of mouth-to-mouth ventilation was described by the Scottish surgeon William Tossach in 1744.¹ Although the method was recommended and used successfully during the eighteenth century, other techniques to assist ventilation such as applying external pressure to the thorax or tilting the body gradually attained more attention and the mouth-to-mouth (or mouth-to-nose) technique was almost forgotten.¹ In 1946, during a Minnesota polio outbreak Dr James Elam successfully performed mouth-to-nose breathing on a boy with acute bulbar poliomyelitis. He went on to prove that expired air was sufficient for adequate oxygenation by blowing into the tracheal tube of postoperative surgical patients in 1954.⁷ James Elan met with Dr Peter Safar and together they performed compelling experiments on anesthetized paralyzed human volunteers. By

1957 they concluded that by tilting a person's head backwards, most will have an open airway, external chest compression is not enough for adequate ventilation in contrast to mouth-to-mouth breathing and that this technique can be used for resuscitation.⁸ In 1958 the method was endorsed by the American Medical Association.⁹

At the Maryland Medical Society meeting on the 16 of September 1960, Kouwenhoven, Jude and Safar presented their findings, connecting chest compressions with mouth-to-mouth breathing, and creating the concept of cardiopulmonary resuscitation (CPR) as we know it today.¹⁰

1.2 DEFINITION

A cardiac arrest is usually a sudden event and if not treated death is inevitable. Several definitions of the condition exist and are to some extent overlapping. An international consensus workgroup has defined cardiac arrest as *“the cessation of cardiac mechanical activity as confirmed by the absence of signs of circulation”*.¹¹

An out-of-hospital cardiac arrest (OHCA) is such an event occurring outside of hospital. If fatal, the term Sudden Death (SD) is defined by the European Society of Cardiology as a *“non-traumatic, unexpected fatal event occurring within 1 hour of the onset of symptoms in an apparently healthy subject. If death is not witnessed, the definition applies when the victim was in good health 24 hours before the event”*. Sudden cardiac death (SCD) is used when a cardiac condition was known to be present during life, or autopsy revealed a cardiac or vascular anomaly, or no obvious extra-cardiac causes have been identified.¹²

1.3 INCIDENCE

OHCA is a major cause of death worldwide. It is estimated that a total of 275 000 people in Europe and 180 000 in the US suffers from OHCA treated with resuscitation attempts by the Emergency Medical Services (EMS) each year, with an overall survival rate of 7-10 %.¹³⁻¹⁵

However, exactly how OHCA contribute to the burden of public health is unknown. Reported incidences vary widely between and within countries.^{13,16,17} This may reflect true regional variances due to differences in population risk factors and socioeconomic factors. But it may also be a result of differences in reporting, organization of EMS systems and epidemiological methods. Also, not all OHCA are treated by the EMS. This could be because of ethical reasons, “do not resuscitate orders” as well as cultural reasons.

In the European Cardiac Arrest Register, a report of cardiac arrests in 27 European countries in one month, revealed an overall incidence of EMS assessed OHCA of 81/100 000 and EMS treated OHCA of 47/100 000 (varying from 19 to 104) with an overall survival to hospital discharge of 10.3 %.¹⁷ In Sweden the reported incidence of EMS treated OHCA in 2011 was 52/100 000, with an overall survival to 30-days of 10.7 % in 2011.¹⁸

In 1990 a meeting to establish a system for coherent reporting in resuscitation was held in Utstein abbey, Norway, giving rise to the “Utstein style” templates.¹⁹ These offer a base of uniform definitions and suggest core data elements to collect, enabling comparison, quality improvement and research.^{11,20} These templates have been widely adopted in resuscitation registries globally.^{17,21-24}

1.4 ETIOLOGY

The clinical manifestation of OHCA can arise from numerous conditions ultimately leading to reduced cardiac output and cardiac arrest. These can be divided into medical and non-medical (external) causes.²⁰ Medical causes can be further divided into cardiac and non-cardiac causes. (Table 1)

Cardiac disease is the predominant cause, estimated to account for 2/3 of all OHCA.²⁵⁻²⁷ However, the determination of the exact cause of a cardiac arrest is difficult, especially in an out-of-hospital setting. Furthermore, information on comorbidities and symptoms prior to the cardiac arrest is often missing. The gold standard for assessing cause of death is autopsy, but far from all patients suffering a fatal cardiac arrest will undergo this investigation.^{28,29}

According to current definitions a OHCA can be presumed to be of cardiac etiology unless it is likely to be caused by trauma, submersion, drug overdose, asphyxia, exsanguination or any other non-cardiac cause as best determined by rescuers.¹¹ Therefore, EMS reports might overestimate the proportion of cardiac etiology.

In a series of 569 cardiac arrest resuscitated and admitted to a hospital in Vienna, cardiac causes accounted for 69 %. A cardiac cause presumed by attending physicians at the emergency department showed a high sensitivity (93 %) but was less specific (77 %). Pulmonary embolism, cerebral disorders and bleeding were among the most frequently overlooked conditions.³⁰ In parallel, in a study of 809 prospectively collected OHCA in Helsinki, cardiac causes accounted for 65.6 %. Of patients with a non-cardiac causes, the correct cause was suspected in the prehospital setting in only 63.8 %, in the remaining patients the non-cardiac cause of arrest was revealed after in-hospital examination or autopsy.³¹

Of all patients successfully resuscitated from OHCA more than 50 % will have significant coronary heart disease.³² In a prospective Parisian study of successfully resuscitated OHCA patients 61% had no obvious extra-cardiac cause of arrest. Of those, 70 % had at least one significant lesion (96 % among those with ST-segment elevation and 58 % among those without ST-segment elevation on the initial ECG).³² In a trial of urgent coronary angiography among patients presenting with ventricular fibrillation, without ST-segment elevation on initial ECG, 64.5 % had significant coronary disease, and 17 % had an acute unstable lesion or coronary occlusion.³³ Finally, causes of OHCA are different in different age groups. Cardiac causes accounted for 69 % among individuals aged > 65 years, but only 10 % among individuals between 16-40 years of age in the Swedish register for cardiopulmonary resuscitation (SRCR) in 2018.³⁴

Table 1: Causes of OHCA

Medical		Non-medical
Primary Cardiac	Primary Non-cardiac	
Ischemic heart disease	Pulmonary embolism	Trauma
- Acute myocardial infarction	Lung disease (hypoxemia)	Drowning
- Chronic ischemic cardiomyopathy	- COPD	Drug overdose
- Non-arteriosclerotic coronary disease	- Pneumonia	Electrocution
Cardiomyopathies	Hypovolemia (bleeding)	Asphyxia
- Acute on chronic heart failure	Intracerebral bleeding	Hypothermia
- Dilated cardiomyopathy	Electrolyte disturbances	Intoxication
- Hypertrophic cardiomyopathy	Hypoglycemia	
- Arrhythmogenic right ventricular cardiomyopathy	Septic shock	
Primary electrical abnormalities	Aortic dissection	
- Long QT-syndrome		
- Brugada syndrome		
- Wolf-Parkinson White syndrome		
Valvular heart disease		
Inflammatory myocardial disease		
Congenital heart disease		
Pericardial disease, tamponade		

Table 1: This list is not intended to be exhaustive and causes are not listed in order of frequency

1.5 RISK FACTORS

Since cardiovascular disease is a dominant cause of OHCA, it naturally shares many risk factors of ischemic heart disease such as age,¹⁵ male sex,³⁵ smoking, hypertension³⁶ and lower socioeconomic status.³⁷

Manifest heart disease is a strong marker of an increased risk of SCD, in particular previous myocardial infarction and heart failure. However, and most importantly, the majority of SCD victims have not been previously diagnosed with heart disease.³⁵ There is an inverse relationship between the number of cases of SCD observed in different risk groups and the individual risks of SCD. The largest number of SCDs in society will occur in the general population with a low risk. Therefore, risk stratification can be sensitive for a small subgroup of patients, but have a low power to as regards large, low-risk groups.

Figure 1: Proportion of SCD in different subgroups

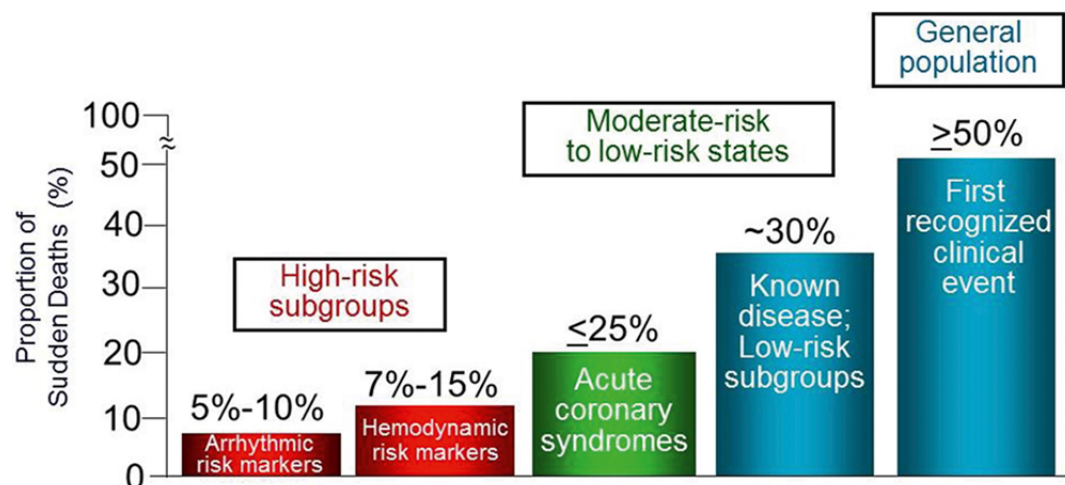


Figure 1: Proportion of Sudden Cardiac Death (SCD) in different subgroups.

Al-Khatib et al.³⁸ Reproduced with permission from Circulation

A prediction model calculated from two American cohorts of individuals with no previous cardiovascular disease, three-fourths of the participants could be identified as being “low risk” (with a 10-year risk of less than 1 %). However, among the highest risk decile, the 10-years risk was not greater than 5 %.³⁹

Also, among patients with known heart disease the risk assessment of SCD is complex. The risk of ventricular arrhythmia after myocardial infarction is time-dependent, with the highest risk in the first 48 hours.⁴⁰ The risk factors with the best predictability (ischemic heart disease, low ejection fraction, inherited genetic disorders and patients with previous documented sustained ventricular arrhythmias or previous cardiac arrest) are susceptible to preventive treatment with implantable cardioverter defibrillators (ICDs).¹² Several other markers of risk have been evaluated such as heart-rate variability, QT-intervals dispersion, T-wave alternans and biomarkers such as BNP, without influencing clinical practice.⁴¹ Risk stratification of patients with heart disease is extensively described elsewhere,³⁸ and is beyond the scope of this thesis.

1.6 PREDICTORS OF SURVIVAL

There is substantial variability in survival across EMS systems and several factors that influence the probability of survival after OHCA have been studied. These factors can be patient related such as sex,⁴² age,⁴³ and cause of arrest,²⁵ or event related. Examples of event related factors are witnessed event, CPR prior to EMS arrival, first recorded rhythm, location of the arrest, and time to defibrillation. Some of these factors will be discussed below.

1.6.1.1 Location

Around 2/3 of all OHCA occur at home and this is associated with lower survival compared to a cardiac arrest in a public location.⁴⁴ Individuals suffering a cardiac arrest at home are usually older, less frequently receive bystander CPR, have longer EMS response times and a lower incidence of VT/VF as first rhythm.⁴⁴ However, the association between location and chance of survival is independent, and might reflect unmeasured factors such as co-morbidities or lower degree of physical activity among patients suffering OHCA at home.

1.6.1.2 Witnessed event

A witnessed event is defined as a collapse seen or heard by another person, or monitored.²⁰ Since time to treatment is crucial, it is only logical that individuals who suffer an unwitnessed cardiac arrest have a poorer prognosis.⁴⁵ Cardiac arrests witnessed by the EMS are a separate group. This group usually have had symptoms prior to the arrest necessitating call for an ambulance prior to the arrest, and the time to treatment is very short. Cases of OHCA witnessed by the EMS have been found to have better prognosis.⁴⁶

1.6.1.3 Sex

Female sex accounts for about 1/3 of all OHCA. Females sex is associated with OHCA at home and a lower percentage of bystander CPR and VT/VF as first rhythm.⁴² This can explain the lower survival reported for females.^{42,47} The reason for the lower rate of VT/VF among those with female sex is not entirely clear and might have biological explanations. In contrast, others have found female sex to be associated with higher survival among the subgroup presenting with VT/VF as first rhythm.⁴⁸

1.6.1.4 Age

The incidence of OHCA increases with age. Advanced age is also associated with lower survival in OHCA. In one study the chance of a positive outcome after OHCA decreased with 22% for each decade of life.⁴⁹ However, the correlation appears to be weaker than many other event related factors such as initial rhythm.⁵⁰

1.6.1.5 First recorded rhythm

The arrhythmia at the time of collapse is for natural reasons unknown. The first recorded ECG rhythm at EMS arrival or by an AED can be divided into; a) Ventricular Fibrillation (VF) and Ventricular Tachycardia (VT) susceptible to defibrillation, and b) Asystole and Pulseless Electrical Activity (PEA), not susceptible to defibrillation. VT/VF as first recorded rhythm is the strongest predictors of survival in OHCA.⁵¹ For patients found in VT/VF, and treated with a public AED, survival can be as high as 59-71%.^{52,53}

1.6.1.6 Ventricular Fibrillation

VF can be described as an electrical chaos, causing asynchronous activity of cardiac muscle with subsequent cessation of pump function.^{38,54} The pathophysiology of VF is complex. Heterogeneity of repolarization and conduction properties in myocardial tissue can cause electrical wave fronts to break up (functional re-entry) into multiple wavelets that cause fibrillation.⁵⁵ Structural predisposition (cardiac scarring, hypertrophy, myopathies or electrical abnormalities) and transient factors (ischemia, hypoxia, electrolyte disturbances, hemodynamic alternation, neurophysiological factors or drugs) interact to make the myocardium susceptible to VF.⁵⁶

If VF is left untreated it will deteriorate from “coarse” to “fine” VF and finally to asystole.⁵⁷ This explains the association of greater probability of finding a patient in VT/VF with a shorter time interval from cardiac arrest to rhythm analysis.^{58,59} The proportion of OHCA with VT/VF as first recorded rhythm is around 20 – 30 % for witnessed OHCA.⁴⁷ However, the incidence of VT/VF as first recorded rhythm has declined during the last decades.^{60,61} The reasons are not clear but longer EMS response times,¹⁸ improved cardiovascular and heart failure care with subsequent reduction in mortality,⁶⁰ and the implementations of ICD⁶² are possible reasons.

1.6.1.7 Ventricular Tachycardia

VT is an abnormal cardiac rhythm originating from the ventricle at a rate > 100 beats per minute. VT can originate from myocardial cells with altered conductance and repolarization properties compared with adjacent myocardium that form electrical re-entry circuits, or due to increased automaticity. VT in the setting of myocardial ischemia is often polymorphic whereas sustained monomorphic VT is typically due to a myocardial scar or fibrosis re-entry.⁶³ VT proceeding to VF is thought to be the most common mechanism of SCD among patients with ischemic heart disease.⁶⁴ In a study of 157 SCD in patients wearing ambulatory ECG-monitoring, VT proceeding to VF was found in 62 %, primary VF in 8 %, Torsade de pointes VT in 13 % and bradyarrhythmia in 17 %.⁶⁵

1.6.1.8 Asystole

Asystole is defined as cessation of myocardial electrical activity. In a prehospital setting the finding of asystole on initial rhythm analysis usually represents a dying heart with cardiac standstill. Survival in OHCA with asystole as the first recorded rhythm is extremely poor, ranging from 0,2 % to 1.3 %.⁶⁶⁻⁶⁹

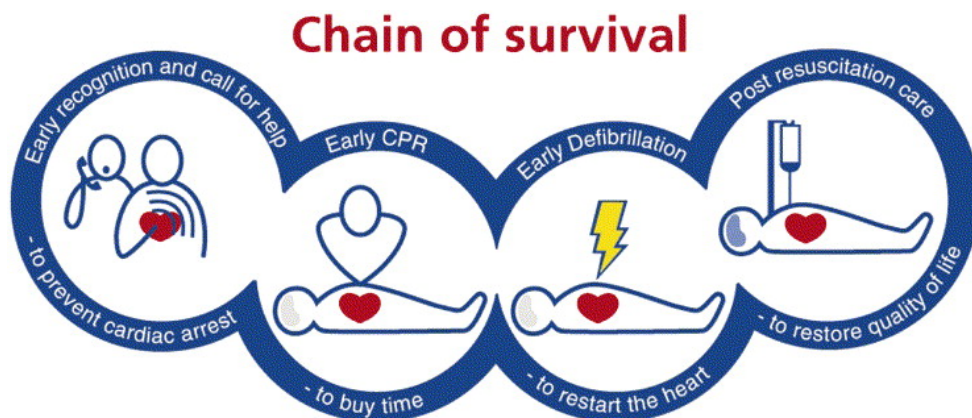
1.6.1.9 Pulseless Electrical Activity

PEA is defined as an organised electrical rhythm on ECG but no palpable pulse. PEA can arise from electromechanical dissociation (organized electrical cardiac rhythm but no myocardial pump motion) or mechanical obstruction such as tamponade, pulmonary embolism and hypovolemia causing profound hypotension. The incidence of PEA has increased in recent years, and the prognosis after PEA has been found to be better in comparison with asystole.⁶⁷⁻⁶⁹

2 TREATMENT

Survival after OHCA is highly dependent on a fast response from citizens, emergency dispatch organisations and EMS-services all working together. A framework for this concept is “the chain of survival” introduced in an AHA statement from 1991.⁷⁰⁻⁷² The links in the chain of survival are (1) early recognition of symptoms and placing an alarm call, (2) early CPR (3) early defibrillation and (4) post-resuscitation care.

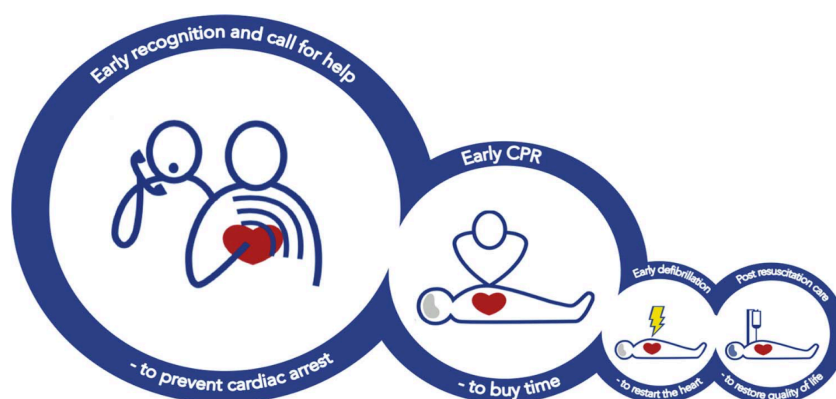
Figure 2:



Nolan et al.⁷² Reproduced with permission from Elsevier

The number of patients susceptible to each intervention decreases for every link in the chain. An alternative demonstration of the chain of survival has been proposed, reflecting the number of patients susceptible to each intervention.⁷³

Figure 3: Revised chain of survival



Deakin et al.⁷³ Reproduced with permission from Elsevier

Figure 3: The revised representation of the chain of survival is adjusted so the area of each link graphically represents the number of patients in each step.

2.1.1 Early recognition and call for help

Early recognition is naturally crucial for the subsequent resuscitation efforts to be effective. A person who is unresponsive and not breathing normally should be considered to be in cardiac arrest.⁷⁴ Victims of cardiac arrest often gasp during the first minutes, the so called "agonal breathing".⁷⁵ This reflex appears to be triggered by ischemia of the brainstem and decreases with time from cardiac arrest. In experimental studies agonal breathing can be maintained if effective chest compressions are continued,⁷⁶ and the presence of agonal breathing at EMS arrival is associated with increased survival.⁷⁵

Emergency dispatchers can play an important role as they can assist in recognising a cardiac arrest. Different protocols to aid dispatchers in cardiac arrest recognition are used.⁷⁷ The proportion of OHCA recognition during alarm calls ranges from 14 % and 83 %.⁷⁸⁻⁸² The median rate of recognition across dispatch system have been found to be 73 % in a systematic review.⁸³ Agonal breathing is one of the main barriers for recognition during an alarm call.^{77,84} Agonal breathing can be present in up to 40 % of all calls,⁸⁴ and can account for half of the calls with missed diagnosis.⁸² The importance of the emergency dispatcher together with the caller, forming the "first resuscitation team" is highlighted in European Resuscitation Council (ERC) guidelines.⁸⁵ When a OHCA is recognised, callers can be offered instruction over telephone on how to perform CPR - dispatcher assisted CPR (DA-CPR).⁸⁶ Implementation of DA-CPR programs have been found to be associated with higher CPR rates⁸² and survival.⁸⁷⁻⁹⁰ DA-CPR can be associated with significant time delays, ranging from 138 – 183 s from call to CPR instruction^{81,82,91}

2.1.2 Early CPR

The aim of cardiopulmonary resuscitation is to create an artificial circulation providing essential blood flow to crucial organs, mainly the brain and heart, until restoration of spontaneous circulation can be achieved. Initiation of bystander CPR prior to EMS arrival is independently associated with survival rates 2-3 fold higher compared with no such initiation.^{51,92} There are wide differences in incidence of bystander CPR, ranging from 86% in Denmark,⁹² 42% in Japan.²³ Factors associated with higher probability of receiving early CPR are among others cardiac arrest in a public location,⁴⁴ male sex,⁴² and younger age.⁴³

2.1.3 Early defibrillation

Defibrillation is the only definitive treatment of VT/VF. Time to defibrillation is crucial and survival decreased for every minute without CPR or defibrillation in VF cardiac arrest.⁹³ Traditionally defibrillation is carried out by EMS personnel. However, there are challenges in reducing EMS response time.¹⁸ Therefore, alternative strategies to enable faster defibrillation has emerged. The concept of “dual dispatch” refers to dispatching first responders such as fire-fighters or Police units equipped with an AED. In a project in Stockholm, the implementation of a dual dispatch in parallel to the traditional EMS response was associated with higher survival, in spite that time to defibrillation was marginally reduced.⁹⁴ Publicly available AED used by bystanders can be associated with survival rates well over 50% in VT/VF arrest.⁵² However, in spite the fact that the numbers of AED is increasing, they are seldom used.⁷⁴ Different strategies to optimize AED placements have been proposed.⁹⁵ The implementation of AED-registers can enable emergency dispatchers to guide callers to the location of a nearby AED.⁹⁶ Another concept based on AED registers, is to use a smartphone application to dispatch lay volunteers to retrieve an AED to nearby OHCA.⁹⁷ Finally, in rural areas the concept of drone delivered AED has been proposed.⁹⁸ In summary, time to defibrillation is the most crucial factor for surviving a VT/VF arrest and new strategies to decrease time to defibrillation are under investigation.

2.1.4 Advanced Life Support

The concept of Advanced Life Support (ALS) in EMS includes CPR and defibrillation, but also advanced airway management, intravenous access and administration of drugs. The benefit of ALS compared to more basic life support (BLS) in the prehospital setting have been debated. In one study in Ontario, the implementation of ALS in the ambulances (opposed to BLS) resulted in higher rates of survival to hospital admission but not to hospital discharge.⁴⁵ Some components of ALS interventions will be discussed below, but ALS as a whole is beyond the scope of this thesis.

There is controversy about optimal airway management in ALS.⁹⁹ Several RCT's have compared Endotracheal Intubation (ETI) to simpler techniques such as bag-mask ventilation,¹⁰⁰ laryngeal tube,¹⁰¹ and supraglottic airway devices.¹⁰² Optimal method of airway management might depend on local EMS organization and the training level of EMS staff. Adrenaline is used to increase systemic pressure and coronary and cerebral blood flow during CPR and anti-arrhythmic drugs are recommended for VT/VF not responding to defibrillation.¹⁰³ The use of drugs in ALS have been found to increase the rate of return of spontaneous circulation (ROSC) and survival to hospital admission,¹⁰⁴ but the effect on long term survival and neurological function is less clear. In a recent double-blind RCT including more than 8 000 patients, adrenalin was found to increase survival, but not a favorable neurological outcome.¹⁰⁵ In a RCT comparing Amiodarone, Lidocaine and placebo found no difference in survival to discharge, although there was an interaction between drug effect and witnessed status, indicating a potential benefit among cases of witnessed OHCA.¹⁰⁶ The routine use of mechanical chest compressions devices has not been found to increase survival.^{107,108} However, mechanical chest compressions are recommended for prolonged CPR and during transport. In summary, ALS interventions include advanced airway management and administration of intravenous drugs, but the impact on survival is lower compared to early CPR and defibrillation.

2.1.5 Post-resuscitation care

The goal of post-resuscitation care is to stabilize the circulation and ventilation, find and treat the cause of arrest, and to optimize recovery.¹⁰⁹ Depending on the length of the arrest, most patients achieving ROSC are comatose with an indication for intubation and assisted ventilation. Shock is common and can be treated with fluids or vasopressors. Targeted temperature management (TTM) to 32-36 degrees for 24 hours at is recommended for specific subgroups of patients.¹¹⁰ This is based on the results of two trials comparing TTM to 32 degrees with no temperature control.^{111,112} A larger trial comparing TTM at 33 to 36 degrees did not demonstrate any difference in survival or favorable neurological function,

¹¹³ but a recent RCT including non-shockable rhythms found higher survival for TTM 33 degrees compared to normothermia.¹¹⁴ Coronary angiography for patients with ST-segment elevation on initial ECG is recommended, but for patients presenting without ST-segment elevation the benefit of early angiography is unclear.³³ Many resuscitated patients will develop a “post cardiac arrest syndrome” with hyperinflammation and sepsis-like features. Targeted goals for intensive-care management and neurologic prognostication exist and are extensively described elsewhere.¹¹⁰ However, controversies regarding optimal blood-pressure targets, oxygenation and ventilation strategies remain.¹¹⁵

2.2 PHYSIOLOGICAL ASPECTS OF CPR

2.2.1 Chest compressions

Traditional CPR is composed of repetitive chest compressions with interruptions for ventilation. It has been estimated that 25 % of systemic perfusion pressure and 12-27 % of normal cardiac output can be maintained with CPR.^{116,117}

The exact mechanism of how chest compressions generate a forward blood flow is complex. According to the cardiac pump theory the heart is directly compressed between the sternum and vertebrae, creating a higher pressure in the ventricles than in surrounding compartments, with closure of the mitral valve and opening of the aortic valve, creating a forward blood flow.^{6,118}

This theory has been complemented with the thoracic pump theory, by which pressure fluctuations in all intrathoracic compartments, including the intrathoracic aorta, generate blood flow.^{119,120} If patent, jugular venous valves or collapsing veins at the thoracic outlet are thought to prevent backward venous flow.¹²¹ Opening of both aortic and mitral valves during compression transmits the intrathoracic pressure to extra thoracic arteries. According to this theory the heart acts as a passive conduit. During decompression the chest wall recoils and intrathoracic pressure drops, enabling venous return from extra-thoracic veins.¹²²

It is likely that both mechanisms apply to chest compressions in clinical practice, and the magnitude of each component might be time-dependent.¹²³ Kim et al performed contrast enhanced transesophageal echocardiography (TEE) in 10 patients during CPR (all in asystole) and found aortic valve opening and mitral valve closing during compression (supporting the cardiac pump theory), and mitral regurgitation in all patients.¹²⁴ However, they found large variations in retrograde mitral valve flow, and concluded that the cardiac pump theory was predominant although both mechanisms may be contributing.

2.2.2 Coronary perfusion pressure

During CPR coronary perfusion pressure (CPP) is defined as the difference between aortic pressure and right atrial pressure during decompression phase.¹²⁵ CPP has been shown to correlate well with coronary blood flow in experimental models.¹²⁶ The probability of ROSC in both animals and humans appears to be low when CPP is below 15 mmHg.^{127,128} Blood-flow through the coronary vessels is higher during decompression.¹¹⁶ Therefore, the heart is mainly perfused during the decompression phase.¹²⁹

After onset of VF, the aortic pressure drops and there is a gradual increase in the right-atrial pressure, with distention of the right ventricle. Eventually there is equilibrium between aortic pressure and right-atrial pressure, rendering CPP to zero. Steen et al. found in an experimental study that chest compressions promptly increased extra-thoracic aortic pressure and carotid blood flow but it took up to two minutes of mechanical chest compression to establish an adequate CPP after VF was untreated for 6.5 min.¹³⁰

The optimal rate of chest compressions has been found to be between 100 – 120 per minute.¹³¹ If compressions are too fast, the left ventricle will not have sufficient time to refill before next compression. The optimal compression depth has been found to be around 4 – 5.5 cm.¹³² There appears to be an inverse relationship between compression rate and depth, faster chest compression in real life scenarios will result in inadequate depth.¹³³

2.2.3 Ventilation

Ventilation is the movement of air from outside the body to the alveoli to enable gas exchange. During bystander CPR ventilation is provided by positive-pressure breaths (PPV). Intermittent positive airway pressure can maintain oxygenation, increase carbon dioxide clearance and prevent from lung atelectasis.¹³⁴ However, PPV also effects circulation in a complex way. In mechanically ventilated patients increased intrathoracic pressure “squeezes” blood from the lung capillaries to the left side of the heart, momentarily increasing left ventricular filling pressures and stroke volume.¹³⁵ On the other hand, increased intrathoracic pressure reduces venous return to the right side of the heart and has been found to inversely correlate to CPP and cerebral blood flow.¹³⁶ In summary, hypoventilation can cause hypercapnia and hypoxia,¹³⁷ while hyperventilation can have adverse effects on cerebral and myocardial circulation.¹³⁶ There is arguably a balance between too much and too little ventilation during CPR.

2.2.4 Compression-only CPR

Interruptions in chest compressions can have a deleterious effect on hemodynamics during CPR^{138,139} and long interruptions have been found to correlate with a decreased rate of ROSC in ALS.¹⁴⁰ The concept of CO-CPR, continuous chest compressions without rescue breaths, has been extensively evaluated in experimental models.^{76,127,139}

There is conflicting evidence from observational human studies. A number of register-based observational cohort studies have been carried out to compare CO-CPR with S-CPR, many of which have shown neutral results.¹⁴¹⁻¹⁴³ Differences in favour of S-CPR have been found in connection with paediatric arrests,¹⁴⁴ individuals younger than 18 years,¹⁴⁵ and when EMS response-time were longer than 15 minutes.¹⁴⁶ Others have found higher survival for CO-CPR among patients found in VT/VF or treated with public AED.^{147,148} One study showing a higher survival rate with CO-CPR was conducted during a community program promoting CO-CPR.¹⁴⁹ In a Japanese population of OHCA of medical origin, CO-CPR was associated with a higher survival with CPC 1-2 in a propensity score matched cohort (7.2% vs 6.5%, OR 1.12 $p < 0.001$).¹⁵⁰

Three randomized trials have compared dispatcher assisted CO-CPR with S-CPR (in a 15:2 ratio), involving bystanders without previous CPR training, and the results have been neutral.¹⁵¹⁻¹⁵³ In a meta-analysis of these trials there was a modest but statistically significant increase in survival with CO-instructions. (RR 1.22, 95% CI 1.01-1.14)¹⁵⁴

Techniques to minimize interruptions in chest compressions during ALS is typically involve placement of an ETI device and positive pressure ventilation (PPV). Alternatives are continuous chest compressions and desynchronised PPV via a bag-mask device, or passive oxygenation with an oropharyngeal airway or oxygen mask.¹⁵⁵ This concept was compared to bag-mask ventilation in a 30:2 ratio in a cluster RCT, including 23 711 patients, showing neutral results in the ITT analysis but, in a PP analysis those treated with 30:2 had a favourable neurological outcome.

2.3 CURRENT RECOMMENDATIONS FOR CPR

In 1992 resuscitation scientists formed a forum for collaboration, the International Liaison Committee on Resuscitation (ILCOR), publishing treatment recommendations.¹⁵⁶ The ILCOR “consensus statement on science and treatment recommendations” has been periodically updated to serve as a foundation for regional resuscitation guidelines.^{85,157,158} In 2005, there was a shift in the compression to ventilation ratio from 15:2 to 30:2, and CO-CPR was introduced as an option if the bystander was unable or unwilling to perform rescue breaths.¹⁵⁷ In 2010 CO-CPR was recommended for dispatcher assisted CPR.¹⁵⁹ Because of the controversies regarding the optimal compression to ventilation ratio, ILCOR reviewed all available evidence in 2017 and made the following recommendations for bystander CPR.¹⁶⁰

“We continue to recommend that bystanders perform chest compressions for all patients in cardiac arrest (good practice statement)”.

“We suggest that bystanders who are trained, able, and willing to give rescue breaths and chest compressions do so for all adult patients in cardiac arrest (weak recommendation, very-low-quality evidence)”.

For dispatcher assisted CPR, CO-CPR is recommended for adults with suspected OHCA.¹⁶¹ This recommendation is cited as a strong recommendation, but based on low quality evidence. The level of evidence was downgraded because of a serious risk of bias.¹⁶⁰

In the process of reviewing the current evidence knowledge gaps identified by ILCOR were the effect of delayed ventilation versus 30:2 high-quality CPR, the impact of continuous chest compressions on outcomes of CA arising from noncardiac causes and the ability of bystanders to correctly perform mouth-to-mouth ventilation.

In Summary, guidelines on how to perform CPR have changed. Changes in CPR rates, methods of CPR, and the impact on 30-day survival after these modifications in recommendations are unclear. Furthermore, there is conflicting data regarding the effect of dispatcher assisted CPR and survival. Finally, to address the question of whether CO-CPR leads to survival no worse than, equally effective or superior to S-CPR for bystanders with previous CPR training the TANGO2 pilot trial was launched in 2017.

3 AIM OF THIS THESIS

The overall aim of this research project was to assess the association between different forms of CPR prior to EMS arrival and survival in cases of OHCA.

Study specific aims:

1. To assess survival after CPR prior to EMS arrival compared with no CPR prior to EMS arrival in OHCA (Study I)
2. To describe temporal changes in CPR rates and type of CPR prior to EMS arrival and survival in relation to three time periods of different CPR guidelines in Sweden (Study II).
3. To assess survival after CPR with dispatcher CPR instructions compared with no CPR and CPR not requiring dispatcher instructions (Study III).
4. To assess feasibility in a pilot study of a national, investigator-initiated, multicentre, RCT designed to compare survival after dispatcher instructions of chest compressions and rescue breaths versus dispatcher instructions of chest compressions only, to trained bystanders in OHCA (study IV).

4 METHODS

4.1 DESIGN, STUDIES I - IV

Studies I-III are observational cohort studies including patients reported to the SRCR.

Study IV is a pilot study of a prospective, investigator-initiated, multicenter, randomized clinical trial. The data for Study IV relies on automatically stored event times obtained from the national Swedish emergency dispatch organization SOS Alarm and reviews of audio files of emergency calls. Patients characteristics and follow up are collected through the SRCR.

Overview of design, data sources, patients, years, statistical methods and outcomes in study I - IV				
	Study I	Study II	Study III	Study IV
Design	Observational cohort study	Observational cohort study	Observational cohort study	Feasibility assessment of a randomized controlled trial
Data-sources	- SRCR	- SRCR	- SRCR	- Automatically stored time data from dispatch centrals - Audio log of emergency calls - SRCR
Inclusion criteria	Bystander witnessed OHCA	Bystander witnessed OHCA	Lay bystander witnessed OHCA	- Randomized in the TANGO2 trial - EMS treated OHCA
Years	1990 – 2011	2000 – 2017	2011 – 2017	2017 -
Number	N = 30 381	N = 30 455	N = 15 471	N = 381
Statistical methods	- Multiple logistic regression - Propensity score	- Multiple logistic regression - Multiple imputation	- Propensity score matching - Multinomial propensity score	- Descriptive statistics - Pearson χ^2 - Wilcoxon rank sum test
Outcome	30-days survival	30 days survival	30 days survival	Feasibility and safety measurements

4.2 SETTING

4.2.1 The Swedish emergency medical services system

The Swedish EMS system is organized in regional EMS agencies. Ambulances are in general staffed with registered nurses with additional training in emergency medicine/anesthesiology. Ambulances are equipped with AEDs. The ambulance crew performs ALS in accordance with ERC guidelines.⁸⁵ In some regions fire fighters and/or police are dispatched in parallel to EMS.^{94,162} These units, in this text referred to as “first responders”, are equipped with AEDs and the personnel trained in BLS. A cardiac arrest typically generates an EMS response of two ambulances, and in some regions a second tier of ALS units, each equipped with an emergency physician.

Rules for termination of resuscitation are defined by local EMS advisory guidelines in adherence to the “universal” termination of resuscitation rule.^{103,163} In Stockholm, the criterion for termination of resuscitation is 20 minutes of ALS without electrical activity (asystole). Criteria for *early* termination of resuscitation are; non-witnessed event, no CPR prior to EMS arrival, > 15 minutes from call to EMS arrival and asystole at first rhythm analysis.

4.2.2 Swedish emergency dispatch organization

Sweden has a population of 10 120 242 inhabitants (31 December 2017), covering an area of 450 000 km². All emergency calls in Sweden are answered by a SOS Alarm. SOS Alarm is organized in 18 dispatch centers, all operating nationwide. In 2018 SOS Alarm handled 3.2 million emergency calls of which 44 % were related to medical issues.¹⁶⁴ Emergency calls are primarily answered by emergency dispatch telecommunicators. For medical emergencies SOS Alarm coordinates the triage and dispatch of EMS according to a criteria-based dispatch protocol.⁷⁷ (If the caller is situated in one of three regions [Uppsala, Södermanland and Västerås] calls are redirected to local medical dispatch centers run by local EMS organizations for triage and dispatch). A cardiac arrest should be suspected when a person is described as unconscious with no breathing, or not breathing normally. Dispatchers are instructed to deliver CPR instructions to bystanders untrained or unable to initiate CPR.¹⁶⁵ For adult victims of CA instructions are compression-only. For presumed asphyxia-related CA and for children, the instructions are compressions and rescue breaths in a 30:2 ratio. For children CPR is to be initiated by five rescue breaths. In some regions a smart-phone application is used to locate and recruit lay volunteers to perform CPR or retrieve a nearby AED. This system is activated by the emergency dispatchers.⁹⁷

4.3 THE SWEDISH REGISTER FOR CARDIOPULMONARY RESUSCITATION

The Swedish Register for Cardiopulmonary Resuscitation (SRCR) is a National Quality Register founded in 1990 in Gothenburg. It has expanded gradually and since 2010 all EMS organizations in all 21 regions in Sweden report to the register. The register is one of the Swedish national quality registers of health-care measurements¹⁶⁶ and contain variables in accordance with the “Utstein” guidelines of reporting in OHCA.¹⁶⁷ The register is composed of three parts.

1) The first part is completed by EMS crew after attending an OHCA. Reports are entered in the register only if EMS or bystanders attempted resuscitation and the patient was not declared dead at EMS arrival. The variables in the first section describe the circumstances of the OHCA, patient related factors, treatment variables and patient status at the end of the prehospital treatment.

2) The second part contains variables regarding in-hospital treatment and follow up. Survival to 30 days is obtained by linkage with the Swedish National Population Register through the 10-digit personal identification number.¹⁶⁸ Neurological function is assessed according to the Cerebral Performance Category (CPC) scale at hospital discharge.¹⁶⁹ According to this scale, 1 is good cerebral performance, 2 is moderate disability, 3 is severe disability, 4 is coma or vegetative state and 5 is brain death. This section is completed by a local CPR coordinator.

3) The third part is composed of Patient Reported Outcome Measurement (PROM) and is completed by patients and nurses at follow-up visits. The PROM includes health related quality of life assessment (EQ-5D, EQ VAS) and anxiety assessment (HADS). The PROM evaluation occurs between 3-6 months after the cardiac arrest and have been part of the register since 2013. As of 2018 a total of 52 hospitals (73 %) report PROM to the register.

Between 1990 and 2007 reports were written manually on paper, since 2008 data has been reported electronically. The accuracy of inclusion of all cardiac arrests between 1992 to 2010 is estimated to range from 70–100%.^{18,170} Today, cross-checking of EMS record to identify missing OHCA and retrospective inclusion in the register is performed by a local register coordinator (usually an experienced nurse).

4.4 DESCRIPTION OF THE TANGO2 TRIAL

4.4.1 Background and aim

Current guidelines advocate CPR provided by trained bystanders to be carried out with both rescue breaths and chest compressions. However, if the bystander is untrained, uncertain or unwilling to provide rescue breaths, CO-CPR is recommended.¹⁶¹

There is a lack of conclusive evidence regarding the effect of CO-CPR compared to S-CPR when performed by bystanders with previous CPR training for adult OHCA.^{151-153,171,172} This knowledge-gap is highlighted by the International Liaison committee on resuscitation (ILCOR) consensus-report in 2017.¹⁶⁰

In the light of the equipoise and the very-low quality of the available evidence the TANGO2 trial aims to investigate whether survival after instructions to perform CO-CPR to bystanders with prior CPR-training is no worse, or better than instructions to perform S-CPR in witnessed, adult OHCA of presumed cardiac origin.

4.4.2 Overview

TANGO2 is an interventional, prospective, 1:1 open label, multicenter randomized trial (Clinical Trials, NCT02401633). TANGO2 is conducted at the dispatch center. Emergency calls concerning suspected OHCA (unresponsive patient with no, or agonal breathing) are eligible for inclusion. Study inclusion criteria are:

- *Witnessed collapse (seen or heard)*
- *The caller or anyone at the scene has previous CPR-training*
- *Victim's age above 18*
- *No signs of trauma, asphyxia, intoxication or pregnancy*

Included calls are randomized 1:1 to instructions to provide either S-CPR (control) or CO-CPR (intervention).

Post-randomization exclusion criteria for final data analysis are: Not EMS treated OHCA.

Primary outcome is 30 days survival.

Secondary outcomes are survival to hospital admission, survival to 1-year survival, survival with good neurological outcome at discharge (defined as CPC 1-2) and survival with good neurologically outcome (defined as CPC 1).

4.4.3 Study phases

The overall study project is conducted in three phases:

1) Pre study RUN-IN period

Objective: In order to test the technical inclusion procedures, logistics, feasibility and data collection a pre-study RUN-IN period started in Stockholm during 2015 (completed).

2) PILOT study

The aim of the pilot study was to assess safety and feasibility of the TANGO2 trial, as well as intermediate clinical outcomes.

3. MAIN study

The aim of the main study is to evaluate survival to 30 days following instructions to perform CO-CPR is non-inferior compared to instructions to perform S-CPR bystanders in witnessed adult OHCA of presumed cardiac origin and where the bystander has CPR training. The main trial will include patients from both the pilot and main trial.

4.4.4 Description of the TANGO2 Pilot study (Study IV)

The aim of the pilot study was to assess safety and feasibility of the TANGO2 trial, as well as intermediate clinical outcomes. (Clinical Trials NCT02401633)

Feasibility measures are: evaluation of automated inclusion and randomization, adherence to protocol by dispatchers and callers, validation of data collection and rate of inclusion.

Safety measures are: time losses during screening for inclusion and randomization. Time to CPR instructions and time to start of CPR. Correct inclusion and proportion of patients correctly identified as cardiac arrests.

Intermediate clinical outcomes are: proportions of patients with VT/VF as first recorded rhythm, and survival to hospital admission.

4.4.4.1 Screening for inclusion and randomization:

The TANGO2 pilot study is conducted at dispatch centers throughout Sweden, including all SOS Alarm dispatch centrals and the local medical dispatch centrals in Uppsala, Västmanland and Södermanland.

For the purpose of this trial a screening tool was developed and integrated in the dispatcher's software to enable fast screening and randomization. The screening tool becomes visible for the dispatch operators only after a call is characterized as a suspected OHCA. The screening tool is composed of four checkboxes corresponding to the inclusion criteria described above. If all inclusion criteria are present the call can undergo

randomization. Randomization is performed by activating a web-based random constructor (Windows Int 32), generating a random assignment to either control or intervention.

4.4.4.2 Study intervention:

After randomization a pop-up window appears on the dispatcher's desktop with instructions to provide to the caller. In the intervention group, dispatchers are instructed to deliver the following phrases to the caller:

- An ambulance is dispatched and is on its way to you.
- Perform CPR with chest compressions only.
- Push hard on the chest at a pace of 100/minute without interruptions for rescue breathing.

The intervention continues until arrival of EMS or first responders at the patient's side.

In the control group, dispatchers were instructed to deliver the following phrases to the caller:

- An ambulance is dispatched and is on its way to you.
- Perform CPR with chest compressions and rescue breathing.
- Push hard on the chest 30 times and give two rescue breaths. The pace of the compressions should be 100/minute.

4.4.4.3 Data collection

Automatically generated event times, stored at the dispatch organization's computer system, were retrieved for all randomized calls. The randomized assignment for each call was stored in a separate data-file generated by the random sequence constructor.

To assess event times not automatically generated at the dispatch organization and to evaluate call processes, all included calls were audited. For this purpose a standardized template was used,⁸¹ with the specific inclusion criteria of the study added as auxiliary variables. All evaluators were blinded to randomized assignments during the call evaluation, and inter-rater reliability was assessed.

Patient characteristics and data on resuscitation efforts were collected from the SRCR. All data was entered in a study-specific database at the Center for Resuscitation Science, Karolinska Institutet, Stockholm. The randomized assignment of each case was blinded during the data collection to avoid any bias in reporting or collecting data.

4.5 ETHICAL CONSIDERATIONS

All studies in this thesis are approved by a regional board of Ethics. Study I was approved by the regional board of ethics in Gothenburg (Dnr 174-96). Study II – IV obtained ethical approval from the regional board of ethics in Stockholm. (Study II & III, Dnr 2016/1532-31, study IV, Dnr 2014/97-31/2 and Dnr 2015/1833-32).

In OHCA, the victim is unconscious and therefore incapable of providing informed consent to participate in a clinical trial or to be part of a national register. OHCA, however is also a medical emergency with a mortality rate of around 90 %. Treatment has to be started immediately, making informed consent by a relative or legally authorized representative impossible for practical reasons. Therefore, introducing new treatments in this population raises ethical questions regarding autonomy.

The TANGO2 trial has ethics approval by the regional board of ethics (Dnr 2014/97-31/2 and Dnr 2015/1833-32). Approval was given without the use of informed consent. The use of deferred consent in emergencies has been used by our and other research groups. It is supported by the Paragraph 30 in the Helsinki declaration of 2013, which states that involving subjects can be done *“if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group (...) specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol (...)has been approved by a research ethics committee.”*¹⁷³ All patients who regain consciousness

Potential risk and benefit of the intervention in the TANGO2 trial. (is there equipoise?)

Whether or not CO-CPR leads to a survival rate no worse than, equal to, or even superior to S-CPR in situations where the bystander has previous CPR training remains unclear. There is conflicting data from available evidence and meanwhile the CO-CPR method has gained widespread acceptance and is used in about half of all OHCA patients receiving CPR. Also, guidelines on to perform either S-CPR or CO-CPR differ internationally. Therefore, more studies are warranted.

In OHCA, effective chest compressions are an absolute necessity to increase the otherwise low chance of survival. Experimental studies and previous randomized trials have shown that successful CPR can be achieved with CO-CPR.¹³⁹ In OHCA of cardiac origin, blood oxygenation at the time of cardiac arrest might be good, and therefore, rescue breathing might be less important in the first minutes of CPR.¹⁴⁷ Even if trained in CPR, mouth-to-mouth breathing is relatively difficult to perform, and it takes time away from chest compressions. During this time coronary perfusion pressure and cerebral perfusion pressure are very low. Therefore, there might be a risk that too much time is spent on performing

mouth-to-mouth breathing when the value of uninterrupted chest compressions could be higher. Performing mouth-to-mouth breathing could also be a barrier to initiation of CPR or it could delay CPR start. CO-CPR could lead to an earlier start of CPR, no interruptions in chest-compressions and could therefore be beneficial for a majority of cases.

A small but important group of all OHCA are due to external causes inducing hypoxia, i.e. drowning, strangulation, hanging or opioid intoxication. These patients are supposed to be excluded from the study as described in the study protocol. We believe there might be a risk that a small group of patients with an OHCA caused by hypoxia, not identified by either the witness or by the dispatcher, could experience harm with this intervention.

A simplified method of CPR could be disseminated in a more cost-effective manner throughout society, in companies and schools and could enhance the care for this patient group nationally and internationally.^{149,174} The potential benefits of this study are two-fold in the sense that the results can lead to increased survival rates: 1) simplified CPR might be better than traditional CPR for adult OHCA of presumed cardiac origin 2) simplified CPR could lead to more people performing it.

5 RESULTS

5.1 STUDY I – “EARLY CPR IN OUT-OF-HOSPITAL CARDIAC ARREST”

The aim of Study I was to assess survival after CPR prior to EMS arrival compared with no CPR prior to EMS arrival in OHCA.

6.1.1 Main Results

Witnessed OHCA between 1990-2011 were included (N = 30 381). CPR prior to EMS arrival was performed in 51 % of all OHCA. Survival to 30 days was 10.5 % for patients receiving CPR prior to EMS arrival compared with 4.0 % among those where no CPR was performed (unadjusted OR 2.80; 95 % CI 2.47 – 3.18). Similar associations were found for all subgroups analyzed, as shown in figure 4.

Figure 4: Subgroup analysis of survival rates.

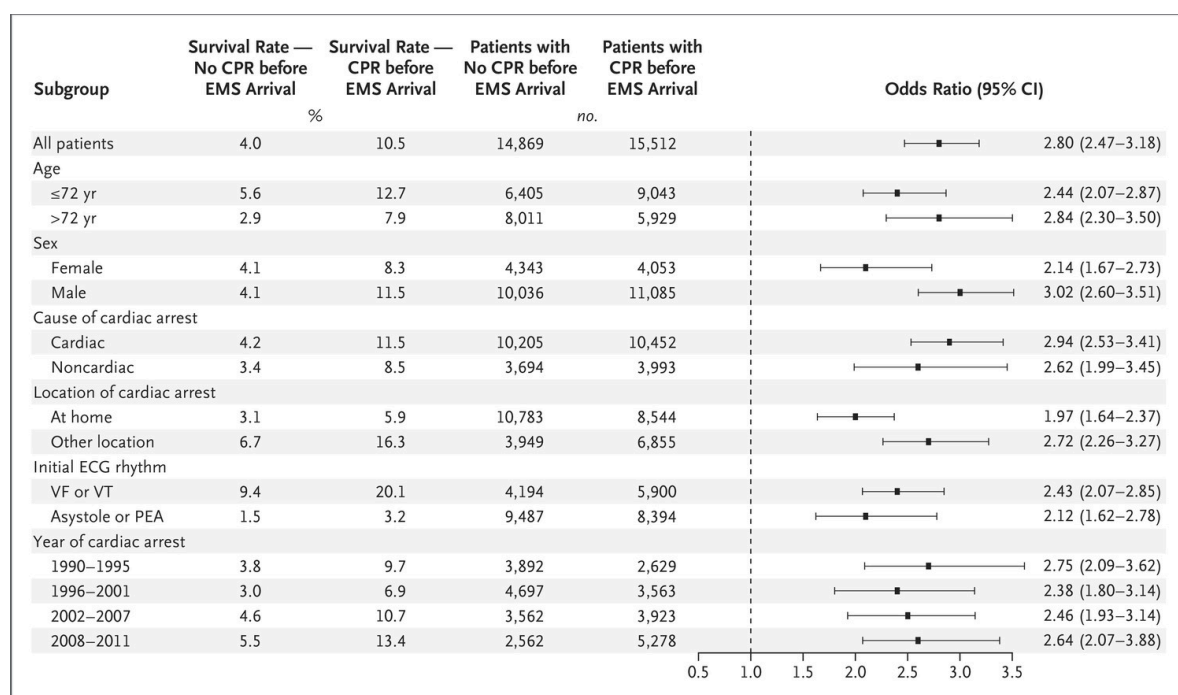


Figure 4 shows the subgroup analysis of survival rates. ECG denotes electrocardiographic, PEA pulseless electrical activity, VF Ventricular fibrillation, and VT ventricular tachycardia.

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We also found higher proportion of persons who received CPR prior to EMS arrival over time as shown in figure 5.

Figure 5: Changes over Time in CPR Training and the Performance of Early CPR.

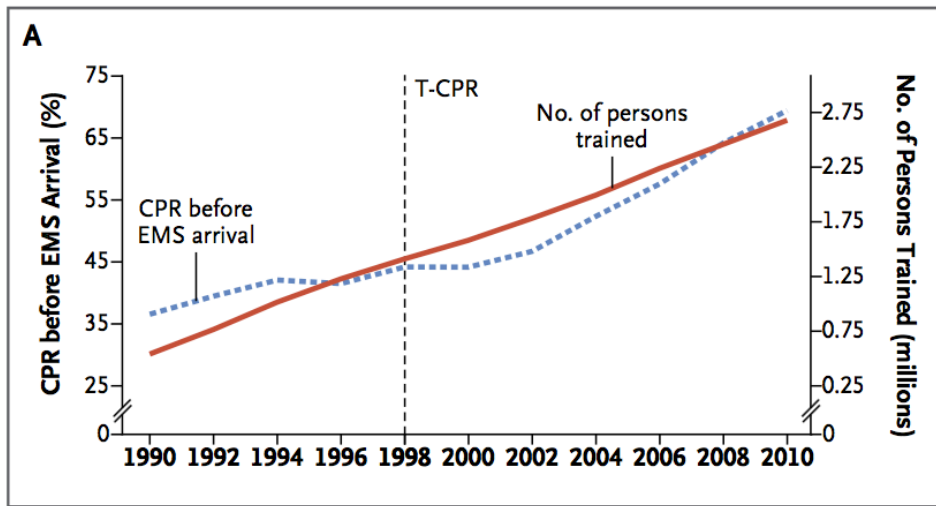


Figure 5 shows the cumulative number of attendees at CPR training sessions in Sweden and the proportion of patients receiving CPR prior to EMS arrival. T-CPR denotes the introduction of DA-CPR to untrained witnesses.

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Patients not receiving CPR prior to EMS arrival were older, more frequently of female sex, more likely to have collapsed at home and were less likely to have VT/VF as first recorded rhythm. After adjusting for differences in baseline characteristics, using propensity score as an adjustment factor in a logistic regression model, CPR prior to EMS arrival was associated with a higher rate of survival to 30 days (odds ratio 2.15; 95 % CI 1.88 – 2.45).

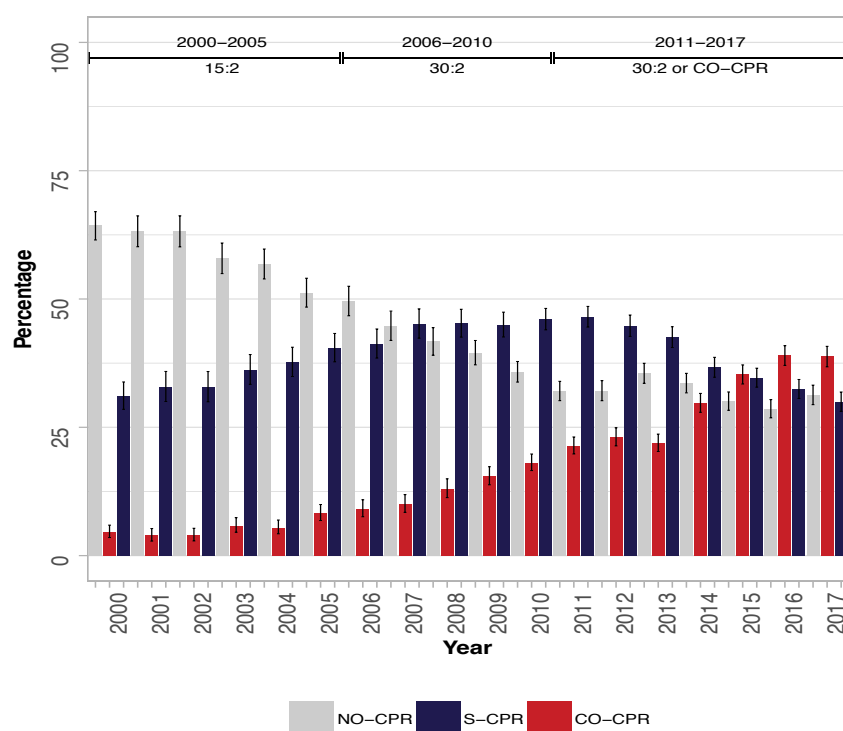
5.2 STUDY II – “TEMPORAL CHANGES IN FREQUENCY OF CPR, TYPE OF CPR PRIOR TO EMS ARRIVAL AND SURVIVAL DURING THREE GUIDELINE PERIODS”

In Study II we aimed to describe temporal changes in CPR rates, type of CPR prior to EMS arrival and survival in relation to three time periods of different CPR guidelines in Sweden. Patients were divided into three groups, reflecting different guideline time periods (2000 – 2005, 2006 – 2010, 2011 – 2017) and exposure was divided into three categories; no-CPR before EMS arrival, S-CPR with chest compressions and rescue breaths or CO-CPR.

6.2.1 Main results

Witnessed OHCA between 2000 – 2017 were included (N = 30 455), 40.0 % received no-CPR, 39.2 % received S-CPR, and 20.8 % received CO-CPR. The overall proportions of patients receiving CPR prior to EMS arrival changed from 40.8 % in the first time period to 68.2 % in the last period. S-CPR changed from 35.4 % to 38.1 % and CO-CPR changed from 5.4 % to 30.1 % respectively.

Figure 6: Percentages of no-CPR, S-CPR, and CO-CPR, by year and guideline period.



Guideline period	2000–2005	2006–2010	2011–2017
NO-CPR, n (%)	3834/6472 (59.2)	3050/7403 (41.2)	5240/16463 (31.8)
S-CPR, n (%)	2288/6472 (35.4)	3318/7403 (44.8)	6273/16463 (38.1)
CO-CPR, n (%)	350/6472 (5.4)	1035/7403 (14.0)	4950/16463 (30.1)

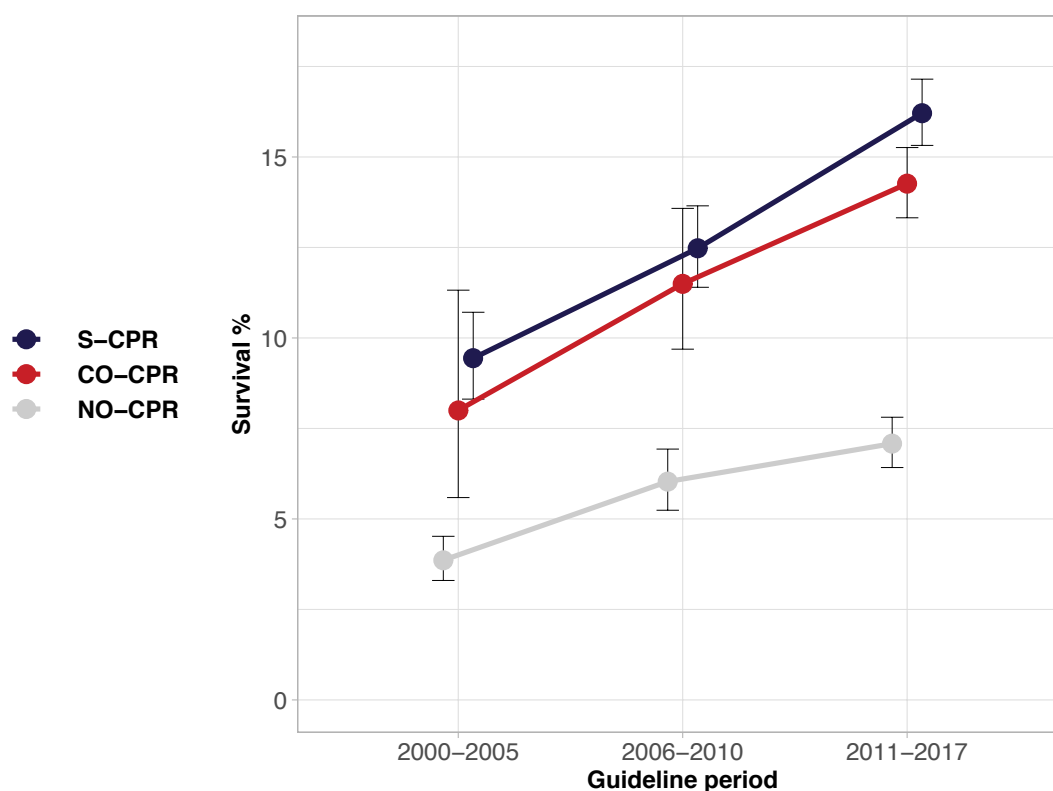
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Figure 6: CO-CPR indicates chest compression–only cardiopulmonary resuscitation; NO-CPR, no cardiopulmonary resuscitation; and S-CPR, standard cardiopulmonary resuscitation.

Overall, survival to 30 days changed from 6.1 % in 2000 – 2005 to 12.7 % in 2010 – 2017. Survival to 30 days for each category of CPR in the three guideline periods respectively is shown in Figure 7. Notably, survival was higher in all groups in the later time-periods in the study, including patients not receiving CPR prior to EMS arrival, indicating that several other factors aside from CPR contributed to the observed higher rate of survival over time.

Compared to no-CPR, the adjusted OR for 30-day survival were 2.6 (95 % CI, 2.4–2.9) for S-CPR and 2.0 (95 % CI, 1.8–2.3) for CO-CPR. S-CPR was superior to CO-CPR (adjusted OR, 1.2; 95 % CI, 1.1–1.4).

Figure 7: Thirty-day survival for each category of CPR, by guideline period (%)



Type of CPR		2000–2005	2006–2010	2011–2017
30-day survival	NO-CPR	148/3834 (3.9 %)	184/3050 (6.0 %)	371/5240 (7.1 %)
	S-CPR	216/2288 (9.4 %)	414/3318 (12.5 %)	1017/6273 (16.2 %)
	CO-CPR	28/350 (8.0 %)	119/1035 (11.5 %)	706/4950 (14.3 %)
MI AOR*	NO-CPR	ref	ref	ref
	S-CPR	3.07 (2.44–3.87)	2.44 (2.02–2.95)	2.61 (2.28–2.97)
	CO-CPR	1.90 (1.23–2.94)	1.85 (1.44–2.38)	2.11 (1.84–2.43)

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Figure 7: AOR indicates adjusted odds ratio; CO-CPR, chest compression–only cardiopulmonary resuscitation; CPR, cardiopulmonary resuscitation; EMS, emergency medical services; MI, multiple imputations; NO-CPR, no cardiopulmonary resuscitation; OHCA, out-of-hospital cardiac arrest; and S-CPR, standard cardiopulmonary resuscitation. *Adjusted for age, sex, cause, location, EMS response time, and year of OHCA.

5.3 STUDY III – “SURVIVAL AFTER DISPATCHER-ASSISTED CPR”

The aim of Study III was to assess survival after CPR with dispatcher CPR instructions compared with no CPR and CPR not requiring dispatcher instructions. Exposure was categorized as: no-CPR, DA-CPR and spontaneously initiated CPR (SP-CPR) prior to EMS arrival.

6.3.1 Main Results

In total, 15 471 lay-bystander witnessed OHCA patients were included and distributed as follows: no-CPR 41.6 %, DA-CPR 31.0 % and SP-CPR 27.4 %. Survival rates to 30 days were 7.1 %, 13.0 % and 18.3 %, respectively. Patients not receiving CPR prior to EMS arrival were older, more frequently of female sex, more likely to have collapsed at home and less frequently found in ventricular fibrillation. The baseline characteristics of the DA-CPR group had a close resemblance to the unfavorable baseline characteristics found in the no-CPR group.

After propensity score matching 3 091 patients remained in each group. Using DA-CPR as reference, SP-CPR was associated with a higher survival rate (conditional OR 1.21, 95 % CI 1.05–1.39) and no-CPR was associated with a lower survival rate (conditional OR 0.61, 95 % CI 0.52–0.72).

Figure 8: 30-day survival after propensity score matching

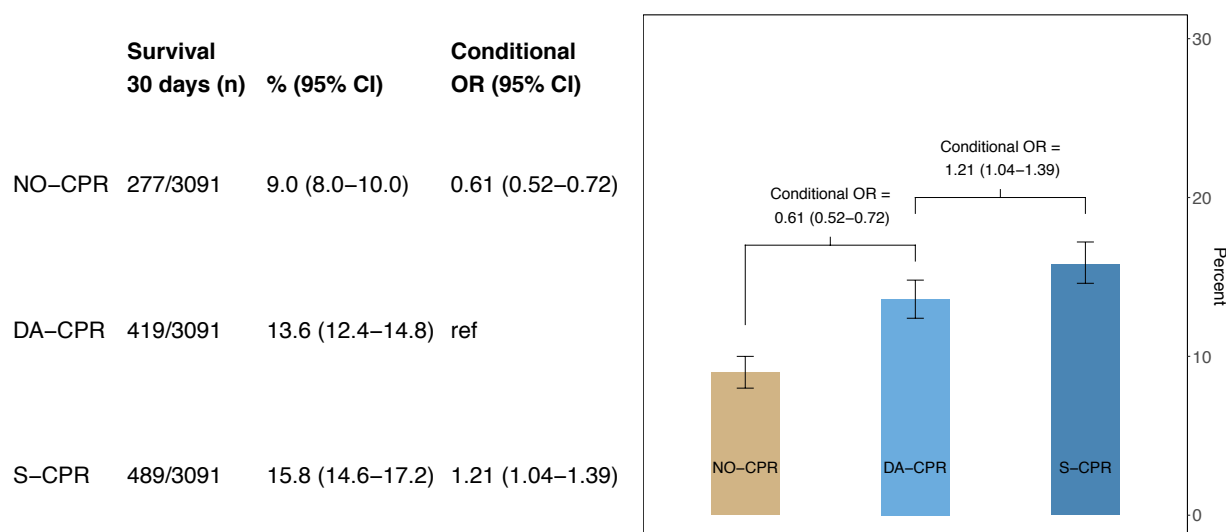


Figure 8: CPR = Cardiopulmonary Resuscitation, DA = Dispatcher-Assisted, SP-CPR = Spontaneously initiated CPR without dispatcher assistance, OR = Odds Ratio

5.4 STUDY IV – “FEASIBILITY ASSESSMENT OF THE RANDOMIZED CLINICAL TRIAL TANGO2”

In Study IV we aimed to assess feasibility, safety and intermediate clinical outcomes in a pilot study of the nationwide TANGO2 trial.

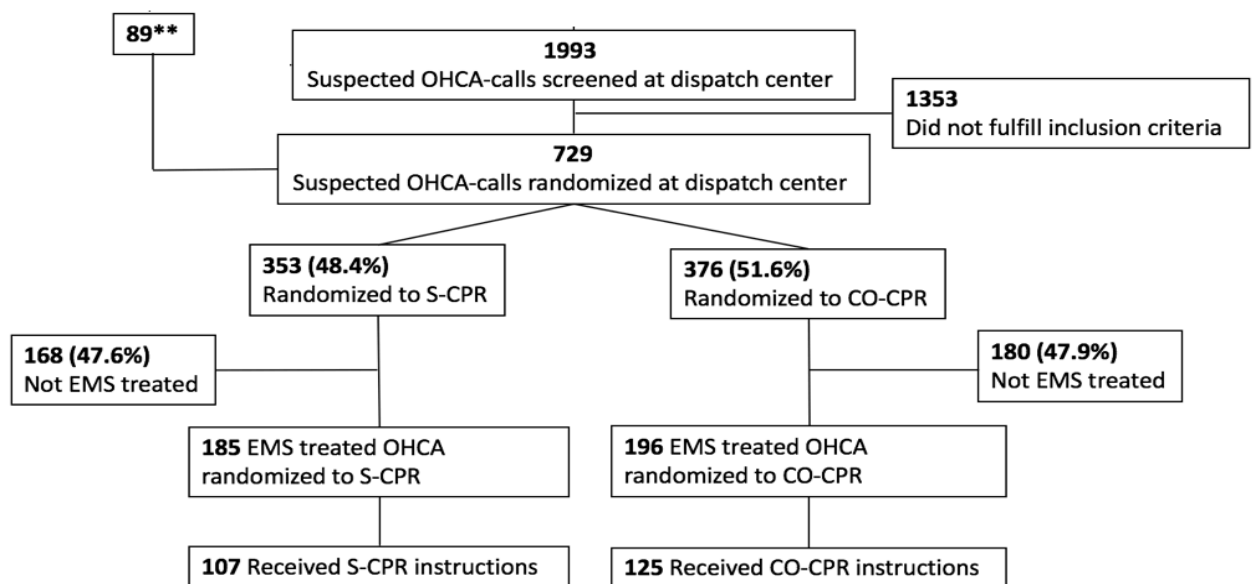
6.4.1 Main results

Between January 1 and December 31, 2017, a total of 1 993 emergency calls were screened for inclusion and 729 emergency calls were randomized at 17 dispatch centers in Sweden. Of these, 381 (51.4 %) were later confirmed to be EMS treated OHCA included in the analysis, 185 (48.6 %) were assigned to S-CPR and 196 (51.4 %) were assigned to CO-CPR.

Overall, CPR instructions were provided in 326/365 calls (89.3%) and CPR was initiated during the emergency call in 341/365 (93.4%). Median time to CPR instructions was 210 s in the S-CPR group (IQR 140 – 301) and 180 s in the CO-CPR group (IQR 135 – 275). Cross over from the S-CPR group to CO-CPR instructions was found in 40 calls (22.3 %), and from the CO-CPR group to S-CPR instructions in 30 calls (16.1 %).

The numbers of patients with VT/VF at first rhythm analysis were 39 (21.1 %) in the S-CPR group and 47 (23.9 %) in the CO-CPR group (NS). The numbers of patients surviving to hospital admission were 32 (17.3 %) versus 40 (20.4 %) for S-CPR and CO-CPR respectively (NS).

Figure 9: Flowchart of patient inclusion:



* 89 calls were randomized without completion of formal screening.

Table 2: Feasibility measurements:

	S-CPR	CO-CPR	p
Number	185	196	
Audio logs available, no. (%)	179 (96.8)	186 (94.9)	
CPR in progress at time of call, no. (%) *	14 (7.8)	8 (4.3)	n.s.
Time call to EMS dispatch, s (median [IQR])	60.0 [37.0, 88.0]	49.0 [32.0, 81.0]	n.s.
Time call to CA recognition, s (median [IQR]) *	90 [60, 180]	80 [45, 125]	0.016
Time call to CPR instructions, s (median [IQR]) *	210 [140, 301]	180 [136, 275]	n.s.
Time call to first compression, s (median [IQR]) *	200 [125, 310]	197.5 [140, 300]	n.s.
CA witnessed, no. (%) *	147 (82.1)	144 (77.4)	n.s.
Bystander with CPR training, no. (%) *	145 (81.0)	149 (80.1)	n.s.
Age above 18, no. (%) *	178 (99.4)	186 (100.0)	n.s.
Cardiac or unknown medical cause, no. (%) *	170 (95.0)	184 (98.9)	n.s.
CPR instructions started, no. (%) *	155 (86.6)	171 (91.9)	0.074
Dispatcher instructions S-CPR, no. (%) *	107 (59.8)	30 (16.1)	< 0.001
Dispatcher instructions CO-CPR, no. (%) *	40 (22.3)	125 (67.2)	
Chest compressions started, no. (%) *	167 (93.3)	174 (93.5)	n.s.

CPR = Cardiopulmonary Resuscitation, EMS = Emergency medical services, CA = Cardiac Arrest

** Information is based on review of audio logs. Percentages correspond to total number of available audio logs.*

Table 3. Patient baseline characteristics

	S-CPR	CO-CPR	p
Number	185	196	
Call to EMS arrival, min. (median [IQR]) *	11.3 [7.6, 17.7]	11.6 [7.4, 16.8]	n.s.
Age (median [IQR])	73 [65, 82]	73 [62, 82]	n.s.
Sex, male, no. (%)	127 (68.6)	112 (57.1)	0.048
Location, residential, no. (%)	136 (73.5)	162 (82.7)	0.035
Public AED connected during call, no. (%) *	12 (6.7)	7 (3.8)	n.s.

EMS = Emergency medical services, AED = Automated external defibrillator

* Information based on review of audio logs. Percentages correspond to total number of available audio logs

Table 4. Outcome measurements

Intention to treat*	S-CPR	CO-CPR	p
Number	185	196	
VT/VF at first rhythm analysis	39 (21.1)	47 (23.9)	0.724 (n.s)
Transferred to hospital	96 (51.9)	101 (51.5)	0.993 (n.s)
Admitted to hospital, n (%)	32 (17.3)	40 (20.4)	0.512 (n.s)

Per protocol**	S-CPR	CO-CPR	p
Number	107	125	
VT/VF at first rhythm analysis	22 (20.6)	23 (18.4)	0.373 (n.s)
Transferred to hospital	56 (52.3)	66 (52.8)	0.992 (n.s)
Admitted to hospital, n (%)	19 (17.8)	27 (21.6)	0.404 (n.s)

VT/VF = Ventricular Tachycardia/Ventricular Fibrillation

* All randomized EMS-treated OHCA

** All randomized EMS-treated OHCA cases in which the dispatcher provided instructions in accordance with randomized assignment.

6 DISCUSSION

6.1 MAIN FINDINGS

The main finding in this work include reinforcement of the independent association between CPR prior to EMS arrival and survival in OHCA. This association was found irrespectively of whether or not CPR was performed with compressions and ventilation, compressions-only or with dispatcher assistance. In addition, the results show that there was an almost doubled rate of CPR prior to EMS arrival in Sweden between the years 1990 – 2017. Altogether, the higher rate of CPR prior to EMS arrival is probably one factor contributing to the increased survival rate in OHCA observed in this time period.

Another finding was that the increase in CPR was most marked as regards CO-CPR. This is in line with temporal trends in other parts of the world.¹⁵⁰ However, in contrast to other settings, in Sweden there has never been any public campaign promoting CO-CPR.

We also found in our observational study that both S-CPR and CO-CPR were associated with a doubled chance of survival compared with no CPR, and S-CPR was associated with a smaller but significantly higher chance of survival compared with CO-CPR.

The pilot assessment of the TANGO2 trial revealed the trial to be feasible, and no statistically significant differences in survival to hospital admission were found. However, cross-over was found as a limitation that needs to be addressed in order to make the results from the main survival trial generalizable.

6.2 IS THE ASSOCIATION BETWEEN EARLY CPR AND SURVIVAL CAUSAL?

Study I – III in this thesis all rely on retrospective observational data reported to the SRCR. As such, the observed association between CPR prior to EMS arrival and survival could partially or completely be explained by residual confounding factors. Bystander CPR in OHCA has never been evaluated in a randomized trial, which has raised concerns of its efficacy.¹⁷⁵

Patients receiving CPR prior to EMS arrival in our studies had favorable characteristics compared to those not receiving CPR. They were younger, more likely to have collapsed outside home, had a higher frequency of cardiac cause and a higher frequency of VT/VF at first rhythm analysis. All these are well known factors associated with survival but after adjustment for all these factors the association between CPR and survival still remained in all studies. Of note, we did not have information on comorbidities or socioeconomic factors that might confound part of the observed association.

In summary, even if we cannot say for sure, the association between CPR survival was strong. Similar associations were found in all subgroups in study I. We found evidence suggesting a plausible mechanism for some of the effect of CPR in study II, and we found a biological gradient in study I; the earlier CPR was started, the better the outcome. Finally, this association has been reported by many others.⁵¹ All these factors suggest that there may be a causal relationship between CPR prior to EMS arrival and survival.

6.3 IS VT/VF AT FIRST RHYTHM ANALYSIS A CONFOUNDER?

Should VT/VF be adjusted for in OHCA studies? The proportion of VT/VF decreases with time, but the incidence of VT/VF at time of arrest is unknown. Animal and observational human data suggest that CPR could prolong VT/VF and increase the probability of VT/VF at first rhythm analysis.^{58,176,177} Therefore, the effect of CPR on survival could be partly mediated through this mechanism and we found an interaction between VT/VF, EMS response time and CPR in study II (figure 9). However, the proportion of VT/VF can be unevenly distributed also for other reasons not accounted for. In summary, some of the effect of bystander CPR could be mediated through VT/VF. Therefore, when assessing the effect of early CPR we believe it is reasonable to present data both with and without adjustment for VT/VF as in study II & III.

Figure 10: Probability of VT/VF at first rhythm analysis

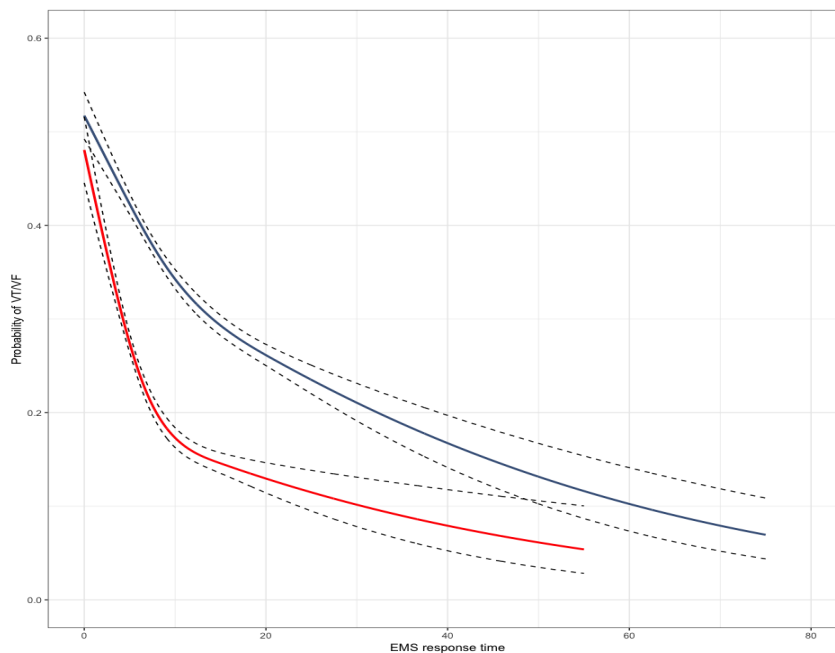


Figure 10: Describes the proportion of patients found in VT/VF as a function of time from call to EMS arrival. The red line is patients without CPR prior to EMS arrival and the blue line is patients that received CPR. Analysis of data from study II.

6.4 WHAT EXPLAINS THE HIGHER RATES OF CPR DURING THE STUDY PERIOD?

We found a dramatic increase in bystander CPR prior to EMS arrival over time. From 35 % in 1990 to almost 70 % in 2017 (study I & II). One explanation may be the continuous dissemination of CPR training to the general population in Sweden. Between 1984 – 2018 over five million attendees to a basic CPR course have been registered.² Of note, this figure should not be interpreted as five million individual participants, since some individuals certainly attended multiple CPR courses. Although the studies presented here cannot conclude a causal relationship of these two temporal trends, similar associations have been observed elsewhere.⁹²

Another explanation is the introduction of DA-CPR in 1998, but during the first years after implementation it was probably underused.^{84,178,179} Information on DA-CPR was not collected in SRCR until 2009, but since 2011 we found CPR performed in conjunction with dispatcher assistance in about one third of all OHCA (study III). This may indicate that dispatcher assistance probably has had large impact on the higher CPR rates in the later years. One can speculate that the final effect of the widespread CPR training and dispatcher assistance could be additive, since trained bystanders could be more willing to act when also receiving CPR instructions from dispatchers.⁹⁰ In study IV, more than 80 % of the bystanders had previous CPR training, but CPR was initiated before the emergency call in only 6 %, indicating that many witnesses require dispatcher assistance, even if they have had CPR training.

A third explanation could be the more frequent use of first responders such as fire fighters or police units to be dispatched in parallel to EMS in certain bigger regions since 2006.^{94,162,180} It is possible that this has confounded some of the observed higher CPR rates, due to ascertainment bias in cases when EMS arrived after fire fighters, which occurred in about one quarter of all cases between 2011 – 2017.

Finally, the implementation of a smartphone application to recruit volunteers to nearby OHCA in some regions may also have contributed in the latest years.^{181 97}

6.5 IS ENDORSEMENT OF CO-CPR ASSOCIATED WITH HIGHER RATES OF CPR PRIOR TO EMS ARRIVAL?

In study II we found a 6-fold increase in CO-CPR over three different guideline time periods. Our findings indicate that the endorsement of CO-CPR in CPR guidelines is associated with higher overall CPR rates, which may be linked with overall survival. This is in line with previous findings from the United States and Japan.^{149,174}

The reasons for the large increase in CO-CPR are probably multifactorial. It is plausible that increased use of dispatcher assisted CPR together with new guidelines is a main contributor to the observed increased CO-CPR rates. Also, during 2005-2009 there was a randomized trial comparing compression-only to compressions and ventilation in Sweden, confounding the increased rates of CO-CPR observed during those years.¹⁵³ One can speculate if this trial also had a hawthorn effect on dispatcher assisted CPR in those years.¹⁸² However, we do not believe dispatcher instructions explain the whole change in CO-CPR. In a study by Nord et al,¹⁸³ CO-CPR was used among both lay bystanders and bystanders with medical education in 2010 to 2014, implying that even highly trained bystanders perform CO-CPR in some situations. Reasons for this are not fully clear but could include focus on minimizing interruptions in chest compressions in CPR training, and the introduction of CO-CPR as an option, during the later time period of the study. Finally, campaigns from abroad such as the AHA's initiative Hands Only CPR¹⁸⁴ could have influenced public awareness and opinion of CO-CPR.

6.6 WHY HAVE WE ONLY INCLUDED WITNESSED OHCA?

In studies I-III we only included bystander witnessed events. The main reason was that the time of arrest is unknown which make time estimates unreliable. Also, any intervention performed late, or very late in a cardiac arrest would probably have minimal effect. Therefore, when comparing different types of CPR, the inclusion of not witnessed OHCA might dilute differences between the groups. To test this assumption, we performed a supplemental analysis of unwitnessed OHCA in study III. Survival ranged from 2.4 % - 4.6 % but neither type of CPR was associated with significant higher survival compared with no CPR. However, our selection could be a reason for criticism since unwitnessed arrest constitute about 1/3 of all OHCA.

6.7 SHOULD ALL OHCA EMERGENCY CALLS BE REVIEWED?

A limitation of study III is that we used the SRCR to define DA-CPR. This variable is less precise than if all emergency calls would have been assessed. In the light of the evolving understanding of the dispatcher's central role in OHCA, it is reasonable to suggest systematic data collection of emergency call processes and linking it to the SRCR.⁸¹ Such information could be a valuable complement and might identify specific elements in emergency call processing to be targeted in research or training. Templates for assessing key processes in emergency calls have been proposed, and these were used in study IV.¹⁸⁵

The AHA has issued performance goals for dispatcher-assisted CPR.¹⁸⁶ A similar initiative has recently been proposed by the Swedish CPR council in collaboration with the national emergency coordination agency (SOS-Alarm) and could serve as a benchmark for dispatcher performance.

6.8 WHICH OUTCOMES SHOULD BE MEASURED IN OHCA?

The first goal of resuscitation efforts is to achieve return of spontaneous circulation (ROSC) as the first step toward survival. Outcomes such as ROSC, survival to hospital admission or to a predefined number of hours are frequently reported in resuscitation research. However, these outcomes might not necessarily translate to what matters to patients.

Neurological function is frequently assessed by the CPC, scale (1-5). However, the CPC-scale might overestimate neurological function.¹⁸⁷ The modified Rankin Scale (mRS) is an alternative that is considered to offer more granularity. Another issue is the timing of neurological assessment, since neurological sequelae can improve over time.¹⁸⁸ To measure at hospital discharge is common, but timing of this assessment may differ substantially across health care organizations, making comparison difficult. Survival to 30-days seems to correlate well with long-term survival,⁹² and could be therefore be reasonable.

The Core Outcome Set for Cardiac Arrest (COSCA), defined in participation with patients and their relatives, suggest survival and neurological function (measured by mRS) at discharge or 30 days, and health related quality of life measurements at 90 days.¹⁸⁷

6.9 WHAT ARE THE WEAKNESSES AND STRENGTHS OF THE SWEDISH REGISTER FOR CARDIOPULMONARY RESUSCITATION?

Data in all registers are prone to selection bias, incomplete data (missing) and information bias, due to recall bias or input errors. The SRCR is a national register including all EMS organizations in Sweden. However, the SRCR has gradually expanded since the start in 1990, and therefore, estimates in the earlier time periods might not be generalizable to the national population. In validation of the register in 2013, 25% of all OHCA were not reported prospectively but were found and included after cross-checking of all EMS reports.¹⁷⁰ This underscores the importance of validation systems for cardiac arrest registers. Today there is a continuous process of cross-checking of EMS reports and retrospective inclusion to the register.

Missing variables constitute another mechanism that can introduce bias (missing is unlikely to be completely at random). In Studies I & II, 37 % and 18.4 % of the patients had missing data as regards at least one variable. To deal with this problem, multiple imputations were performed and did not alter the direction of the results. Missing of the most important variable “survival at 30-days” was very low (1 - 2 %), which is reassuring. Unfortunately, there was a larger proportion of patients with missing data on neurological function. Therefore, we were not able to assess this outcome in Studies II & III, which is a major limitation. Finally, some information gathered by witnesses and/or EMS personnel in a stressful scenario can be somewhat inaccurate, especially time estimations and events that occurred before EMS arrival.¹⁸⁹

However, we believe that with the nationwide coverage, continuous reporting, definitions that have remained constant over time and the retrospective cross-checking of all EMS reports, the register is fairly representative of the EMS-treated OHCA population in Sweden.

6.10 WHAT IS THE RATIONALE AND POTENTIAL BENEFITS OF CO-CPR?

Survival after OHCA is very poor, ranging from 7-12%.^{17,51} However, even in Sweden, a country with high CPR rates, around one third of all witnessed OHCA did not receive any intervention before EMS arrival in 2011 – 2017 (Study II). Barriers to the initiation of bystander CPR include fear of being incapable, causing harm, and infection.¹⁹⁰ Experimental studies and previous randomized trials have shown that successful CPR can be achieved with CO-CPR.¹⁵⁴ And simplified CPR might overcome some of these barriers. Furthermore, the incidence of OHCA is higher in areas with lower socioeconomic status,³⁷ but low socioeconomic status is also associated with lower CPR rates.¹⁹¹ Initiative of CO-CPR campaigns have been associated with substantially increased CPR rates and overall survival.¹⁴⁹ It is possible that simplified CPR training for lay persons could enhance the care for the overall OHCA patient group both nationally and internationally.

6.11 ARE THERE ANY POTENTIAL RISKS WITH CHEST COMPRESSION-ONLY CPR?

There are several potential risks with active promotion of CO-CPR. It is possible that bystanders might choose to omit ventilation, even if they can perform it, in circumstances where ventilation might be crucial. Another consideration is if the method is increasingly used for children who are more prone to hypoxic cardiac arrest.¹⁴⁴ Even if CO-CPR would be equally efficient for restarting the heart, if hypoxia results in worse neurological outcome is unknown.

There are some important differences between the European and American guidelines. The AHA endorses a Hands-Only CPR training program, including ultra-brief training videos and training kiosks to disseminate CO-CPR training to the general population.¹⁹² Even if chest compressions can be taught by ultra-brief training videos,¹⁹³ a real-life CPR training session could also offer a boarder perspective such as early signs and recognition which is fundamental. In summary, these factors have to be weighted carefully against the possibility of higher CPR rates by endorsing a simplified CPR method. Reliable data from a randomized trial could help in assessing this risk.

6.12 HOW RELIABLE IS THE EVIDENCE SUPPORTING CO-CPR?

Regarding dispatcher assisted CPR, there are three randomized trials comparing instructions to perform continuous compressions with instructions to perform 15:2.¹⁵¹⁻¹⁵³

There are some issues to consider when translating the results of these trials. All trials used instructions of a compression to ventilation ratio of 15:2 as a comparator, which inevitably leads to more interruptions in chest compressions than the current compression to ventilation ratio of 30:2. Two of the trials were conducted in urban areas with very short EMS response times, 4 and 6-7 minutes respectively. Since there might be a time dependent effect of omitting ventilation the results might not be generalizable to settings. All trials excluded randomized patients with OHCA that retrospectively was judged to be caused by hypoxia from the analysis. Therefore, the effect in these patients is unknown.

However, in all trials there was a nonsignificant trend towards higher survival in the group assigned to compressions only and in a meta-analysis of these trials there was a significant higher survival in favour of CO-CPR.¹⁵⁴ Also, observational data of emergency call processes indicate that simplified instructions shorten the time interval to CPR start and increases the proportion of CPR actually provided.¹⁹⁴

For observational studies relying on cardiac arrest registers the evidence is more uncertain. First, many of the studies have included selected populations, such as cardiac cause of arrest or among patients found in VT/VF.¹⁹⁵ Retrospective selection is problematic. A more straightforward way is to include all etiologies to evaluate the impact of CO-CPR at a populational level. In Study II we included all etiologies and found both CO-CPR and S-CPR to be associated with improved survival in among cardiac and non-cardiac causes of OHCA, in a similar way.

Secondly, many studies are from a time when the compression to ventilation ratio was 15:2 (instead of 30:2)^{148,196}. Others have included patients during a time when guidelines shifted

from 15:2 to 30:2.^{143,149} Therefore, these results might not translate to current practice. In Study II, we found survival in favor of S-CPR during the last guideline period, 2011 – 2017. This is in line with the results of a large observational Japanese study by Kaneko et al.²³ Our finding is important, but we were not able to adjust for use of DA-CPR or previous CPR training among lay bystanders. Adjustments for confounders is an importing task when drawing conclusions from observational trials. In a publication concerning Japanese cardiac arrest of medical origin there was a lower survival rate with CPC 1-2 among those treated with CO-CPR (5.6% vs 6.5%, OR 0.87 $p < 0.001$) but after propensity score adjustments the association was in favor of CO-CPR (7.2% vs 6.5%, OR 1.12 $p < 0.001$) which makes interpretation difficult.¹⁵⁰

In summary, there is evidence from three RCT's, as regards dispatcher assisted CPR. For trained bystanders, there is a paucity of evidence and there is no RCT evaluating CO-CPR vs 30:2 or including bystanders trained in CPR.

6.13 IS THE SURVIVAL DIFFERENCE BETWEEN CO-CPR AND S-CPR TIME-DEPENDENT?

Is oxygen and positive pressure ventilation necessary during CPR? And if so, immediately after collapse or after a certain period of time? In a subgroup analysis of Study II, stratified by EMS response time, we found CO-CPR not to be associated with higher survival when EMS response times ranged from 10-14 minutes, suggesting that ventilation is crucial when EMS response times are prolonged. This is in line with others who have investigated the relationship with EMS response time.¹⁴⁶ Conversely, Iwami et al reported a higher survival after CO-CPR among the subgroup of patients with VT/VF treated by means of AEDs, indicating a better effect of CO-CPR for patients with that rhythm, and when time to defibrillation is short. However, this was a highly selected subgroup, constituting of less than 2% of all witnessed arrests in that study.¹⁴⁷ All cardiac arrests are dynamic and the question of the relative importance of ventilation is important. The results from the TANGO2 trial might provide a better answer to this question, which could have an impact on current recommendations on dispatcher assisted CPR.

6.14 WHY WAS A PILOT STUDY PERFORMED IN THE TANGO2 TRIAL?

In order to test the planned inclusion and randomization procedure of the TANGO2 trial the steering group decided to carry out a pilot-study. There were several reasons for this.

First, there was a need to assess the potential inclusion rate. The target population intended in the TANGO2 trial was witnessed, adult OHCA of presumed cardiac cause, and bystander

with previous CPR training. This, to our knowledge is the first RCT trying to target this population, the reason being that trained bystanders could be expected to carry out CPR of good quality, thereby creating a more homogeneous population, and providing a better estimation of the effect of the two different instructions. At the start of the trial there was no clear idea of how big the proportion of all calls fulfilling these criteria would be.

Second, there was a need to evaluate the inclusion and randomization procedures. One risk that was identified when introducing a new procedure, interfering with the dispatchers work in a stressful situation, was unintended time delays. Time to EMS dispatch was defined as a key metric that could be measured before implementation of the study and compared with calls not included during the study period. Also, the inclusion and randomization software had to work fast.

Third, previous RCT's had included asphyxia arrests and children. The risk of including obvious asphyxia arrest was identified as an important potential risk that had to be evaluated.

Fourth, one of the previous RCT did not evaluate the actual call process or the instructions provided, yielding uncertainty of interpretation of the results. Therefore, all calls would be reviewed to evaluate adherence to protocol and estimate potential time differences to start of CPR instructions and start of CPR between the two methods. Whether or not callers would adhere to dispatcher instructions was also unknown.

Fifth, in order to assess possible harm, intermediate clinical outcomes such as VT/VF at first rhythm analysis and survival to hospital discharge would be evaluated.

6.15 WHAT ARE THE MAIN FINDINGS FROM THE PILOT TANGO2 TRIAL?

We interpret the results of the pilot study of the TANGO2 trial (Study IV) as a larger survival study is feasible although there are some important limitations that have to be addressed in order to make the results from the main trial generalizable.

Out of 13 495 calls to the emergency dispatch organization only 1993 underwent formal screening for inclusion. In part, this could be due to a stepwise introduction during the spring of 2017. Every individual team at the dispatch centers could decide when to start inclusion after all dispatch operators had received the mandatory training to participate in the trial. There is also a possibility that dispatchers judged a call as not suitable for inclusion, and therefore they did not complete the formal screening. This practice was revealed at follow-up visits and the importance of screening was stressed in repeated information to the dispatchers. Of the 729 calls that underwent randomization a total of 51 % were EMS

treated OHCA. This is well in line with what may be expected. In an evaluation of a smart-phone application system to recruit lay responders to suspected OHCA in Stockholm, 29 % (198 / 685) where the system was activated was EMS treated OHCA.⁹⁷

There was a relatively large proportion of cross over, most prominent from S-CPR to CO-CPR and this may be a major limitation in interpreting the results in the future main study. The reason for this cross over is not entirely clear. We speculate that dispatchers in some calls provided instructions they thought most appropriate or simpler to provide. This can reintroduce confounding and highlights the need of evaluation of adherence to protocol.

Finally, there was no significant difference in survival to hospital admission. Even if this is an important safety aspect, one should be careful in drawing conclusions from a study with a relatively small sample size and survival to hospital admission might not translate to meaningful outcomes for patients. Because of the seamless design of the study, the outcome of 30 days survival was not assessed in the PILOT-study.

6.16 FUTURE PERSPECTIVES:

In summary, these results reinforce the independent association between CPR prior to EMS arrival and survival in OHCA. This association was found irrespectively if CPR was performed with compressions and ventilation, compressions only or with dispatcher assistance.

However, there are still substantial knowledge-gaps concerning several important issues in early CPR. Is rescue breathing necessary during bystander CPR in cases of trained bystanders performing CPR? And if so, should ventilations be started immediately after collapse or after a certain period of time? Here we hope that the TANGO2 trial could add important evidence to answer this question. There is still uncertainty about the optimal methods of dispatcher-assisted CPR that merit further research – how can some of the barriers to dispatcher-assisted CPR be overcome? There is also a need for more research in the field of CPR-training and implementation. What method of training should be used and what would a positive TANGO2-trial (i.e. CO-CPR non-inferior or superior to S-CPR) mean for CPR-training, bearing in mind that some OHCA have a hypoxic cause?

Finally, one of the main limitations of all studies comparing different compression to ventilation ratios is the lack of assessment of CPR quality. To what extent do bystanders perform CPR of good quality? Today, there are technical devices that theoretically could enable measurement of some of these parameters. An optimal study to improve our understanding of bystander CPR in real-life scenarios should include novel measurements of CPR quality.

7 CONCLUSIONS

Study I:

In OHCA, CPR performed prior to EMS arrival was associated with a more than doubled 30-day survival rate compared to if no CPR was performed.

Study II:

In this nationwide study of OHCA there was a nearly two-fold increase of CPR before EMS arrival over three periods of different CPR guidelines. A concomitant 6-fold increase of chest compression only CPR was also observed. Any type of CPR was associated with doubled survival rates in comparison with no CPR.

Study III:

In this nationwide study, dispatcher assisted CPR was found to be associated with a higher chance of survival compared with no CPR, but a lower chance of survival compared to spontaneously initiated CPR.

Study IV:

The pilot study of the randomized clinical TANGO2-trial comparing survival after dispatcher instructions of standard CPR with compressions and rescue breaths vs compressions only CPR to trained bystanders in OHCA was found to be feasible. No statistically significant differences in survival to hospital admission were found. However, cross-over between treatment groups was found as a limitation that needs to be addressed in order to make the results from the main survival trial generalizable.

8 SAMMANFATTNING PÅ SVENSKA

Bakgrund: Hjärtstopp som inträffar i samhället drabbar över 6 000 personer varje år och endast en av tio överlever. En av de viktigaste faktorerna för ökad överlevnad är att basal hjärt-lungräddning (HLR) påbörjas innan ambulansens ankomst. Dock är effekterna av tillgängliga metoder för hjärt-lungräddning, liksom deras koppling till överlevnad, ofullständigt kartlagda. Det övergripande syftet med detta forskningsprojekt är att vid användning av olika HLR-metoder studera överlevnad vid hjärtstopp utanför sjukhus.

Metod: Alla patienter i dessa studier har drabbats av hjärtstopp utanför sjukhus. Studie I – III är observationsstudier baserade på svenska hjärt-lungräddningsregistret. Studie IV är en pilotstudie inför en nationell randomiserad studie som jämför överlevnad efter instruktion från larmoperatör att utföra standard-HLR med bröstkompressioner och inblåsningar, eller enbart bröstkompressioner, till vittnen med HLR-utbildning vid hjärtstopp utanför sjukhus (TANGO2-studien).

Specifika syften och resultat:

I **studie I** jämfördes patienter med bevittnat hjärtstopp utanför sjukhus och där HLR påbörjats innan ambulans anlönt med dem som inte fått HLR vid denna tidpunkt, med avseende på överlevnad till 30 dagar. Alla fall av bevittnade hjärtstopp som rapporterades till hjärt-lungräddningsregistret mellan 1990 – 2011 inkluderades (N = 30 391). I 51 % av fallen hade HLR påbörjats innan ambulans anlönt. Överlevnad till 30 dagar var 10,5% för dem som fått HLR innan ambulans anlönt och 4,0% för dem som inte fått någon HLR vid denna tidpunkt, ojusterat odds ratio (OR) 2.80 (95% CI 2,47 – 3,18), justerad OR 2.15 (95% CI 1,88 – 2,45). Korrelationen mellan överlevnad och HLR som påbörjats innan ambulansens ankomst var starkare när tiden till start av HLR var kort.

Förenklad HLR med enbart bröstkompressioner introducerade som ett alternativ till kompressioner och inblåsningar i europeiska riktlinjer år 2005. År 2010 utvidgades den rekommendationen till att gälla även utbildade livräddare och vid telefonassisterad HLR. Syftet med **studie II** var att beskriva andelen patienter som fått HLR samt vilken HLR-metod som utfördes innan ambulans anlönt, samt samband mellan metodval och överlevnad under tre tidsperioder med olika riktlinjer för hur basal HLR skall utföras. Alla bevittnade fall av hjärtstopp i Sverige år 2000 – 2017 inkluderades (N = 30 455). Hjärtstoppen delades in i tre tidsintervall som motsvarar de olika riktlinjeperioderna (2000 – 2005, 2006 – 2010, 2011 – 2017). Patienterna delades sedan in dem som inte fått HLR, standard-HLR (S-HLR) eller HLR med enbart bröstkompressioner. Andelen som fått någon form av HLR innan ambulansens ankomst ökade under de tre studerade tidperioderna (från 40,8% till 58,2% till 68,2%). Samtidigt sågs en nära sexfaldig ökning av andelen som fått HLR med enbart

bröstkompressioner (från 5,4% till 14,0% till 30,1%). Justerad OR för överlevnad till 30 dagar var 2,6 (95% CI 2,4 – 2,9) för S-HLR och 2,0 (95 % CI 1,8 – 2,3) jämfört med de som inte fick HLR innan ambulansens ankomst. S-HLR var associerat med högre överlevnad jämfört med enbart bröstkompressioner (justerad OR 1,2 (95% CI 1,1 – 1,4).

Syftet med **studie III** var att utvärdera överlevnaden efter telefonassisterad HLR jämfört med ingen HLR och spontant påbörjad HLR innan ambulansens ankomst. Hjärtstopp utanför sjukhus bevitnade av lekmän mellan 2011 – 2017 inkluderades (N = 15 471). Med telefonassisterad HLR som referens var spontant påbörjad HLR associerad med ökad överlevnad, justerad OR 1,2 (95% CI 1,05 – 1,39) och ingen HLR med lägre överlevnad, justerad OR 0,61 (95% CI 0,52 – 0,72).

Syftet med **studie IV** var att utvärdera genomförbarhet och studera tidiga kliniska utfallsmått i TANGO2 pilotstudien. Från 1 januari till 31 december 2017 randomiserades 729 larmsamtal beträffande misstänkta hjärtstopp. Av dessa var 51,4% (n = 381) bekräftade hjärtstopp, som inkluderades i analysen. Instruktioner om att utföra HLR gavs i 89,3% av dessa samtal. Mediantid till HLR instruktion av larmoperatörer var 210 sekunder i gruppen som randomiserats till S- HLR (IKA 140 – 301) och 180 sekunder i gruppen som randomiserats till enbart bröstkompressioner (IKA 135 – 275). Tidsskillnaden var ej statistiskt signifikant. Av de som randomiserats till S- HLR gavs instruktioner om enbart bröstkompressioner i 22,3% (40 samtal) och av de som randomiserats till enbart bröstkompressioner gavs instruktioner om standard HLR i 16,1% (30 samtal). Antalet patienter som överlevde till sjukhus var 17,3 % (n = 32) för S-HLR och 20,4% (n = 40) för enbart bröstkompressioner. Skillnaden var ej statistiskt signifikant.

Slutsats: Dessa resultat ger stöd för att HLR utförd av vittnen före ambulansens ankomst bidrar till förbättrad överlevnad efter hjärtstopp som inträffar ute i samhället, oavsett om HLR utförs med kompressioner och inblåsningar, enbart bröstkompressioner, eller med stöd av telefoninstruktioner från en larmoperatör. Andelen som fått HLR innan ambulansens ankomst dubblerades mellan år 1990 – 2017 och andelen som erhållit enbart bröstkompressioner ökade sexfaldigt mellan år 2000 – 2017. Utvärderingen av pilotstudien inför TANGO2 visade att en huvudstudie är genomförbar. Dock visade studien på bristande följsamhet till randomiserad metod, vilket är en svaghet som behöver åtgärdas för att resultatet från huvudstudien ska kunna generaliseras.

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