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BY
SHAHZLEEN RAJAN

DISSERTATION SUBMITTED 2017

AALBORG UNIVERSITY
DENMARK

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PAPERS

This thesis is based on research conducted during my years as a PhD student at the Department of Cardiology, Gentofte Hospital and the Department of Clinical Medicine, Aalborg University Hospital. The thesis is based on the following three original published epidemiological studies:

Paper I
Rajan S, Folke F, Kragholm K, Hansen CM, Granger CB, Hansen SM, Peterson ED, Lippert FK, Søndergaard KB, Køber L, Gislason GH, Torp-Pedersen C, Wissenberg M. Prolonged cardiopulmonary resuscitation and outcomes after out-of-hospital cardiac arrest. ***Resuscitation***. 2016;105:45-51.

Paper II.
Rajan S, Wissenberg M, Folke F, Hansen SM, Gerds, TA, Kragholm K, Hansen, CM, Karlsson L, Lippert FK, Køber L, Gislason GH, Torp-Pedersen C. Association of bystander cardiopulmonary resuscitation and survival according to ambulance response-times after out-of-hospital cardiac arrest. ***Circulation***. 2016;134:2095-2104.

Paper III.
Rajan S, Folke F, Hansen SM, Hansen CM, Kragholm K, Lippert FK, Karlsson L, Møller S, Køber L, Gislason GH, Torp-Pedersen C, Wissenberg M. Incidence and survival outcome according to heart rhythm during resuscitation attempt in out-of-hospital cardiac arrest patients with presumed cardiac etiology. ***Resuscitation***. 2017;114:157-163.

SUMMARY

Out-of-hospital cardiac arrest (OHCA) is a major public health problem worldwide. The physical location outside of a hospital and the fact that a cardiac arrest can happen anywhere and at any time, imposes risks of delay or absence in recognition of cardiac arrest and treatment. Since time from the collapse till resuscitative treatment is a crucial factor for subsequent survival, OHCA is not only a concern for health professionals, but also for lay people observing the arrest. Proactiveness from any individual with immediate resuscitative treatment efforts while waiting for an ambulance can substantially increase not only a patient's chance of surviving, but also a patient's chance of surviving to a good quality of life.

Key elements and the importance of prompt response by citizens and health care professionals to save the life of an OHCA victim has been summarized in the chain of survival concept consisting of four links: early recognition, early cardiopulmonary resuscitation (CPR), early defibrillation, and advanced post-resuscitation care. The aim of this present thesis was to investigate important questions related to the pre-hospital links of the chain of survival, specifically: study I) to what extent can prolonged resuscitative efforts by the emergency medical services lead to survival, and if so, can it be reached with a subsequent good functional status?; study II) "bystander CPR buys time until advanced treatment arrives" is an often-repeated mantra, but for how long does bystander CPR continue to be associated with increased survival as time before advanced treatment increases?; and finally study III) what is the incidence and prognosis for heart rhythm conversion from non-shockable to shockable rhythm during a resuscitation attempt by the emergency medical services, and what predicts rhythm conversion? In order to investigate these questions, we used data from the Danish Cardiac Arrest Register. In study I, all cardiac arrest patients handled by the largest nationwide ambulance provider Falck A/S and who achieved a pre-hospital return of spontaneous circulation were identified during the study period 2005-2011; for study II, all cardiac arrest patients handled by Falck A/S were identified during the study period 2005-2011; and for study III, all cardiac arrest patients registered in the Danish Cardiac Arrest Register between 2005-2012 were identified. The final included study populations were 1,316 patients for study I, 7,623 for study II and 13,860 for study III.

Study I: Of patients with long pre-hospital resuscitation durations by the emergency medical services (>25 minutes) before achieving a pre-hospital return of spontaenous circulation, more than 13% survived to a minimum of 30 days after the OHCA. Of these surviving patients, the majority were able to return to own homes rather than nursing homes (>90%), and were discharged without a diagnosis of new onset of anoxic brain damage (>70%).

Study II: In fully adjusted models, bystander CPR was associated with a 2.3 fold increase in 30-day survival after 5 minutes of ambulance response time, and a 3.0 fold increase at 10 minutes of ambulance response time. The association decreased thereafter, and was statistically insignificant after 13 minutes compared to no bystander CPR. The adjusted 30-day survival chances were 14.5% with bystander CPR and 6.3% without bystander CPR after 5 minutes; the corresponding figures after 10 minutes were 6.7% and 2.2%, respectively. An additional of 119 patients could potentially be saved every year in Denmark if ambulance response time is reduced from 7 minutes (median in this study) to 5 minutes.

Study III: Conversion to a shockable rhythm from a first-recorded non-shockable rhythm was relatively common: of all patients who received defibrillation by the emergency medical services, 25% were initially found in non-shockable rhythms upon ambulance arrival. Compared to sustained non-shockable rhythms, converted shockable rhythms and first-recorded shockable rhythms were significantly associated with increased 30-day survival in fully adjusted models (odds ratio: 2.6, 95% CI: 1.8-3.8 for converted rhythms and odds ratio: 16.4, 95% CI: 12.4-21.2 for initial shockable rhythms). Thirty-day survival predictions increased significantly for all three rhythms between 2005 and 2012: from 16.3% to 35.7% for first-recorded shockable rhythms; from 2.1% to 5.8% for converted shockable rhythms; and from 0.6% to 1.8% for sustained non-shockable rhythms. Factors predicting rhythm conversion from a first-recorded non-shockable rhythm to a shockable rhythm included younger age, male sex, witnessed arrest, bystander CPR, shorter ambulance response time, and cardiac comorbidities, while psychiatric- and chronic obstructive pulmonary disease were significantly associated with sustained non-shockable rhythms.

The results of this thesis demonstrates that even those OHCA patients who required long durations of resuscitation before return of spontaneous circulation was achieved had meaningful 30-day survival rates and were able to function in their own homes without home care needs, suggesting that prolonged resuscitation is not futile. The thesis also showed that the absolute benefit of bystander CPR seemed to decline with increasing time to advanced treatment. However, bystander CPR was still associated with more than a doubling of 30-day survival even when the time to advanced treatment was more than 10 minutes, compared to no bystander CPR. Reducing time to advanced treatment by even a few minutes could lead to many additional lives saved every year. Finally, this thesis found that converting to a shockable heart rhythm from a first-recorded non-shockable heart rhythm was associated with a two times higher odds of survival 30 days after the arrest compared to sustained non-shockable rhythms. Rhythm conversion was relatively common.

DANSK RESUMÉ

Hjertestop uden for hospital (out-of-hospital cardiac arrest, OHCA) er et stort sundhedsproblem på verdensplan. Grundet den fysiske placering af hjertestoppet uden for hospitalet, samt det faktum, at et hjertestop kan ske hvor-som-helst og når-som-helst, er der risiko for forsinkelse eller helt fravær i erkendelse af hjertestop samt behandling. Da tiden fra kollaps til genoplivningsforsøg er af afgørende betydning for den efterfølgende overlevelse, er OHCA ikke kun en opgave for sundhedspersonale, men for alle borgere i et land. Øjeblikkelig genoplivningsforsøg af lægmand, mens der ventes på en ambulance, kan ikke blot øge patientens chance for overlevelse, men også patientens chance for at overleve med en god livskvalitet.

Nøgle elementer med vigtigheden af hurtig intervention fra lægmænd samt sundhedspersonale er sammenfattet i det velanerkendte koncept ”overlevelseskæden” der består af fire led: (1) tidlig erkendelse, (2) tidlig hjertelungeredning (HLR), (3) tidlig defibrillering, og (4) avanceret behandling efter genoplivning. Formålet med denne afhandling var at forsøge at besvare vigtige spørgsmål der omhandler den præ-hospitale del af overlevelseskæden, herunder specifikt: studie I) i hvilken grad kan langvarig genoplivning udført af ambulance personale føre til overlevelse, og i så fald, vil patienten have en god funktionel status?; studie II) ”HLR udført af lægmand køber tid til den professionelle hjælp når frem” er et mantra man ofte hører, men hvor længe er HLR egentlig fortsat forbundet med øget overlevelse når tiden til professionel hjælp stiger?; og endelig studie III) hvad er incidensen og prognosen af konvertering til stødbar hjerterytme fra en først-registeret ikke-stødbar hjerterytme under et genoplivningsforsøg udført af ambulance personale, og hvilke faktorer kan prædiktere en rytmekonversion? For at komme svarene nærmere, anvendte vi data fra det Danske Hjertestop Register. I studie I blev alle hjertestop patienter der blev håndteret af den største landsdækkende ambulance-udbyder Falck A/S, og som opnåede præ-hospitalt genoprettet spontant kredsløb, i studie perioden 2005-2011 identificeret; I studie II blev alle hjertestop patienter der blev håndteret af Falck A/S identificeret i studie perioden 2005-2011; og i studie III blev alle hjertestop patienter registreret i det Danske Hjertestop Register mellem 2005-2012 identificeret. De endeligt inkluderede studiepopulationer var 1,316 patienter for studie I, 7,623 for studie II og 13,860 for studie III.

Studie 1: Af de patienter der modtog et langvarigt genoplivningsforsøg af ambulance personale (>25 minutter) inden de opnåede genoprettelse af spontant kredsløb, overlevede over 13 % til og med minimum dag 30. Af disse overlevere var de fleste i stand til at vende tilbage til eget hjem i modsætning til plejehjem (>90%) , og størstedelen blev udskrevet uden diagnosen anoksisk hjerneskade (>70%)

Studie II: HLR af lægmand var forbundet med 2.3 gange øget 30-dages overlevelse hvis ambulancen ankom indenfor 5 minutter, og 3.0 gange øget 30-dages overlevelse hvis ambulancen ankom indenfor 10 minutter i fuldt justeret modeller. Den positive association faldt herefter, og efter 13 minutter var der ikke længere statistisk signifikant forskel i 30-dags overlevelsen. Hvis ambulancen ankom inden for 5 minutter, var den fuldt justerede 30-dages overlevelse 14.5 % hvis lægmand havde udført HLR og 6.3% hvis lægmand ikke havde udført HLR; tilsvarende var 30-dages overlevelsen henholdsvis 6.7% samt 2.2% hvis det tog 10 minutter før hjælpen nåede frem med ambulancen. I Danmark vil man potentielt kunne redde yderligere 119 liv hvert år, hvis tiden til avanceret behandling bliver reduceret fra 7 minutter (medianen i dette studie) til 5 minutter**.**

Studie III: Konvertering fra ikke-stødbar rytme til stødbar rytme under genoplivningsforsøg af ambulance personale var relativ hyppig: omkring 25 % af alle patienter der modtog stød af ambulance personale havde en ikke-stødbar rytme ved ankomsten af ambulancen. Konverterede stødbare rytmer, samt første-registrerede stødbare rytmer var, i fuldt justerede modeller, positivt forbundet med øget 30-dages overlevelse sammenlignet med vedvarende ikke-stødbare rytmer (odds ratio: 2.6, 95% CI: 1.8-3.8 for konverterede stødbare rytmer og odds ratio: 16.4, 95% CI: 12.4-21.2 for første-registrerede stødbare rytmer). I prædikative modeller steg 30-dages overlevelsen signifikant for alle tre rytmer mellem 2005 og 2012: fra 16.3% til 35.7% for første-registrerede stødbare rytmer; fra 2.1% til 5.8% for konverterede stødbare rytmer; og fra 0.6% til 1.8% for vedvarende ikke-stødbare rytmer. Faktorer der prædikterede at en ikke-stødbar rytme konverterede til stødbar-rytme, inkluderede yngre alder, hankøn, bevidnet hjertestop, HLR af tilskuer, kortere ambulance responstid, samt hjertesygdom; i modsætning var psykiske lidelser samt kronisk obstruktiv lungesygdom signifikant forbundet med vedvarende ikke-stødbar rytme**.**

Resultaterne af denne afhandling viser, at selv de OHCA patienter, hvor der skulle lange genoplivningsforsøg til før der var opnået genoprettet spontant kredsløb, var 30-dages overlevelsen meningsfuld, og indikerer at langvarig genoplivning ikke er forgæves. Afhandlingen viser også, at den absolutte gavn på overlevelse af HLR af lægmand faldt hurtigt med stigende tid til avanceret behandling. Dog var HLR af lægmand stadig forbundet med mere end en fordobling af 30-dages overlevelse, selv når ventetiden til avanceret behandling var over 10 minutter, sammenlignet med hvis der ikke var givet HLR af lægmand. Hvis tiden til avanceret behandling reduceres med blot få minutter i Danmark, vil det potentielt kunne medføre at mange flere menneskeliv reddes hvert år. Endelig viser afhandlingen, at konversion til en stødbar hjerterytme fra en første-registreret ikke-stødbar rytme var forbundet med to gange højere odds for 30-dages overlevelse i forhold til vedvarende ikke-stødbar rytme. Rytmekonversion til stødbar rytme var relativt almindeligt.

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Shahzleen Rajan,
September 2017

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INTRODUCTION

Out-of-hospital cardiac arrests

Out-of-hospital cardiac arrest (OHCA) poses a substantial public health burden worldwide, with high incidences and high mortality rates. In Europe, more than 275,000 cases are reported every year, while the equivalent rate in the United States is more than 420,000 cases, and varying incidence rates of approximately 35-55 OHCA per 100,000 person-years have been reported.[1-3] The average survival rate after OHCA among studies considering large study populations is around 10%.[3,4] However, substantially higher survival rates can be achieved if circumstances around the OHCA are optimal.[5]

Chain of survival and the impact of time on OHCA patient survival

Improving survival following OHCA requires immediate treatment of the OHCA patient. As the time from the collapse till resuscitative treatment is a crucial factor for subsequent survival, the physical location outside of a hospital imposes risks of delay or absence in recognition of arrest and treatment. OHCA is therefore not only a concern for health care professionals, but also any individual present, as their proactiveness with prompt resuscitative treatment can substanially increase the patient's chance of surviving the arrest.[6-10] The 'chain of survival' concept, initially introduced in guidelines in the early 90s, summarizes four early links/steps that are vital for successful resuscitation of an OHCA patient: 1) Early recognition and call for help, 2) Immediate cardiopulmonary resuscitation (CPR), 3) Rapid defibrillation, and 4) Early advanced care and post-resuscitation care, of which a layperson can be involved in the first three steps.[11] All these interventions are closely linked to increased chances of return of spontaneous circulation before the patient is transported to the hospital for post-resuscitative care[12-19] as well as increased chances of successful long-term survival with good neurologic outcome,[13,14,17,20-22] and where the majority of the surviving patients are able to return to work.[23]

If a patient does not receive prompt response after the OHCA, the chance of survival decreases approximately 10% per minute, but with immediate CPR the chance of surviving is increased 2-3 fold.[24] Early defibrillation within the first four minutes has been associated with survival rates higher than 50%.[5,19,25-29] However, if provision of defibrillation is delayed for longer periods, the chances of successful defibrillation and subsequent increased survival diminishes quickly.[30-32] Thus, several aspects in the treatment of an OHCA patient are time-sensitive. More knowledge on the time-sensitive aspects during treatment can help planning future strategies in handling of OHCA, including knowledge on how survival may be affected by increasing time to advanced care (including defibrillation), as well as survival related to continued resuscitative efforts with increasing downtime (time from collapse to return of spontaneous circulation). This thesis focuses on pre-hospital interventions described in the chain of survival and associated outcomes, including bystander CPR, resuscitation by the emergency medical services and defibrillation, with focus on how increasing time to advanced care (including defibrillation) and increasing downtime can potentially alter outcomes following the interventions.

Resuscitation during increasing downtime

Once the emergency medical services have been alerted about an OHCA, and they arrive on site of an OHCA to initiate resuscitation, resuscitation continues until the patient either achieves return of spontaneous circulation, or until it is decided that further resuscitation is futile. Making a decision about the latter is a very difficult task: a central aspect is not only if the patient will achieve return of spontaneous circulation and subsequently survive if resuscitation is prolonged, but also whether the patient is discharged to a meaningful life. Even though achieving a pre-hospital return of spontaneous circulation is a primary goal during a resuscitation attempt,[33,34] clinicians may give up if return of spontaneous circulation is not readily achieved, mainly due to fear of poor outcomes.[35] Only limited data exists that has examined association of time from initiation of CPR by the emergency medical services till return of spontaneous circulation is achieved, and related survival and neurological outcomes.[36-39] Such data could provide useful information and influence the decision-making on the willingness to continue resuscitation for a longer time if the outlook is otherwise reasonable. Paper I of this thesis deals with this issue.

Bystander-initiated CPR while waiting for an ambulance

Among other time factors, early bystander CPR, early defibrillation and prompt access to advanced post-resuscitative care are important for successful resuscitation after OHCA. Previous work has implied that apart from reducing the risk of death and brain damage by sustaining a small, but crucial blood flow to vital organs, bystander CPR can also postpone the deterioration of a shockable rhythm into a non-shockable rhythm, and thereby prolong the timeframe for potential defibrillation.[40-44] Research has also demonstrated that the sooner a shockable rhythm is defibrillated, the better the chances of survival.[5,29] In this regard, the 3-Phase Time-Sensitive Model concerning resuscitation after cardiac arrest emphasizes a need for time-sensitive ischemia/reperfusion therapy, and suggests that immediate defibrillation is useful if provided within four minutes of the cardiac arrest.[30] Defibrillation represent a potential definitive treatment, but public automated external defibrillator use is unfortunately limited by logistic challenges such as lack of knowledge regarding the location of the automated external defibrillator, accessibility as well as viability at the time of the OHCA, and lack of information to the public.[45] As a result, bystander CPR is the most common resuscitative intervention before EMS arrival. During the last decade, much focus has been on improving and increasing bystander intervention, and the increase in bystander CPR as well as survival has been found in many countries, including Denmark.[12-14,17,19,46-48] However, before paper II of this thesis, not much was known about to what extent bystander CPR continues to be positively associated with survival with increasing time to CPR and potential defibrillation by the emergency medical services. Such information can be useful when planning ambulance distributions, as well as first-responder programs and availability of automated external defibrillators.

Conversion of heart rhythm and defibrillation

One of the main cardiac arrest factors that seem to influence survival rates following OHCA is whether the patients are found in a shockable heart rhythm (ventricular fibrillation or ventricular tachycardia) or a non-shockable heart rhythm (asystole or pulseless electrical activity), with shockable rhythms being linked to higher survival rates and non-shockable rhythms being linked to lower survival rates.[14,49,50] Previous studies suggest that shockable rhythms deteriorate into non-shockable rhythms with increasing time, making time one of the key factors in the chances of survival after an OHCA.[24,40,51] Even though the prognosis for patients with first-recorded shockable rhythms is better than patients with first-recorded non-shockable rhythms,[14,49,50] in some instances, a first recorded non-shockable rhythm can convert into a shockable rhythm during the course of a resuscitation attempt. Previous studies have linked converting to a shockable rhythm to higher survival and favorable neurological outcome compared to rhythms that remain non-shockable throughout the pre-hospital resuscitation attempt.[52-56] However, little is known about which pre-hospital factors, including patient characteristics (age, sex, and comorbidities), that are associated with conversion to a shockable rhythm, and how these factors can aid in explaining the differences between groups of OHCA patients who seem to have the best, middle and worst outcome chances. The temporal survival for converted shockable rhythms is also largely unknown. Paper III of this study has sought to elucidate these factors.

Aims of this thesis

The overall aim of this thesis was to examine important pre-hospital steps initiated by bystanders and the emergency medical services, and their relation to time and outcome (paper I and II). Another overall aim was to gain an understanding of patients who end up converting to a shockable rhythm after initially being found in a non-shockable rhythm by the emergency medical services, and overall differences between patients with first recorded shockable-, converted shockable-, and sustained non-shockable rhythm (paper III). To achieve these overall aims, the following specific aims / questions were pursued:

- **Study I:** Can prolonged resuscitative efforts by the emergency medical services lead to survival, and if so, with a good functional status?
- **Study II:** "Bystander CPR buys time until advanced treatment arrives" is an often-repeated mantra, but for how long does bystander CPR continue to be associated with increased survival as time to advanced treatment increases?
- **Study III:** How often does one patient convert to a shockable rhythm from a first recorded non-shockable rhythm during a resuscitation attempt by the emergency medical services, what is the prognosis, and what predicts rhythm conversion?

METHODS

Data sources and definitions

The study populations for all three papers were derived from the Danish Cardiac Arrest Register.[57] This register was established in 2001 with the purpose of collecting data on all OHCA victims on a national level, for whom resuscitation was attempted (CPR and / or defibrillation) by either bystanders or the emergency medical services. By applying this OHCA definition, patients with obvious late signs of death, e.g. rigor mortis, where resuscitation is not initiated are not included in the register. The completeness of the register is ensured by: 1) contractual agreements with the emergency medical services in all five regions to complete a case report for every attended OHCA where a resuscitation attempt is initiated; and 2) activation of the emergency medical services for all clinical emergencies in Denmark, including cardiac arrests.

The emergency medical service personnel collect data on OHCA cases prospectively after each attended OHCA, using a standardized form that follows the Utstein criteria for reporting of OHCA. This form makes up the Danish Cardiac Arrest Register and includes information on patient identification with civil registration number, as well as cardiac arrest characteristics, including location of arrest (private home vs. public location), witnessed status, whether CPR was initiated by a bystander or whether defibrillation was performed by a bystander, first recorded heart rhythm, defibrillation by the emergency medical services and patient status upon arrival at the hospital. In addition to this information, the largest nationwide ambulance provider in Denmark, Falck A/S, provided electronic data on various time intervals for each OHCA attended by them, including information on time of receipt of emergency call and time of ambulance arrival on site of arrest (ambulance response time, as used in this thesis), in the period 2005-2011.

National administrative registers used

This thesis was centered on a database with data from the Danish Cardiac Arrest Register, supplemented by data from various national administrative registries described below.[58] In Denmark, each individual is provided with a unique civil registration number, and by using this number we were able to link the Danish Cardiac Arrest Register with various national administrative registries. The database was accessed through secure servers at the Statistics Denmark. The civil registration number is encrypted by Statistics Denmark to ensure patient anonymity.

From The Danish Civil Registration System[59] we gathered information on sex, date of birth, and vital status. Information on hospital admission and discharge dates and outpatient information to/from all Danish hospitals as well as discharge diagnosis codes were obtained from the Danish National Patient

Register.[60] Hospital departments are reimbursed on the basis of the recorded diagnosis- as well as procedural codes, and due to this, the data is assumed to be close to complete. Patient comorbidity was identified by studying the diagnosis codes up to ten years before to the OHCA. Finally, from the Danish Register of Causes of Death[61] we acquired diagnosis codes from death certificates. By law, all physicians in Denmark declaring a death are mandated to register the cause of death. In this thesis we used discharge diagnosis codes as well as diagnosis codes from death certificates to categorize patients into OHCA of presumed cardiac cause and presumed non-cardiac cause. Only patients with OHCA of presumed cardiac cause were included in the studies.[62] Presumed cardiac cause of arrest were defined to include cardiac diseases, unexpected collapse or unknown diseases, while other medical disorders and traumas were defined as OHCA of presumed non-cardiac cause and were excluded.

We addtionally obtained data from Statistics Denmark regarding nursing home admissions and patients' need of home care for paper I. Nursing home data has since 1994 been collected using a validated approach that secures a high degree of completion of nursing home information.[63] Home care data for all individuals have been reported since 2008, allowing analyses on this particular outcome since that time. In Denmark, receiving home care is a legally protected right according to the Danish Service Law, and is tax-funded. Any resident can apply for home care free of charge, and after a meeting between the resident and municipal, where the need of care is established, the resident can freely choose between private and municipal home care providers. On average, 96% of all municipalities reported data during the time period from 2008 to 2011. Even though the home care register only contains information on actual home care provided by municipals, the date of the meeting between the resident and municipal where the need of care is established is provided, regardless of the choice of home care provider (municipal vs. private). This date was used to assess the need of care in OHCA patients surviving at least 30 days.

Study design and settings

All three studies included in this thesis were nationwide register-based studies, and all based in Denmark. The size of Denmark is approximately 43,000 square kilometers, with urban, suburban and rural areas. Treatment was given according to the latest resuscitation guidelines throughout the study period in each study.[6]

The emergency medical service is a two-tier system across all five healthcare-divided regions in Denmark; with dispatch of basic life support ambulances with paramedics or ambulance technicians and mobile emergency care units supervised by anesthesiologists or paramedics. These units are dispatched as rendezvous with the ambulances. Although selected locations in Denmark have first-responder programs, no first- or lay rescuers are dispatched on a national level.

Furthermore, the ambulance personnel are not authorized to stop resuscitation without the involvement of a physician.

Study population

Paper I: Prolonged CPR and outcomes after OHCA

All patients handled by the largest nationwide ambulance provider Falck A/S and who achieved a pre-hospital return of spontaneous circulation were identified through the Danish Cardiac Arrest Register during the study period 2005-2011. For this study, Falck A/S provided electronically registered timestamps for when the emergency medical service arrived on site of arrest. Of all the identified patients, those ≥18 years of age with a presumed cardiac cause of arrest were included in the study. Patients were stratified into 5-minute intervals of resuscitation attempt duration by the emergency medical services till return of spontaneous circulation was achieved (0-5 minutes, 6-10 minutes, 11-15 minutes, 16-20 minutes, 21-25 minutes and >25 minutes). Resuscitation duration by the emergency medical services was defined as the time from the arrival of the emergency medical services on site, till the patient achieved return of spontaneous circulation.

Paper II: Association of bystander CPR and survival according to ambulance response times after OHCA

All patients handled by the largest nationwide ambulance provider Falck A/S were identified through the Danish Cardiac Arrest Register during the study period 2005-2011. For this study, Falck A/S provided electronically registered ambulance response times (defined as time from 112-call till the emergency medical service arrived on site of arrest). Adult patients ≥18 years of age with OHCA of presumed cardiac cause were included. Patients who received defibrillation by a bystander before the arrival of the emergency medical services were excluded from the study, as this study sought to elucidate the importance of CPR conducted by bystander in relation to time to CPR and potential defibrillation by the emergency medical services. Patients were stratified according to bystander CPR status (yes/no).

Paper III: Incidence and survival outcome according to heart rhythm during resuscitation attempt in OHCA patients with presumed cardiac etiology

All individuals who had an OHCA between 2005-2012 of presumed cardiac cause, and who were ≥ 18 years at the time of OHCA were identified from the Danish Cardiac Arrest Register. Patients were excluded if a bystander had applied an automated external defibrillator. The study population was then stratified into three groups according to heart rhythm: 1) first recorded shockable rhythm, 2) converted to shockable rhythm from first-recorded non-shockable rhythm, and 3) sustained non-shockable rhythm. The converting group was defined as patients who initially had a first recorded non-shockable rhythm when the emergency medical services arrived, but who subsequently received defibrillation from the emergency medical services at some point before hospital arrival. During the whole study period, a defibrillator decided whether the rhythm was shockable or non-shockable.

Study endpoints / outcomes
The study endpoints were return of spontaneous circulation and 30-day survival (paper I, II and III) and nursing home admission / need for home care / diagnosis of anoxic brain damage (paper I).

Statistics

Paper I
Differences in categorical variables were evaluated by the Pearson's Chi Squared test, while differences in continuous variables were evaluated by the Kruskal-Wallis test. Categorical data was presented as numbers (and percentages), while continuous data was presented as medians with interquartile ranges (Q1-Q3: 25% and 75%). The Kaplan Meier Method was used to calculate cumulative incidences, and significance was tested using the log rank test. Trends in data were evaluated by applying the Cochrane Armitage Trend Test. Associations between stratified time groups and 30-day survival and functional/neurological outcomes were assessed with multiple logistic regression analyses. On the basis of previous work and a directed acyclic graph,[64] the models were adjusted for age, shockable heart rhythm, bystander use of automated external defibrillator, year of arrest, and ambulance response times. The associations were presented as odds ratios with corresponding 95% confidence intervals.

Paper II
Direct standardization / g-computation formula for fixed exposures
For study II we applied causal inference statistics to our data by direct standardization / application of the g-computation formula.[65]

The purpose of this method is to attempt to establish the causal effect that would have been the result if this observational study had the strengths of a randomized study. By "causal effect" is meant the difference in the chance of outcome that the whole population would experience if it had received one exposure (i.e. "received bystander CPR" as in paper II) vs. had not received the exposure (i.e. "did not receive bystander CPR" as in paper II). For the calculated difference to represent a causal effect, the included study groups need to be exchangeable; exchangeability refers to that the risk of mortality in one group would be the same as the risk in the second group, had the first group received the same exposure as group two. When using models the exchangeability can be relaxed a bit by only requiring exchangeability conditioned on the covariates. For obvious reasons, it is not possible to observe the outcomes for the same person being exposed and not exposed (i.e. the same patient cannot both receive bystander CPR, and not receive bystander CPR). The situation opposite to the observed is called the "counterfactual". In an observational study, individual level cause effects cannot be identified due to this 'missing data' problem. However, the average causal effect in a population of individuals can be calculated, as three pieces of information is needed for this: an outcome, exposures to be compared, and a defined population whose outcome given a certain exposure was received can be compared to the outcome given a certain exposure was not received by direct standardization / g-computation.

In order to apply g-computation, we first fitted a multiple logistic regression model to our data, i.e. a model that related our outcome variable to the exposure variable and the identified confounders – this model is known as a "Q-model". Based on previous work we identified potential confounders to be included in the final Q-model, and with the help of a directed acyclic graphs we identified intermediating variables to be excluded from the model.[64] For paper II, the main analysis was therefore based on a multiple logistic regression model for 30-day survival outcome according to bystander CPR and ambulance response time and further adjusted for age, sex, comorbidities, witnessed status, location of arrest and year of arrest. In this model, the relationship between 30-day survival chances and ambulance response time was modeled by the use of restricted cubic splines with pre-specified knots at 5, 10, 15 and 20 minutes.[66]

From the logistic regression model we computed two personalized 30-day survival predictions for each included patient in paper II (under the assumption of exchangeability): this was done by standardizing our data so that every patient had the counterfactual exposure set to "received bystander CPR" but kept the actual observed patient- and OHCA characteristics (including the actual response time), giving the first personalized 30-day survival chance for each patient, and then by standardizing our data so that every patient included had the counterfactual exposure set to "did not receive bystander CPR" but again kept the actual observed patient- and OHCA characteristics (including the actual response time), giving the second personalized 30-day survival chance for each patient. The averages of the personalized 30-day survival chances according to bystander CPR status and ambulance response time were then calculated and reported, along with the ratio between the averaged 30-day survival chances for with vs. without bystander CPR according to response time (g-formula[67-69]). Ninety-five percent bootstrap confidence intervals, based on 2000 bootstrap samples, were calculated and presented.

Paper III

To identify which patient- and cardiac arrest characteristics were predictors of conversion to a shockable rhythm from a first recorded non-shockable rhythm, we analyzed a subset of patients that had a first-recorded non-shockable rhythm when the emergency medical services arrived. We applied a multiple logistic regression with rhythm as an outcome (converted shockable vs. sustained non-shockable) to investigate the following potential predictors: age, sex, selected comorbidities, location of arrest, witnessed status, bystander CPR, and the time from recognition of arrest to rhythm analysis by the emergency medical services. The results were reported as odds ratios with 95% confidence intervals. We also performed multiple logistic regressions in all patients in order to examine the association between all three types of heart rhythm situations (first recorded shockable-, converted shockable-, and sustained non-shockable rhythm) and return of spontaneous circulation as well as 30-day survival. The model was adjusted for age, sex, selected comorbidities, location of arrest, witnessed status, bystander CPR, and the time from recognition of arrest to rhythm analysis by the emergency medical services.[64] Missing data was handled using the method of multiple imputations by chained equation. One hundred imputed datasets were constructed using all covariates and the estimates from the observed and the imputed datasets were compared. Temporal changes in return of spontaneous circulation and 30-day survival were reported as relative frequencies and predictions from a logistic regression model, where the relationship between the outcome and calendar year was modeled using restricted cubic splines with pre-specified knots at years 2007, 2009 and 2011.[66]

Best- and worst case scenarios

For papers II and III, we also presented personalized 30-day survival chances for specific combinations of patient- and OHCA characteristics (best- and worst case scenarios): in paper II the best case scenario was defined as a person having a witnessed arrest in public, no known comorbidities and working age ≤65 years, while worst case scenario was defined as having an unwitnessed arrest in a private home, one or more comorbidities and age above 65 years. In paper III, the corresponding scenarios were defined as a person having a witnessed arrest in public, no known comorbidities, working age ≤65 years, bystander CPR and median time interval from recognition of arrest to rhythm analysis <15 minutes (best-case scenario); and a patient having an unwitnessed arrest in a private home, one or more comorbidities, age above 65 years, no bystander CPR and median time interval from recognition of arrest to rhythm analysis ≥15 minutes (worst-case scenario). These results are presented as predicted 30-day survival chances (percentages) with 95% confidence intervals.

For descriptive purposes, the response time in study II was divided into 5-minute intervals of 0-5, 6-10, 11-15 and >15 minutes. For main analyses, response time was kept as a continuous variable.

For all analyses in papers I, II and III, the level of significance was set at 5%. All statistical analyses were performed using SAS, version 9.4 (SAS Institute Inc., Cary, NC, USA) and R, version 3.2.3.[70]

Ethics

All three studies included in this thesis were approved by The Danish Data Protection Agency (J. ref: 2007-58-0015 / local J ref: GEH-2014-017 / I-Suite: 02735). All patients in the studies were anonymous as the civil registration numbers were encrypted. Ethical approval is not required for retrospective register-based studies in Denmark.

RESULTS

This section contains summarized overviews of the main findings of paper I, II and III. The presentation format is the same for all papers: a summary of the background to highlight the clinical importance of the main objectives, followed by the main results, including main figures, and finally, the conclusion and relevance. Detailed descriptions for each paper with all results can be found in the Appendix section.

Paper I
Prolonged cardiopulmonary resuscitation and outcomes after out-of-hospital cardiac arrest

Background and objectives

When the emergency medical services are dispatched to an OHCA and they initiate resuscitation, the resuscitation attempt may be terminated in two cases: 1) the patient has achieved return of spontaneous circulation and resuscitation is no longer necessary, or 2) further resuscitation is deemed futile for whatever reason. Even though many guidelines are fairly standardized for the practical conduct of advanced resuscitative efforts, recommendations on how long to continue resuscitation in the field are less clear. In cases where the resuscitation attempt is prolonged, an important question is not only if a patient has a chance of achieving return of spontaneous circulation, even though pre-hospital return of spontaneous circulation is the first primary goal during resuscitation, but also whether the patient will survive to a meaningful life. We therefore analysed associations between the duration of the resuscitation attempt and 30-day survival and functional outcomes in patients who achieved a pre-hospital return of spontaneous circulation.

Results

A total of 1,316 adult OHCA patients who achieved return of spontaneous circulation and were handled by the largest nationwide ambulance provider in Denmark were included during the study period 2005-2011.

The median time from resuscitation was initiated by emergency medical services to a pre-hospital return of spontaneous circulation was achieved was 12 minutes (Q1-Q3: 7-18) for the whole population. Figure 1 portrays the cumulative incidence of return of spontaneous circulation according to bystander CPR and shockable heart rhythm. Of the whole study population, 20.4% of the patients achieved return of spontaneous circulation after more than 25 minutes of resuscitation by the emergency medical services had passed.

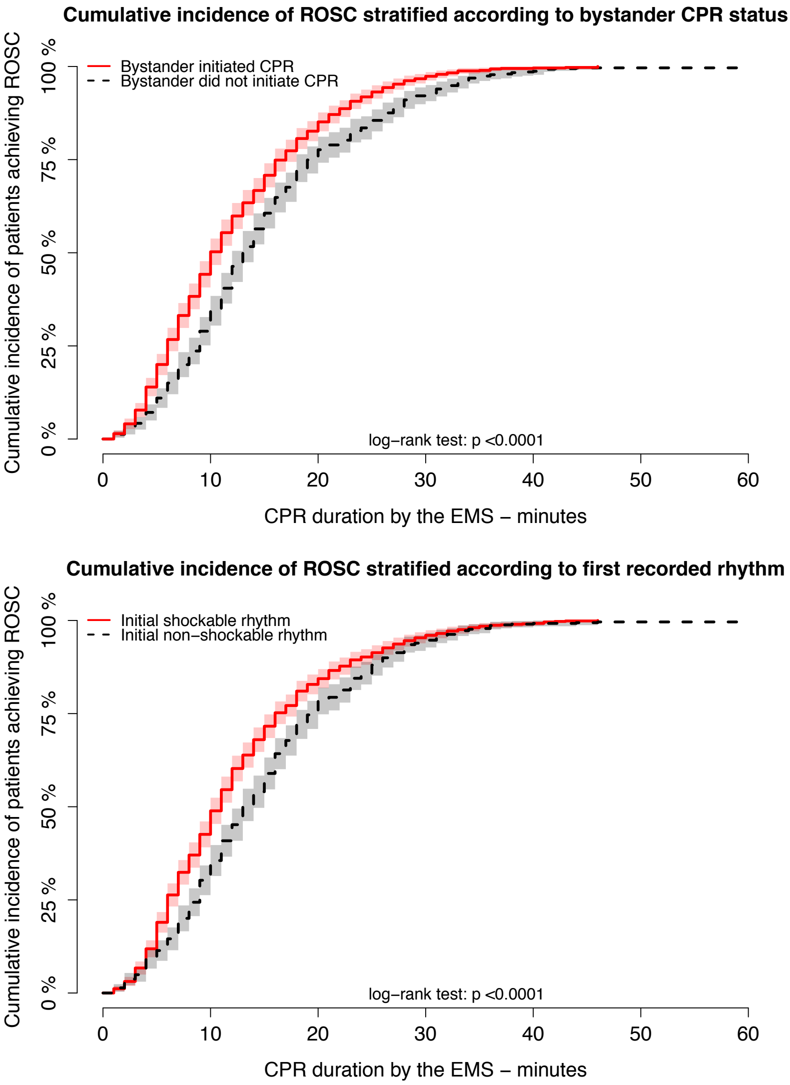
Overall, 37.5% (494 patients) of the study population achieved 30-day survival. Thirty-day survival decreased as resuscitation duration to return of spontaneous circulation increased: ranging from 59.6% (127/213 patients) for patients with ≤5 minutes of resuscitation by emergency medical services to 13.8% (19/138) for patients with >25 minutes of resuscitation by emergency medical services (p-value for trend: 0.001). When the population was stratified according to whether a bystander initiated CPR before the arrival of the ambulance, corresponding 30-day survival ranged from 70.4% (102/152) to 21.8% (12/55) for patients where bystanders had initiated CPR before ambulance arrival, and from 45% (27/60) to 7.3% (6/82) for patients where bystanders had not initiated CPR before ambulance arrival (Figure 2). Associations between 30-day survival and resuscitation duration time by the emergency medical services, with ≤5 min as the reference group, are portrayed in Figure 3. Compared to the ≤5 min group, 30-day survival decreased significantly with increasing resuscitation duration in both crude and adjusted analyses. Of all the patients surviving to day 30, the patients discharged to own home rather than nursing home ranged from 95% (124/127) to 94.7% (18/19) for the time intervals ≤5 minutes and >25 minutes, respectively, p-value for trend: 0.2 (Figure 4), while the patients discharged without a diagnosis of anoxic brain damage ranged from 98.4% (125/127) to 73.7% (14/19) for the corresponding intervals, p-value for trend: <0.0001 (Figure 4).

Conclusion and relevance

In this nationwide study, we demonstrated that even those OHCA patients requiring prolonged durations of resuscitation by the emergency medical services prior to return of spontaneous circulation had meaningful 30-day survival rates with the majority of the surviving patients being able to live in own homes rather than nursing homes. These data suggest that prolonged resuscitation is not futile.

Figure 1

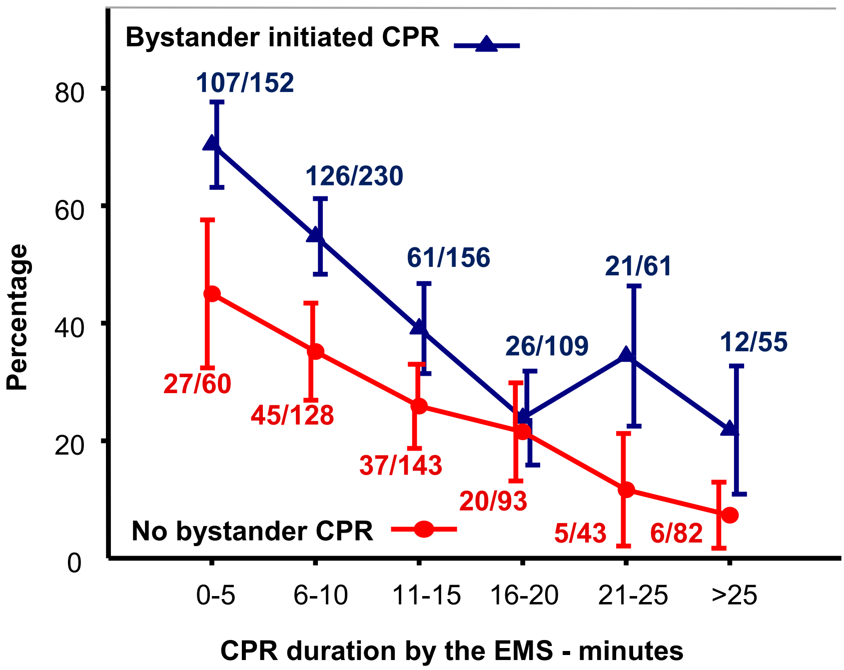
Cumulative incidence to achieved ROSC according to CPR duration by the emergency medical service (n=1,316)



The top graph shows the cumulative incidence to achieved ROSC according to CPR duration, stratified by whether bystander initiated CPR. The bottom graph shows the cumulative incidence to achieved ROSC according to CPR duration, stratified by first recorded heart rhythm. ROSC = return of spontaneous circulation. CPR = cardiopulmonary resuscitation. EMS = emergency medical service.

Figure 2

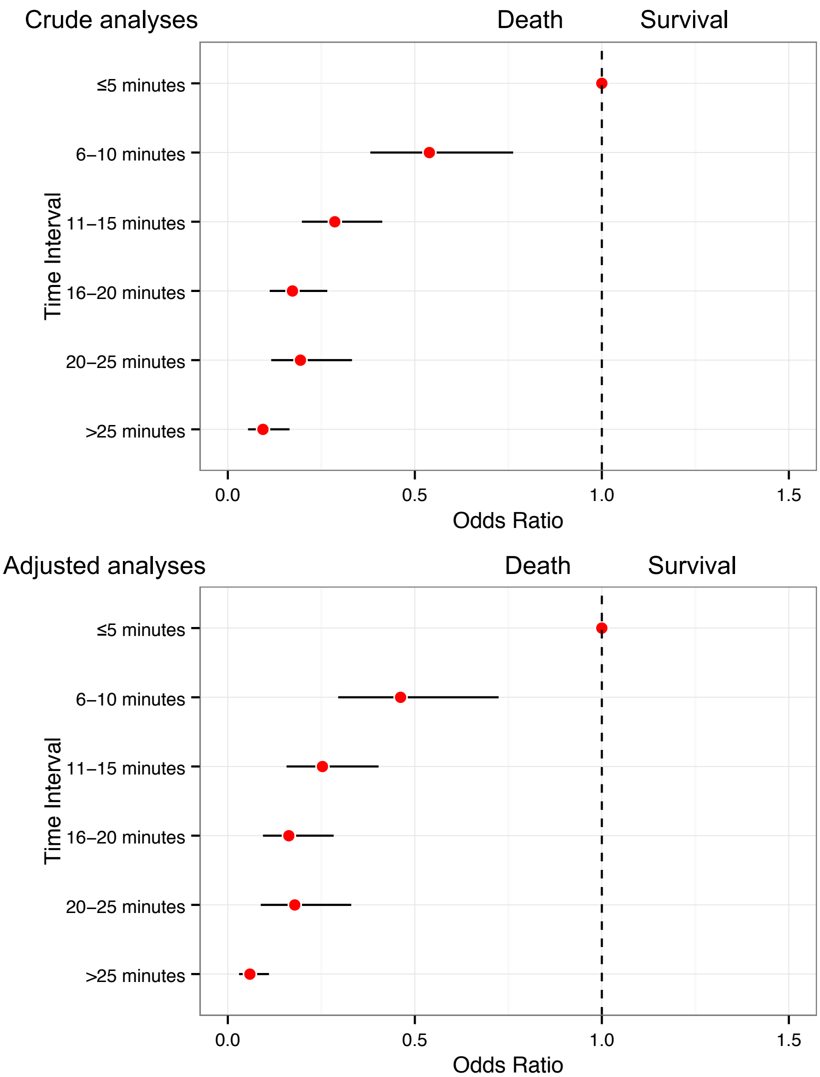
Thirty-day survival related to duration of CPR by the EMS stratified according to bystander CPR status (n = 1,316)



The graph depicts 30-day survival related to CPR duration by the EMS until return of spontaneous circulation was achieved, stratified according to bystander CPR.
The numbers next to each point on the figure refer to the numerator and denominator for the percentages.
EMS = emergency medical service.
CPR = cardiopulmonary resuscitation.

Figure 3

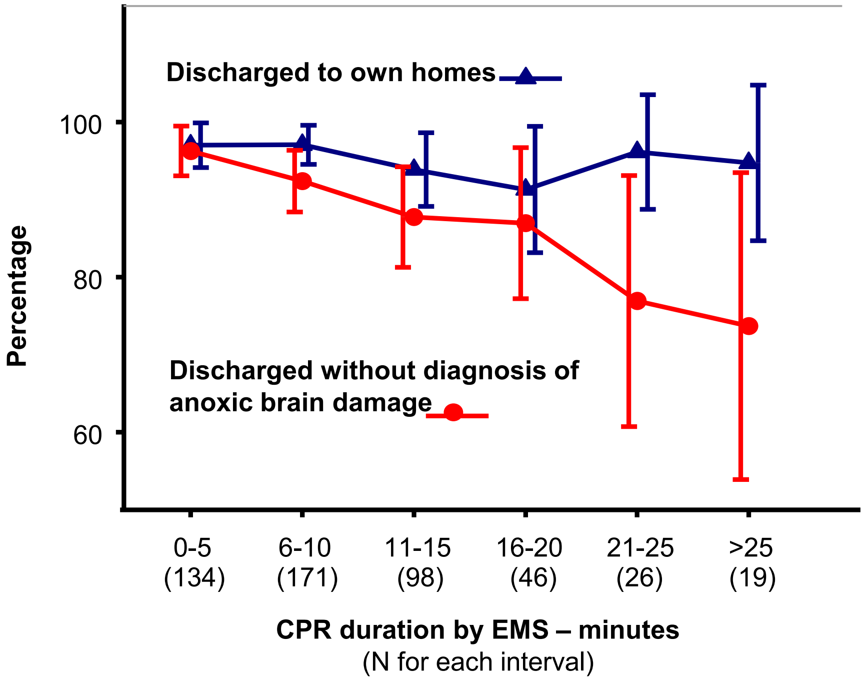
Associations between 30-day survival and resuscitation duration time by the EMS



The graphs demonstrate associations between 30-day survival and CPR duration time by the EMS until return of spontaneous circulation was achieved, with ≤5 minutes as the reference. The top graph shows crude results and the bottom graph shows adjusted analyses. The bottom model was adjusted for: age, shockable heart rhythm, bystander use of automated external defibrillator, ambulance response times and year of arrest.
EMS =emergency medical service. CPR = cardiopulmonary resuscitation.

Figure 4

Thirty-day survivors discharged to own home / without anoxic brain damage diagnosis according to duration of resuscitation by EMS (n = 494)



The graph shows the rate of 30-day survivors discharged to own home and without anoxic brain damage according to duration of CPR by the EMS until return of spontaneous circulation was achieved. The number in parenthesis under the X-axis refers to the total number of patients in each interval.

EMS = emergency medical services.

CPR = cardiopulmonary resuscitation.

Paper II
Association of bystander cardiopulmonary resuscitation and survival according to ambulance response times after out-of-hospital cardiac arrest

Background and objectives

Bystander-initiated CPR has been associated with increased patient survival following OHCA. However, it remains less clear to what extent bystander CPR continues to be associated with a beneficial impact on survival when time to advanced treatment including potential defibrillation increases. Information on this could be useful when planning ambulance distributions, potential first-responder programs as well as availability of automated external defibrillators. The main objective of this study was to examine the association between bystander CPR and 30-day survival as time to advanced treatment and potential defibrillation increases. The secondary aim was to highlight potential maximum survival in personalized best-case and worst-case scenarios. Ambulance response time was used as a proxy for time to CPR by trained rescuers and potential defibrillation.

Results

A total of 7,623 patients were included in the final population during the study period 2005-2011. The adjusted 30-day survival chances decreased for increasing response time for both patients with bystander CPR and patients without bystander CPR. However, the difference in survival chances between the two groups seemed to increase over time: within 5 minutes of response time, 30-day survival was 14.5% (95% CI: 12.8-16.4) for those with bystander vs. 6.3% (95% CI: 5.1-7.6) for those without bystander CPR, corresponding to 2.3 times higher chances of 30-day survival with bystander CPR; within 10 minutes the corresponding 30-day survival chances were 6.7% (95% CI: 5.4-8.1) vs. 2.2% (95% CI: 1.5-3.1), corresponding to 3.0 times higher chances of 30-day survival with bystander CPR. Even when the contrast in 30-day survival became statistically insignificant at 13 minutes (bystander CPR vs. no bystander CPR: 3.7% [95% CI: 2.2-5.4] vs. 1.5% [95% CI: 0.6-2.7]), 30-day survival was still 2.5 times higher with bystander CPR (Figure 5).

When applying statistics from the latest Danish Cardiac Arrest Report[71] to this model (annual incidence, annual rate of bystander CPR and annual survival in Denmark), we found that an additional of 233 patients could potentially be saved every year if response time was reduced from 10 minutes to 5 minutes, and 119 patients if response time was reduced from 7 minutes (the median response time in this study) to 5 minutes (Figure 6).

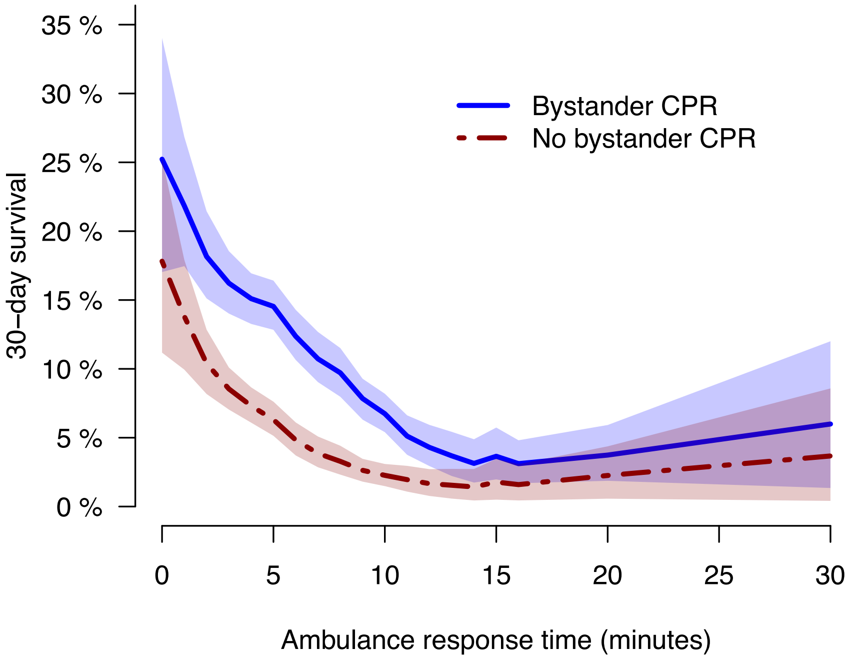
In the current study population, 3.6% of the population presented with the best-case scenario (having a witnessed arrest in public, no known comorbidities and working age ≤65 years) while 11.8% of the population presented with worst-case scenario (having an unwitnessed arrest in a private home, one or more comorbidities and age above 65 years). In both scenarios, the personalized 30-day survival chances decreased with increasing response time, and in both scenarios, bystander CPR was associated with highest 30-day survival chances: By 5 minutes of response time, the probability of 30-day survival was 54.2% with bystander CPR, and 30.2% with no bystander CPR for best-case scenarios, and by 10 minutes, the figures were 33.1% vs. 12.2% respectively; corresponding 30-day survival in worst-case scenarios was 4.1% and 1.5% for bystander CPR vs. no bystander CPR by 5 minutes, and by 10 minutes the corresponding figures were 1.7% and 0.5% (Figure 7).

Conclusion and relevance

The absolute benefit of bystander CPR seemed to decline rapidly with increasing response time. However, bystander CPR while waiting for the ambulance was associated with more than doubling of 30-day survival, even when the waiting time was long. Increasing the rate of bystander CPR, and/or decreasing time to potential defibrillation with even a few minutes could lead to many additional lives saved every year – in this study, more than one hundred additional lives saved every year when reducing response time from seven minutes to five minutes.

Figure 5

Standardized 30-day survival chances according to duration of response time and bystander CPR status

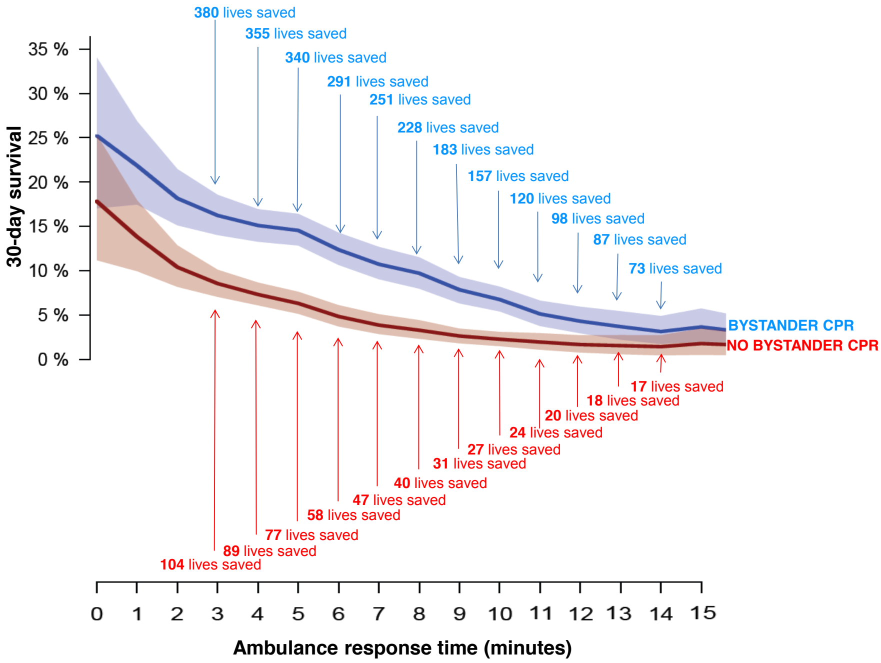


The survival chances based on multiple logistic regression were standardized to settings where all patients vs. no patients received bystander CPR according to ambulance response time. The model is adjusted for age, sex, witnessed status, location of arrest and comorbidities (ischemic heart disease, previous myocardial infarction, heart failure, and chronic obstructive lung disease)

CPR = cardiopulmonary resuscitation.

Figure 6

Potential lives saved annually in Denmark if response time is deceased



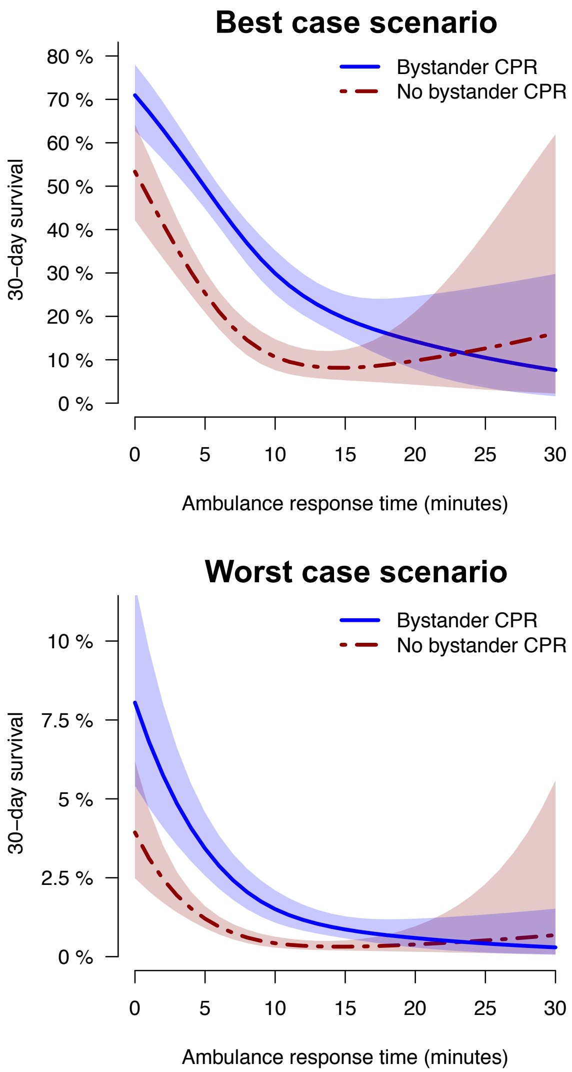
This figure is based on the adjusted logistic regression model using g-formula from Figure 5, combined with latest Danish OHCA Statistics, which reported that 3570 OHCA, not witnessed by the emergency medical services, took place during the latest year, of which 65.8% received bystander CPR.

OHCA = out-of-hospital cardiac arrest.

CPR = cardiopulmonary resuscitation.

Figure 7

Thirty-day survival predictions in best-case scenario and worst-case scenario, stratified according to bystander CPR status



The upper panel shows 30-day survival chances for an individual in a best-case scenario, having a witnessed arrest in public, no comorbidities, and younger age (≤65 years). The lower panel shows 30-day survival chances for an individual in a worst-case scenario, having an unwitnessed arrest in private homes, one or more comorbidities, and older age (>65 years). Note different Y-axis scales. CPR = cardiopulmonary resuscitation.

Paper III
Incidence and survival outcome according to heart rhythm during resuscitation attempt in out-of-hospital cardiac arrest patients with presumed cardiac etiology

Background and objectives

Survival following OHCA is highly dependent on a patient's presenting heart rhythm: shockable heart rhythms have been associated with higher survival rates compared to non-shockable heart rhythms. Not much is known about the chance of converting from a first-recorded non-shockable rhythm to a shockable rhythm during a resuscitation attempt. The main objectives of this study were 1) identifying predictors of rhythm conversion, 2) investigating 30-day survival according to first-recorded shockable-, converted shockable- and sustained non-shockable rhythm, and 3) highlighting maximum survival in personalized best-case and worst-case scenarios for each heart rhythm. In this study, converted rhythms were defined as patients who had a first-recorded non-shockable rhythm upon arrival of the emergency medical services, but who subsequently received defibrillation by the emergency medical services.

Results

A total of 13,860 patients were included in the final study population. Twenty-five percent of all patients who received defibrillation by the emergency medical services were initially found in non-shockable rhythms. Factors that were significantly associated with rhythm conversion to a shockable rhythm from a first-recorded non-shockable rhythm included younger age, male sex, witnessed arrest, bystander CPR, shorter response time, and heart disease, while psychiatric- and chronic obstructive pulmonary disease were significantly associated with sustained non-shockable rhythms (Figure 8).

Compared to sustained non-shockable rhythms, converted shockable rhythms and first-recorded shockable rhythms were significantly associated with increased 30-day survival in fully adjusted models (OR: 2.6, 95% CI: 1.8-3.8 for converted rhythms and OR 16.4, 95% CI: 12.4-21.2 for initial shockable rhythms). When examining temporal trends, 30-day survival chances increased significantly for all three rhythms between 2005 and 2012: from 16.3% (CI: 14.2%-18.7%) to 35.7% (CI: 32.5%-38.9%) for first-recorded shockable rhythms; from 2.1% (CI: 1.6%-2.9%) to 5.8% (CI: 4.4%-7.6%) for converted shockable rhythms; and from 0.6% (CI: 0.5%-0.8%) to 1.8% (CI: 1.4%-2.2%) for sustained non-shockable rhythms (Figure 9).

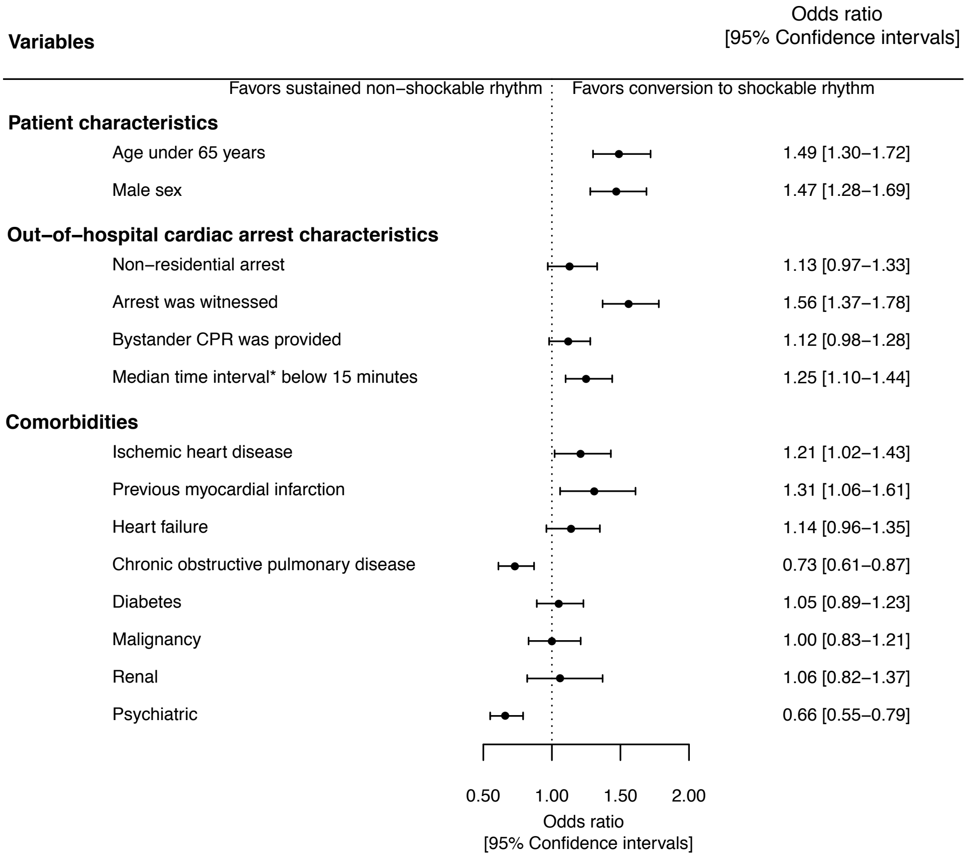
The predicted 30-day survival chance for a patient with best-case scenario (having a witnessed arrest in public, no known comorbidities, working age ≤65 years, bystander CPR and median time interval from recognition of arrest to rhythm analysis <15 minutes) was 60.2% for first-recorded shockable rhythms, 20.1% for converted to shockable rhythms, and 8.7% for patients remaining in non-shockable rhythms. The highest predicted 30-day survival chance in the worst-case scenario (having an unwitnessed arrest in a private home, one or more comorbidities, age above 65 years, no bystander CPR and median time interval from recognition of arrest to rhythm analysis ≥15 minutes) was 2.8% for first-recorded shockable rhythms, 0.5% for converted to shockable rhythms, and 0.2% for patients remaining in non-shockable rhythms (Figure 10).

Conclusion and relevance

Twenty-five percent of all patients defibrillated by the emergency medical services were initially found in non-shockable rhythms. Hence, rhythm conversion was relatively common. Converting to a shockable rhythm from a first-recorded non-shockable rhythm was associated with more than two times higher odds of surviving 30 days compared to sustained non-shockable rhythms.

Figure 8

Factors associated to conversion from non-shockable to shockable heart rhythm

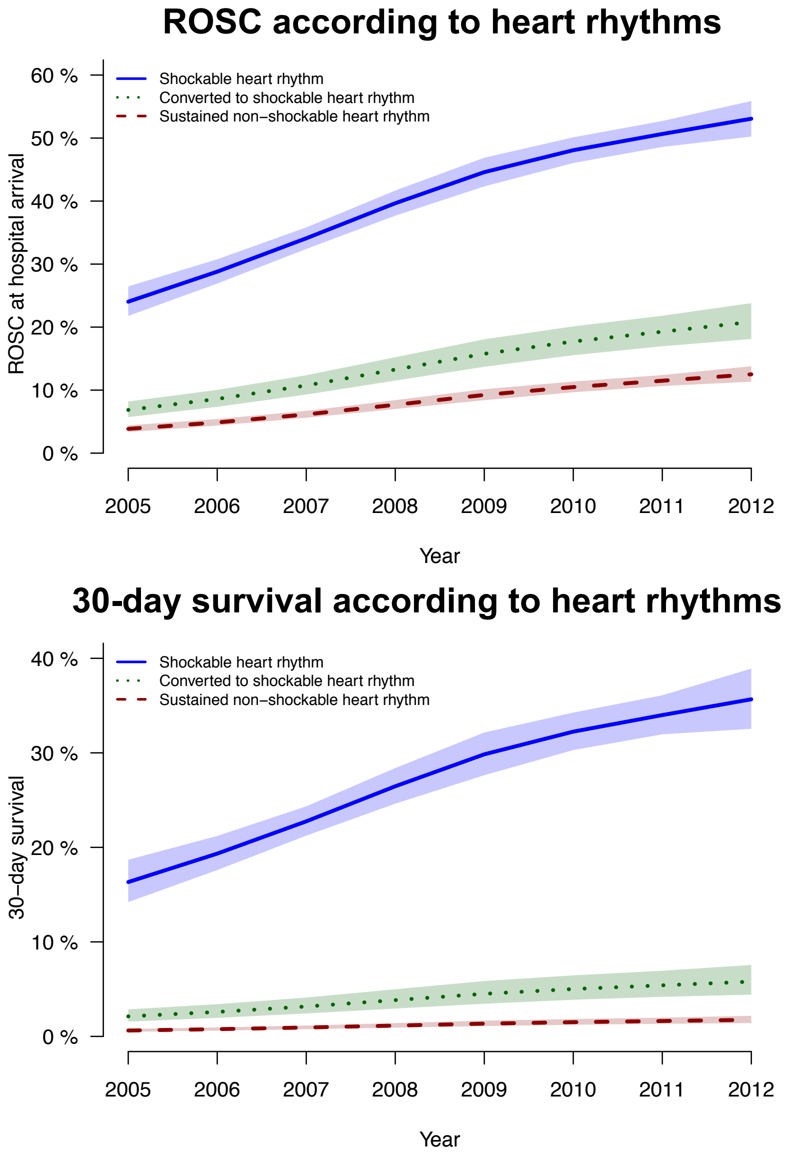


Patient- and arrest-related factors associated with converting from a first-recorded non-shockable rhythm to a subsequent shockable rhythm during pre-hospital resuscitation attempts by the emergency medical services.

*Time from recognition of arrest to first rhythm analysis by the emergency medical services.

Figure 9

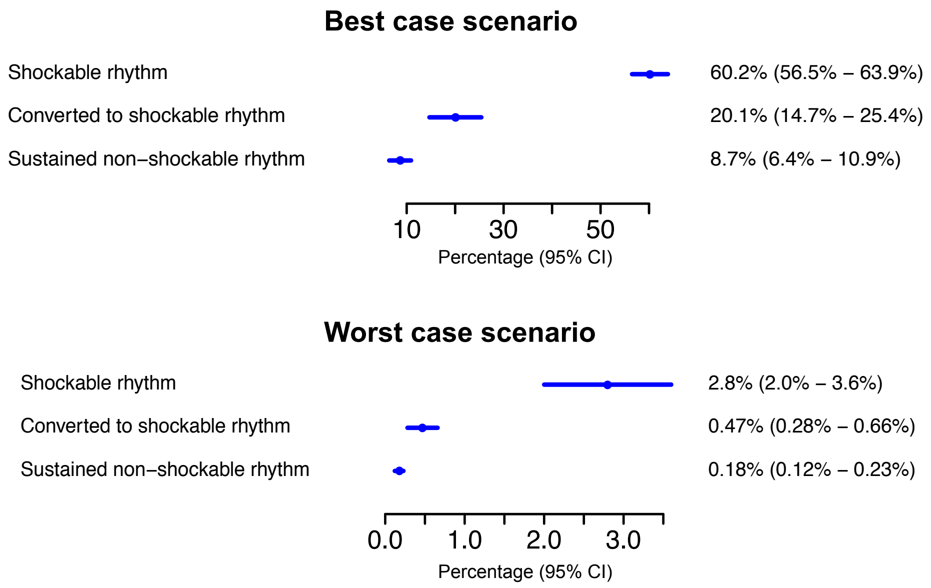
Predicted ROSC and 30-day survival chances according to rhythm and calendar year



Top figure portrays the predicted yearly development in pre-hospital ROSC chances and bottom figure portrays the predicted yearly development in 30-day survival chances of the three rhythms. The figures are based on logistic regression models using restricted cubic splines. ROSC = return of spontaneous circulation.

Figure 10

Thirty-day survival chances in best- and worst case scenarios stratified by heart rhythm



The upper panel portrays 30-day survival chances for an individual in a best-case scenario (age ≤65 years, witnessed arrest in public, no comorbidities, bystander CPR, median time interval below 15 minutes). The lower panel portrays 30-day survival chances for an individual in a worst-case scenario (>65 years, unwitnessed arrest in private homes, one or more comorbidities, no bystander CPR and median time interval of ≥15 minutes). In this current study population, 2.0% presented with a best-case scenario, and 5.0% presented with a worst-case scenario. Note different x-axis for the two figures.

DISCUSSION

Overall findings

The main objective of this thesis was to investigate aspects in the chain of survival that could potentially elucidate how OHCA patients may achieve higher and meaningful survival rates.

The first major question addressed in this thesis was related to the length of the resuscitation attempt by the emergency medical services before return of spontanous circulation is achieved: is meaningful survival possible in spite of very long resuscitation durations? In **paper I** we found that more than 13% of patients with long pre-hospital resuscitation durations by the emergency medical services (>25 minutes) before achieving a pre-hospital return of spontaenous circulation were able to achieve 30-day survival. Of these surviving patients, the majority were able to return to own homes rather than nursing homes (>90%), did not need home care, and were discharged without a diagnosis of new onset of anoxic brain damage (>70%).

The next major issue we wanted to investigate was the role of a bystander during an OHCA. “Bystander CPR buys time until advanced treatment arrives” is an often-repeated mantra, but not much is known about the impact of time on bystander CPR. How long does bystander CPR continue to be associated with increased survival as time to CPR by trained rescuers and potential defibrillation increases? Using ambulance response time as a proxy for time to CPR by emergency medical services and potential defibrillation, **paper II** of this thesis attempted to quantify the often-repeated mantra. In this paper we found that bystander CPR was associated with more than a doubling in 30-day survival even in cases of long ambulance response time; but the absolute 30-day survival decreased rapidly with increasing ambulance response time, regardless of bystander CPR status. However, with increasing response time, the associated relative survival gain of bystander CPR compared to no bystander CPR seemed to increase. Based on our model we calculated that if time to CPR by trained rescuers and potential defibrillation is reduced from for example 7 minutes (the median time found in paper II) to 5 minutes in Denmark, we would be able to save more than one hundred additional lives every year. Currently, an average of 400 OHCA victims survive anually in Denmark; hence 100 additional survivors matter and constitute a survival gain of about 20%.[71]

The third aspect we wanted to examine was in regards to the first recorded heart rhythm when the emergency medical services arrive at the site of an OHCA. It is well known that 30-day survival is heavily dependent on the heart rhythm being shockable or non-shockable. In some cases, non-shockable rhythms can convert to shockable rhythms, but not much is known about the incidence of such conversion and which factors predict whether a non-shockable rhythm will convert into a shockable rhythm. There is also limited knowledge about differences in survival according to heart rhythm and changes over time. **Paper III** investigated these aspects, and found that nearly 25% of all the patients who received defibrillation by the emergency medical services had converted from a non-shockable rhythm. Although such conversion was associated with increased 30-day survival compared to patients with sustained non-shockable rhythm, 30-day survival was still significantly higher for patients with first recorded shockable rhythm compared to those patients with converted shockable rhythms (in unadjusted as well as adjusted models). Factors associated with conversion of rhythm was younger age, male sex, a witnessed arrest, bystander CPR, shorter duration between arrest recognition and rhythm analysis by the ambulance crew, and a history of cardiovascular disease; while a history of non-cardiovascular diseases was associated with sustained non-shockable rhythms.

Paper I

When emergency medical services attend an OHCA in the pre-hospital setting, they continue the resuscitation attempt until one of the two situations arises: 1) the patient achieves return of spontaneous circulation, or 2) it is decided that further resuscitation is futile (in Denmark this decision can only happen if a physician is involved). Futility refers to the situation where further resuscitation is of no benefit in terms of long-term survival with an acceptable quality of life.[72] Deciding on the latter can put the clinician in a very difficult dilemma. These complicated decisions are often made within seconds or minutes and are often based on the clinician's hunch on the outcome of the patient suffering the OHCA. Even though a pre-hospital return of spontaneous circulation is the first primary goal during a resuscitation attempt,[33,34] clinicians may be reluctant to continue resuscitation if this has not been achieved fairly quickly. In cases where the resuscitation attempt is prolonged, an important question is not only whether the patient will be able to achieve return of spontaneous circulation and subsequently long-term survival, but also whether the patient will survive to a meaningful life. However, despite the importance, studies examining prolonged pre-hospital resuscitation attempts in OHCA patients and the associations to survival and functional outcomes are limited.

A study by Reynolds et al.[39] in 2013 evaluated the probability of survival to hospital discharge with good neurological status with increasing CPR duration time. They found that by approximately 16 minutes of CPR, close to 90% of patients who subsequently survived with favorable functional status measured as modified Rankin Scale 0-3 had achieved return of spontaneous circulation. The data in this study was derived from a single site, with varying sophistication of treatment in the hospital after the OHCA. Furthermore, the authors stated that during the study period, patients treated from other emergency medical service systems displayed good functional recovery even in CPR durations exceeding 21 minutes, and importantly, the authors advised caution about using the presented data to guide CPR duration into termination of resuscitation guidelines. Although paper I of this thesis did not directly examine the CPR duration that yielded >90% survivors with good functional status, it did find that more than 13% of patients who had CPR durations above 25 minutes subsequently survived to 30 days, and of these surviving patients, the majority returned to their own homes (>90%) and without the diagnosis of anoxic brain damage (>70%). In paper I of this thesis, data was collected from an emergency medical provider that treated OHCA nationwide rather than a single site. Recently, Reynolds et al.[73] published another similar study, this time using a large multi-center cohort where they identified that it required 37 minutes of CPR to yield 99% of patients with an eventual survival with good functional outcome. They also found that patients with favorable case features were more likely to survive prolonged resuscitation up to 47 minutes. These results are in accordance with the findings of paper I of this thesis that prolonged resuscitation is not futile.

A recent study by Goto et al.[74] investigated 17,238 adult OHCA patients who achieved return of spontaneous circulation, and examined 30-day survival and functional status according to increasing resuscitation duration by the emergency medical services. The established threshold for medical futility of <1%[75] has been widely discussed and questioned especially in the field of resuscitation.[76,77] However, as it still seems to remain the basis for current futility research, Goto et al. aimed to identify the critical pre-hospital CPR duration where return of spontaneous circulation was achieved for >99% of the patients who subsequently survived a minimum of 30 days with good functional recovery (defined as cerebral performance category [CPC] 1-2). Stratified by heart rhythm, the CPR duration that produced approximately 99% of survivors with CPC 1-2 was 35 minutes for shockable rhythms and pulseless electrical activity, and 42 minutes for asystole. The authors therefore identified the critical CPR duration for OHCA being at least 35 minutes. Overall, the findings of this large-scale study were similar to the findings of paper I of this thesis. While Goto et al. presented baseline characteristics according to initial heart rhythm, baseline characteristics in paper I of this thesis were presented according to increasing CPR duration, thus giving an insight into characteristics of patients that required long durations of CPR. This could elucidate whether patients with long resuscitation durations may be a selected population where emergency medical providers may have provided extra efforts. A third study, conducted by Arima et al.[78] in 2015, examined the duration of pre-hospital resuscitation and favorable prognosis in OHCA patients with first recorded ventricular fibrillation. Of these, 69 patients required prolonged resuscitative efforts (>30 minutes), of which 6 patients survived 24 hours (8.7%), and of these surviving patients, 1 patient (16.6%) had a good functional status (CPC 1-2). They concluded that favorable results are less likely in cases of prolonged pre-hospital CPR (>30 minutes). However, the population in the study was small (179 patients) and excluded patients with heart rhythms other than ventricular fibrillation which could account for some of the discrepancies in results between this study and paper I of this thesis.

Fear of severe brain damage is a prominent argument against prolonged resuscitation. While the mentioned studies used other scales to measure functional status (mRS and CPC), paper I aimed to address this fear by examining the relationship between resuscitation length and the proportion of surviving patients being discharged to own home rather than nursing home, the proportion of surviving patients being discharged without a diagnosis of anoxic brain damage, and the proportion of patients not needing home care; hence, we were able to get an indication of a patient's functional status after the OHCA in relation to the length of resuscitation attempt by the emergency medical services. Previous reports have shown that these outcomes can serve as proxies of neurological and functional status.[79-81]

Termination of resuscitation is a difficult subject, as survival predictions can be complex and challenging to determine. In order to overcome these challenges, extensive research has been dedicated in this area, and "termination of resuscitation" rules have been proposed.[34,72,75-77,82-89] Apart from attempting to reduce the risk of resuscitated patients having severe brain damage, such rules have also been developed in order to reduce costs associated with futile resuscitation attempts, to more efficiently allocate resources of busy emergency medical service systems and emergency departments, and to reduce the number of high-speed ambulance transportations to hospitals, which could otherwise pose a hazard to the ambulance staff as well as surroundings.[89] Currently, guidelines recommend termination of resuscitation when the following conditions are met: 1) no return of spontaneous circulation before transport is initiated, 2) no shock is delivered before transport is initiated, and 3) the arrest was not witnessed by the emergency medical services.[90] Since clinicians may be reluctant to continue resuscitation if return of spontaneous circulation is not readily achieved due to fear of prominent brain damage, using the termination of resuscitation rules without considering a minimum resuscitation duration could be problematic. In paper I of this thesis we demonstrated that a substantial proportion of the study population achieved return of spontaneous circulation with good functional status also after prolonged resuscitation attempts (>25 minutes). Using the predictive rule of termination of resuscitation could therefore impose the risk of prematurely terminating resuscitation for patients who could have achieved return of spontaneous circulation with subsequent long-term survival of an acceptable quality had the resuscitation attempt lasted longer. Hence there is a risk that the termination of resuscitation rules can become a self-fulfilling prophecy.

It has been suggested that termination of resuscitation rules should remain advisory.[91] European guidelines have also stated that there are reports of exceptional cases that do not support the general rule.[72] Each case must hence be assessed individually, and ultimately, it is based on the clinician's judgment that an arrest is not responding to advanced life support. The findings in paper I are not in direct discrepancy of current guidelines, but these data suggest that patients with long resuscitation attempts can have a successful outcome.

Paper II

Early CPR saves lives – a series of studies have confirmed this very crucial and strong association between bystander-initiated CPR and survival.[13,14,17,20-22] The basic idea behind CPR is that CPR sustains a small, but crucial blood flow to vital organs that apart from reducing the risk of brain damage may also prolong the time window for defibrillation as deterioration of a shockable rhythm to a non-shockable rhythm is delayed.[42,44]

In many cases, the ambulance response time can be long, which leaves bystanders in a critical position with the potential to improve a patient's prognosis by intervening before the ambulance arrives.[15,92] In recent years, there has been a substantial focus on increasing the rate of bystander CPR, including in Denmark.[14] Fifteen years ago, the bystander CPR rate in Denmark was below 20%.[71] Several national strategies were implemented in order to strengthen resuscitation attempts by bystanders as well as advanced care. These initiatives included implementation of mandatory CPR training in elementary schools; mandatory CPR training when acquiring a driver's license; increased voluntary first aid training;[93] free distribution of around 150,000 CPR self-instruction training kits; nationwide telephone guidance from the emergency dispatch centers to bystanders calling in about a cardiac arrest; addition of health care professionals at dispatch centers; large increase in the number of automated external defibrillators outside of hospitals,[94] updating clinical guidelines; and overall strengthening of the emergency medical service system with implementation of paramedics, and mobile emergency care units staffed with specialized anesthesiologists. Associated to the efforts to educate and train the population in resuscitation, the bystander CPR rate has been increasing steadily, and in recent years, the rate has been well over 60%.[71] However, time also plays a critical role in the success of resuscitation following OHCA.[24] Hence it is important to acknowledge that even though bystander CPR is strongly associated to increased survival, the survival rate decreases rapidly if time to potential defibrillation / advanced care are prolonged regardless of bystander CPR status, as found in paper II of this thesis. Ambulance response time was used as a proxy for time to CPR by emergency medical services and potential defibrillation in this paper. We identified that the association between bystander CPR and 30-day survival is somewhat dynamic according to time, and that the absolute 30-day survival decreases rapidly despite received bystander CPR. This finding implies that even though much focus should be made on increasing the rate of bystander CPR, it is also important to focus on strategies to reduce time to potential defibrillation and advanced treatment in order to fully leverage the survival benefit of bystander CPR.

Apart from increasing general information and training in the use of publicly available automated external defibrillators, such strategies can include the following: 1) increasing ambulance density and 2) implementation of first-responder programs, where nearby trained lay-responders or professional first-responders (e.g. police or firefighters) equipped with a defibrillator are dispatched to respond to an OHCA at same time as an ambulance is dispatched. Increasing ambulance density could be complex and costly: one study calculated that the annual cost to reduce ambulance response time by one minute for one ambulance service would be 1.68 million pounds in the United Kingdom.[95] The second strategy of implementing dispatch of nearby trained lay-responders or professional first-responders could represent a good alternative to increase survival, and some experiences on first responder programs already exist.[96,97] In North Carolina in the United States, first-responders are systematically dispatched and include police officers, firefighters, rescue squad, or life-saving crew that are trained to perform basic life support (including using a defibrillator) until the emergency medical services arrive.[13] Data from this region indicates that such first responder program is associated with a survival gain; in this region, survival following bystander CPR and first-responder defibrillation was 24.2%, while survival following bystander CPR and defibrillation by emergency medical services was 15.2%.[13] The inverse relationship between time to defibrillation and patient survival are in line with our study findings in paper II, and in this regard, we found that if bystander CPR was started before arrival of the emergency medical services, the rate of defibrillation by the emergency medical services was 1.5 times higher compared to patients without bystander CPR. Hence, it is important to recognize that apart from early CPR, prompt arrival and deployment of defibrillation is essential in order to increase the absolute number of OHCA survivors. In Denmark, approximately 3,500 patients suffer from an OHCA annually, and only approximately 400 patients survive at least 30 days.[71] In this study, we constructed a statistical model to calculate potential survival gain of reducing ambulance response time / time to defibrillation minute-for-minute. Based on our model, we calculated that by reducing the time to potential defibrillation by even just two minutes, more than one hundred additional patients could be saved every year. This corresponds to a survival gain of about 20% in Denmark.

A recent randomized controlled study from Sweden has examined the effect of CPR-trained mobile-dispatched laypersons.[18] The trained laypersons were dispatched if they were within 500 meters of the arrest. In 23% of the cases, the CPR-trained layperson arrived before the emergency medical services and provided CPR. A similar randomized controlled study with dispatch of nearby first-responders with automated external defibrillators to assist with defibrillation in addition to CPR alone is warranted.

In paper II we also examined best- and worst-case scenarios for patients with and without bystander CPR, and found large variations in predicted survival as expected. Notably, in both scenarios bystander CPR was associated with markedly increased survival compared to no bystander CPR, indicating the robustness of this single factor on survival. However, the absolute survival probability in especially worst-case scenario was particularly dependent on time, regardless of bystander CPR status – in these cases, if potential defibrillation is not conducted relatively early, any chance of survival seems to be minimal.

Taken together, the results from paper II can be useful when planning distributions of ambulances, first-responder programs and availability of automated external defibrillators. We suggest that dispatch of nearby trained lay-responders or professional first-responders to assist with CPR and potential defibrillation before emergency medical services arrive, for example by mobile-dispatch, could potentially save a substantial amount of more lives every year, even if the first responders arrive just a couple of minutes before the ambulance.

Paper III

A cardiac arrest patient's heart rhythm is closely related to the survival: if the heart rhythm is shockable, chances of surviving are much higher compared to patients with non-shockable heart rhythms.[14,49,50] In a limited time period, the heart rhythm is dynamic, and depends on a range of factors, including time from collapse to rhythm analysis, age and comorbidities of patients, the cause of arrest, and treatment. For example, a shockable rhythm will deteriorate to a non-shockable rhythm over time,[24,40,51] while early CPR can prolong the window of the patient remaining in a shockable rhythm.[42,44] In some instances, it can also work the other way around: a non-shockable rhythm can in a limited time period convert into a shockable rhythm during a resuscitation attempt.

In 2007, Hallstrom et al.[98] reported, based on observations on data from the ASPIRE trial, that 22% of all patients with initial non-shockable rhythms converted to a shockable rhythm during the course of resuscitation, but survival to hospital discharge was greater for patients who remained in a non-shockable rhythm compared to those who converted (4.9% vs. 0.6%). As a result, the authors questioned the traditional approach of pauses in CPR for rhythm evaluation and defibrillation, and suggested alternative treatment for patients with initial non-shockable rhythms, including focus on high-quality CPR with minimal interruptions rather than defibrillation. In response to this report, several authors reported contradictory findings; Herlitz et al (2008)[55] studied the Swedish OHCA register and reported that 25% of all patients with initial non-shockable rhythm converted to shockable rhythms, but defibrillation was identified as one of six key factors associated with improved survival. Other key factors included younger age, witnessed arrest, bystander CPR, public arrest and short ambulance response time. Kajino et al (2008)[54] reported a conversion rate of 5% from non-shockable to a shockable rhythm in Osaka, Japan but noted that in patients with presumed cardiac cause of arrest, conversion to a shockable rhythm was associated with improved 30-day neurologically favorable survival compared to those remaining in non-shockable rhythms with adjusted odds ratio of 4.3 (95% CI: 2.8-6.7). In 2008 Olasveengen et al.[52] studied OHCA cases in Oslo and reported a conversion rate from non-shockable to subsequent shockable rhythm of 13%, and found that survival was higher for patients who subsequently converted to shockable rhythms compared to those remaining in non-shockable rhythms (7% vs. 2%). Olasveengen et al. also examined the quality of chest compressions and hands-off ratio, and found no significant difference in compression or ventilation rates, while the converted group had more pauses in chest compressions, likely related to defibrillation attempts. Thomas et al. (2013)[99] reported a conversion rate of 18%, and found no difference in survival between those who converted to a shockable rhythm, and those who remained in non-shockable rhythms. Finally, a recent study by Wah et al. (2017)[100] reported a conversion rate of 6.8% and improved survival among those who converted to shockable rhythms compared to those who remained in non-shockable rhythms with an odds ratio of 2.0 (95% CI: 1.10-3.65).

Paper III of this thesis reports a conversion rate of 25%, similar to Hallstrom et al (2007) and Herlitz et al (2008). The highest survival rate in paper II was found among those with initial shockable rhythm (27.1%), while survival was 4.2% for converted shockable rhythm and 1.2% for sustained non-shockable rhythm, in accordance with the findings of Herlitz et al., Kajino et al, Olsaveengen et al. and Wah et al. who all found higher survival rates for patients converting to shockable rhythms compared to those in sustained shockable rhythms. Possible explanations of the discrepancies in conversion rates and subsequent survival in the reported studies may be found in differences in the included study populations, differences in treatment protocols, including when CPR is initiated by the emergency medical services, and differences in emergency medical systems across the studies, including response times.[101] None of these previous studies have examined differences in comorbidities between all three rhythm groups (shockable, converted shockable and sustained non-shockable) as a potential explanation of conversion and survival differences between the groups.[102] In paper III of this thesis we examined patient comorbidities up to ten years prior to the OHCA event, and, found that patients with first recorded shockable rhythms and converted shockable rhythms were more likely to have a history of cardiovascular disease, while patients with non-shockable rhythms were more likely to have a history of chronic obstructive pulmonary disease and psychiatric diseases. Chronic obstructive pulmonary disease has previously been linked to adverse survival outcomes following OHCA as well as non-shockable rhythms.[103] In contrast, cardiovascular disease seemed to serve as a predictive factor of shockable, as well as converted shockable rhythm – this could be driven by the close association between shockable rhythms and ischemic heart disease.[104] The finding that cardiac comorbidities were predictors for conversion to a shockable rhythm from initial non-shockable rhythm is important as it emphasizes the importance of considering the underlying substrate when studying outcomes after resuscitation, and may explain some of the conflicting results in the existing literature.

In paper III of this thesis we also examined temporal predictions of pre-hospital return of spontaneous circulation as well as 30-day survival according to the rhythm groups during the study period from 2005-2012. Return of spontaneous circulation and 30-day survival increased over the study period for all three groups, but the increase in 30-day survival was less prominent compared to the increase in return of spontaneous circulation for all three groups. Changes in return of spontaneous circulation, as it is measured upon arrival to hospital in our study, are reflective of improvements made in the pre-hospital setting, while changes in 30-day survival are likely to reflect both pre- and in-hospital treatments. In-hospital treatment could potentially be more conservative for those with a non-shockable rhythm, as physicians may withdraw care for these patients due to a poor prognosis. This would be difficult to register, but may serve as a crucial factor contributing to the lower 30-day survival among the vulnerable patients with a first recorded non-shockable rhythm who initially achieved return of spontaneous circulation in the pre-hospital setting. Another explanation for the lower survival could be that patients with first recorded non-shockable rhythms simply are a specifically vulnerable population with poor long-term prognoses despite initially having achieved return of spontaneous circulation.

When examining predicted survival in best-case and worst-case scenarios, we observed large variation in survival with reasonably high survival rates in best-case scenarios, even for patients in sustained non-shockable rhythms, but with 30-day survival rates below 1% in worst-case scenarios. These predictions models show that even though the heart rhythm is an important predictor of survival, other factors in addition to heart rhythm are also of importance. Even if the overall prognosis for patients initially found in non-shockable rhythms may not be as favorable as patients with first recorded shockable rhythms, the former group can be successfully resuscitated especially under favorable circumstances. Taken together, our results suggest that patients initially found in non-shockable rhythms should be given the benefit of the doubt, and aggressive resuscitation should be attempted until reasonable options have been exhausted. Some of these patients may convert to a shockable rhythm with better chances of achieving 30-day survival.

Strengths and limitations

It was possible to conduct the studies described in this thesis due to the Danish registers in combination with the unique and permanent civil registration number assigned to each individual residing in Denmark. This arrangement has made it possible to conduct studies with a relatively large sample size, which reduces the risk of selection bias caused by differences in demographic and geographical factors. Nationwide studies on OHCA are relatively rare, but of great importance, especially when applying implications on a nationwide level. However, the included studies in this thesis have a range of limitations that are important to address.

Firstly, all of the three included studies are observational in nature, which means that highlighted relationships are associations and may not be causal. However, in paper II we applied causal statistics to our data, which allows a more "causal" conclusion – nevertheless, one assumption of causal statistics that needs to be fulfilled in order to establish a causal relationship is that there are no unmeasured confounders, which is difficult to accomplish. Furthermore, we unfortunately did not have any data on in-hospital treatment, including information on hypothermia treatment, acute coronary arteriography and revascularization, which could influence long-term survival results.[105] Secondly, another important limitation specifically for **paper I** was that we were only able to present resuscitation duration results from patients who achieved a pre-hospital return of spontaneous circulation, rather than the total number of patients who had a resuscitation attempt. However, unless a study in the future is able to ensure that the total study population receives prolonged resuscitation, it is not possible to make an estimation of how many patients need prolonged resuscitation for one to survive without prominent brain damage. The patients in paper I with resuscitation durations >25 minutes were older than the shortest CPR duration group (0-5 minutes) and the second-longest CPR duration group (21-25 minutes), but slightly younger than the CPR duration groups in the middle, which could indicate a possibility that the emergency medical providers may have put in extra efforts during the long CPR durations in younger patients (potential risk of selection bias). However, the longest CPR duration group (>25 minutes) also seemed to have higher rates of comorbidities compared to the other groups, and lower rates of bystander intervention, which has previously been associated with poorer prognosis. Even thought that the amount of comorbidities may be difficult to estimate during a pre-hospital resuscitation attempt (and therefore, is likely not to have affected the emergency medical service's willingness for continued CPR), knowledge of bystander intervention is readily available; and since the patients with longest resuscitation durations had lower rates of bystander intervention, selection bias, where the emergency medical services may have put in extra efforts during the long CPR durations compared to other patients, seems unlikely.

Furthermore, for paper I, we did not have qualitative data on neurological outcomes. Obtaining information on the surviving patients' CPC or mRS scores after the OHCA would have allowed a better insight into the patients' neurological status.[106] We also did not have any information on the quality of life of the surviving patient after the OHCA – questionnaires with patient reported outcome measures (PROM) could have aided in highlighting each surviving patient's quality of life after the OHCA, related to duration of resuscitation.[107] However, we were able to get an indication of a patient's functional status by examining how many patients had a diagnosis of new onset of anoxic brain damage, how many were admitted to nursing homes or received home help after the cardiac arrest. Although the sensitivity of the diagnostic coding of anoxic brain damage is unknown, there are not any obvious reasons that would explain any reasons leading to inequality in the coding or reporting of anoxic brain damage. Yet it is not possible to rule out that patients we concluded to have favorable functional / neurological outcomes had discrete impairments, but we argue that severe impairments among surviving patients was most likely captured by the diagnosis of anoxic brain damage, nursing home admission or the need of home care. Finally, we cannot dismiss that some patients with severe brain damage may have been treated in their homes without any public help. However, given that nursing homes and home care is state financed, this number is likely to be very low.

Thirdly, specifically for **paper II**, we did not have information on the time of the actual collapse and the duration of bystander CPR. Hence, ambulance response time, as used in the study, may not fully portray the duration of actual CPR provided by the bystander, or the duration of the cardiac arrest before arrival of the ambulance. However, we conducted a sensitivity analysis examining a subset of the study population who had witnessed arrests, as in this group of patients, the ambulance response time is more likely to be closely related to the duration of no-flow time and the duration of CPR by a bystander. Survival chances were expectedly higher in this subpopulation, but the overall results did not differ from our main analysis. However, it cannot be ruled out that a bystander may have initiated CPR before calling the emergency medical services. A recent study showed that this happened in 20% of OHCA cases in the Central Region of Denmark.[108] Other important factors that we did not have information on included the quality of the CPR given, whether the bystander CPR was telephone-assisted, or whether the bystander was trained in CPR. Not many patients had very long ambulance response times, which is, of course, a good thing, but it also meant that towards long ambulance response time durations the reported results had large confidence intervals, reflecting uncertainties on the calculated estimates due to a lack of power.

Fourthly, specifically for **paper III**, heart rhythm was evaluated as the first rhythm recorded by the emergency medical service personnel upon arrival at the site of the arrest. This first recorded rhythm could naturally be different from the very first rhythm present after the collapse. Conversion to a shockable rhythm was determined indirectly by the event of defibrillation by the emergency medical services. However, during the entire study period an external defibrillator determined whether the rhythm was classified as shockable or not, and only patients with a shockable rhythm were defibrillated. Previous studies have shown that external defibrillators are highly accurate in determining the heart rhythm.[109-111] Defibrillation is therefore likely to be a reliable proxy of conversion.

Finally, in the Danish Cardiac Arrest Register, approximately 10% of the patients have initially been excluded due to missing or invalid civil registration number. Previous work has shown that these patients were not associated with lower return of spontaneous circulation rates compared to patients with a valid civil registration number, indicating low risk of selection bias with exclusion of the patients with the poorest prognoses.[112]

Conclusions

The three studies presented in this thesis contribute with valuable information to the field of OHCA research. Even after very long intervals of resuscitation (>25 minutes) by the emergency medical services before a pre-hospital return of spontaneous circulation was achieved, 30-day survival remained above 13%, and the majority of patients were able to return to own home rather than nursing home, did not need of home care and did not have a diagnosis of anoxic brain damage. The data suggests that prolonged resuscitation is not futile. We also demonstrated that as ambulance response time increased, the absolute 30-day survival decreased regardless of bystander CPR status. Yet, the relative survival difference between patients receiving bystander CPR and those not receiving bystander CPR was more than twice as high even when ambulance response time was long. Decreasing time to potential defibrillation by a couple of minutes, for example through mobile-dispatched first-responder programs, could potentially lead to many additional lives saved every year in Denmark. Finally, we observed that a quarter of all patients defibrillated by the emergency medical services in the pre-hospital setting were initially found in non-shockable rhythms. Patients converting to a shockable rhythm from a first recorded non-shockable rhythm were associated with more than doubled odds of surviving at least 30 days compared to patients remaining in non-shockable rhythms, even after adjusting for various patient- and arrest related factors. Factors that were associated with conversion of non-shockable rhythm to a shockable rhythm were younger age, male sex, witnessed arrest, shorter duration between recognition of cardiac arrest and rhythm analysis by the emergency medical services, and cardiovascular comorbidities, while non-cardiovascular comorbidities were associated with sustained non-shockable rhythms.

Implications

The present findings in this thesis strongly encourage persistent efforts to improve cardiac arrest management, especially initiatives aimed at increasing early resuscitative efforts conducted by bystanders. This includes targeting a bystander's willingness to start early CPR, which can largely influence the outcome of a cardiac arrest patient. The ultimate goal is that bystander-initiated resuscitative efforts are conducted for all OHCA patients where the collapse is not witnessed by the emergency medical services. The latest reported rate of bystander CPR in Denmark is approximately 65% (2014). In Denmark, several national campaigns and commercials have been launched to raise awareness about OHCA. The campaigns strongly encourage all Danish residents to learn basic life support and to intervene immediately if a cardiac arrest victim is seen. The Danish foundation TrygFonden has set an overall goal of increasing the rate of bystander CPR in Denmark to 85% by 2018. Moreover, as demonstrated in this thesis, apart from focusing on increasing the rate of bystander CPR, focus should also be on implementation of first responder programs equipped with defibrillators, as absolute survival rates seem to decrease rather rapidly regardless of bystander CPR status if time to advanced treatment and potential defibrillation is increased.
The above-mentioned goals may be achieved by:

1) Continued efforts to educate the public in resuscitation. These efforts could be strengthened by implementing basic life support as a class-scheduled component in various steps during the educational career (i.e. introduced in elementary school, further built on in middle school, and then in high school). This could also be achieved by implementing resuscitation training at work places with ongoing refresher courses, web-based training, et cetera.

2) Increasing dissemination of automated external defibrillators outside of hospitals, placed in easily accessible places, along with registration to the Danish public defibrillator network "www.hjertestarter.dk" to ease location of nearby automated external defibrillators.

3) Implementation of first responder programs with laypersons and/or professionals such as policemen or firefighters, where the first responders are equipped with defibrillators and are dispatched at the same time as an ambulance. Such programs could be an important tool in order to decrease time to potential defibrillation.

Perspectives for future research

Looking to the future, more studies are needed. One potential 'game changer' in the early treatment of OHCA in Denmark would be to be able to activate nearby laypersons using smartphone technologies in case of an OHCA, where two laypersons are activated simultaneously, one to start early CPR and one to bring a nearby defibrillator to the site of arrest before the ambulance arrives. This could potentially help bring down the response time for treatment after arrest and increase the subsequent survival rate. A recent study has shown that the majority of the patients with defibrillation attempts by bystanders before the arrival of the emergency medical services, survived without brain damage or risk of discharge to a nursing home rather than own homes.[113] A randomized study examining the effect of such layperson activation is highly warranted.

During the last decade, various national initiatives have been implemented in Denmark to improve resuscitation, and these initiatives have been associated with increased survival.[14] However, the associated impact of the initiatives may vary between different patient populations. One vulnerable patient population is patients with diabetes. Determining how the national initiatives may have affected the prognosis of patients with diabetes could help identifying if patient-specific improvements in resuscitation are warranted. This study is currently in progress.

Another vulnerable OHCA population is nursing home residents, and resuscitation attempts in this aging population could raise ethical dilemmas. Studying this population of patients, and comparing characteristics and outcomes to other OHCA patients, may shed some light on the issue. This study is also currently in progress.

Examining whether different socioeconomic statuses of OHCA patients, including household incomes and educational levels, may affect CPR rates and potential outcomes after OHCA is important, as it may imply that patient-specific prevention strategies are needed. Studying how population densities may influence bystander CPR rates, ambulance response times, and outcomes after OHCA could provide valuable information in for example planning of ambulance distributions. We are currently working on both of these mentioned studies.

Future studies that examine patient- and cardiac arrest characteristics with first-recorded shockable-, converted-, and sustained non-shockable rhythms over time to get a better understanding of why the incidence of non-shockable arrests seem to be increasing are warranted. We are on the planning stage of conducting such study.

This thesis also encourages further research in various other areas, including ways to improve post-resuscitation care, as this is also imperative for favorable outcomes, including rehabilitation. Furthermore, and very importantly, this thesis encourages every citizen to learn CPR and to not be afraid of stepping in when needed – this to not only save a life, but also to preserve the same functional level of the surviving patient as he or she had prior to the cardiac arrest.

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APPENDICES

The following papers are attached as appendices:

Paper I

Rajan S, Folke F, Kragholm K, Hansen CM, Granger CB, Hansen SM, Peterson ED, Lippert FK, Søndergaard KB, Køber L, Gislason GH, Torp-Pedersen C, Wissenberg M. Prolonged cardiopulmonary resuscitation and outcomes after out-of-hospital cardiac arrest. ***Resuscitation***. 2016;105:45-51.

Paper II.

Rajan S, Wissenberg M, Folke F, Hansen SM, Gerds, TA, Kragholm K, Hansen, CM, Karlsson L, Lippert FK, Køber L, Gislason GH, Torp-Pedersen C. Association of bystander cardiopulmonary resuscitation and survival according to ambulance response-times after out-of-hospital cardiac arrest. ***Circulation***. 2016;134:2095-2104.

Paper III.

Rajan S, Folke F, Hansen SM, Hansen CM, Kragholm K, Lippert FK, Karlsson L, Møller S, Køber L, Gislason GH, Torp-Pedersen C, Wissenberg M. Incidence and survival outcome according to heart rhythm during resuscitation attempt in out-of-hospital cardiac arrest patients with presumed cardiac etiology. ***Resuscitation***. 2017;114:157-163.

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Clinical paper

Prolonged cardiopulmonary resuscitation and outcomes after out-of-hospital cardiac arrest☆

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ABSTRACT

Aim: It is unclear whether prolonged resuscitation can result in successful outcome following out-of-hospital cardiac arrests (OHCA). We assessed associations between duration of pre-hospital resuscitation on survival and functional outcome following OHCA in patients achieving pre-hospital return of spontaneous circulation (ROSC).

Methods: We included 1316 adult OHCA individuals with pre-hospital ROSC (2005–2011) handled by the largest nationwide ambulance provider in Denmark. Patients were stratified into 0–5, 6–10, 11–15, 16–20, 21–25 and >25 min of cardiopulmonary resuscitation (CPR) by emergency medical services until ROSC was achieved. Nursing home admission and diagnosis of anoxic brain damage were measured as proxies of poor neurological/functional outcomes.

Findings: Median time from CPR initiation to ROSC was 12 min (IQR: 7–18) while 20.4% achieved ROSC after >25 min. Overall, 37.5% (494) of the study population achieved 30-day survival. Thirty-day survival was inversely related to minutes of CPR to ROSC: ranging from 59.6% (127/213) for ≤5 min to 13.8% (19/138) for >25 min. If bystander initiated CPR before ambulance arrival, corresponding values ranged from 70.4% (107/152) to 21.8% (12/55). Of 30-day survivors, patients discharged to own home rather than nursing home ranged from 95.0% (124/127) to 84.7% (18/19), respectively. Of 30-day survivors, patients discharged without diagnosis of anoxic brain damage ranged from 98.4% (125/127) to 73.7% (14/19) for corresponding intervals.

Conclusion: Even those requiring prolonged resuscitation duration prior to ROSC had meaningful survival rates with the majority of survivors able to return to live in own homes. These data suggest that prolonged resuscitation is not futile.

Introduction

Each year, 71.5 out of 100,000 adult individuals in the US are estimated to have an out-of-hospital cardiac arrest (OHCA), and of these, approximately 89% of the patients die following the OHCA, mostly before arriving at a hospital.[1] With the high incidence and high mortality rates, even a moderate improvement in survival can have a substantial impact.

When the emergency medical services attempt to resuscitate patients in the field, the attempts are continued until the patient achieves return of spontaneous circulation (ROSC), or until it is decided that further resuscitation may be futile. In cases where resuscitation attempts are prolonged, an important question is not only if the patient has a chance of achieving ROSC and subsequently

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achieving survival to discharge, but also if the patient survives to a meaningful life. Achieving pre-hospital ROSC is the first primary goal during a resuscitation attempt,[2,3] however, clinicians might be reluctant to continue resuscitation if ROSC is not achieved fairly quickly, as it may be thought that downstream prognosis will remain grim.[4] Unfortunately, data on the association of time from initiation of cardiopulmonary resuscitation (CPR) by the emergency medical services to ROSC and related long-term survival outcomes are limited.[5–8] There is therefore an urgent need to examine the association of duration of resuscitation with survival outcomes as it could have a high impact on the willingness to continue resuscitation if the outlook is otherwise reasonable.

The objective of this study was to assess length of pre-hospital resuscitation in patients achieving ROSC, and examining the association of resuscitation length with survival and functional outcomes using data from the Danish Cardiac Arrest Register. We also examined the role of bystander-initiated CPR before ambulance arrival.

Methods

Data source and definitions

From the nationwide Danish Cardiac Arrest Register, OHCA between 2005 and 2011 were identified. The Danish Cardiac Arrest Register and the Danish emergency medical service system have been described in detail elsewhere.[9–11] OHCA cases handled by the largest nationwide ambulance provider in Denmark (Falck A/S) were included in this study, as this ambulance provider could provide electronic data on time intervals for each OHCA, including information on time of ambulance arrival. We focused on OHCA cases who achieved ROSC and who had information on time to ROSC available.

Using the permanent and unique Civil Registration number provided to all Danish residents we were able to identify age, gender, survival status, and hospital diagnoses from the national administrative registries as described previously.[9–11]

To compare a homogenous group of patients, patients were categorized into OHCA of presumed cardiac cause, and presumed non-cardiac cause.[12] Cardiac disease, unexpected collapse or unknown diseases were defined as a cardiac arrest of presumed cardiac cause. Other medical disorders were categorized as OHCA of presumed non-cardiac cause. All traumas were defined as non-cardiac causes, regardless of other diagnoses.

Data on individuals entering and leaving nursing home was obtained from Statistics of Denmark. Nursing home data has been collected since 1994 using a validated approach to secure high degree of completion of nursing home information.[13] Similarly, home care has been reported for all individuals since 2008 allowing determination of home care since that time.

We defined the duration of CPR by the emergency medical service as the time when the emergency medical service arrived on site of OHCA till ROSC was achieved.

Study population

All adult first-time OHCA cases of presumed cardiac cause and who achieved ROSC before hospital arrival were included. Inclusion and exclusion criteria are listed in Supplemental Fig. 1.

Study endpoints/outcomes

The outcome measures were 30-day survival and functional/neurological status, measured as nursing home admission, received home care, and diagnosis of anoxic brain damage.

Statistics

The Pearson's Chi Squared test was used to evaluate differences in categorical variables, and the Kruskal–Wallis test was used to evaluate differences in continuous variables. Continuous data was presented as medians and interquartile ranges ([IQR]: 25% and 75%). Cumulative incidence was conducted using the Kaplan Meier Method, and significance was checked using the log rank test. We checked for trends in data by using the Cochran Armitage Trend Test. For all cases a two-sided p-value <0.05 was considered to be statistically significant. Multivariable logistic regression analyses were performed to examine the association between stratified time groups and 30-day survival and functional/neurological outcomes. On the basis of directed acyclic graph and previous work,[14,15] the multivariable logistic regression models were adjusted age, shockable heart rhythm, bystander use of automated external defibrillator, year of the arrest and ambulance response times (Supplemental Fig. 2). Associations are presented as odds ratios with 95% confidence intervals. All statistical analyses were performed using SAS, version 9.2 (SAS Institute Inc., Cary, NC, USA) and R, version 3.0.2 (R Development Core Team).

Ethics

The Danish Data Protection Agency (J. ref: 2007-58-0015/local J ref: GEH-2014-017/I-Suite: 02735) approved this study. Ethical approval is not required for retrospective register-based studies in Denmark.

Results

During the study period, a total of 1316 adult OHCA cases of presumed cardiac cause with pre-hospital ROSC met the inclusion criteria and comprised the final study population (Supplemental Fig. 1).

We conducted a sensitivity analysis comparing the patients included in the study with the patients excluded due to missing time of ROSC (Supplemental Table 1). No statistical difference in patient demographics or rate of bystander CPR was found (p-value >0.05). The excluded patients had higher rates of arrests outside of private home, bystander defibrillation and survival (p-value <0.05).

Duration of CPR until ROSC

Table 1 depicts baseline characteristics stratified according to duration of CPR by the emergency medical service until ROSC was achieved, irrespective of response time and witnessed status. Overall, age increased with longer duration of CPR by the emergency medical services ($p = 0.04$). Increasing time to ROSC achievement was associated with cardiac arrests in private homes ($p < 0.0001$), initial non-shockable heart rhythm ($p < 0.0001$) and was inversely associated with bystander CPR ($p < 0.0001$).

Fig. 1 shows the cumulative incidence of ROSC according to bystander CPR and shockable heart rhythm. Among all the ROSC patients, 20.4% achieved ROSC after more than 25 min of CPR. Receiving bystander CPR prior to ambulance arrival and having a shockable heart rhythm were associated with quicker ROSC achievement ($p < 0.0001$).

Thirty-day survival

Of the final study population of ROSC patients, 30-day survival was 37.5% (494/1316).

Thirty-day survival was inversely related to duration of CPR by the emergency medical service until ROSC was achieved (62.9% (134/213), 47.8% (171/358), 32.7% (98/300), 22.7% (46/203), 25.0%

Table 1
Baseline characteristics stratified according to time intervals of duration of EMS CPR.

	≤5 min (n = 213)	6–10 min (n = 358)	11–15 min (n = 300)	16–20 min (n = 203)	21–25 min (n = 104)	>25 min (n = 138)	p-value
Median age (IQR)	65 (57–75)	68.5 (58–76)	69.5 (61–79)	70 (60–78)	66 (58.5–75.5)	67.5 (59–76)	0.04
Male, n (%)	155 (72.8)	254 (71.0)	199 (66.3)	135 (66.5)	81 (78.0)	101 (73.2)	0.17
Comorbidities							
Peripheral vascular disease	24 (11.3)	39 (10.9)	24 (8.0)	25 (12.3)	11 (10.6)	20 (14.5)	0.43
Cerebral vascular disease	22 (10.3)	33 (9.2)	35 (11.7)	28 (13.8)	11 (10.6)	17 (12.3)	0.66
Ischemic heart disease	70 (32.9)	91 (25.4)	85 (28.3)	60 (29.6)	27 (26.0)	46 (33.3)	0.35
Myocardial infarction	25 (11.7)	35 (9.8)	45 (15.0)	22 (10.8)	13 (12.5)	20 (14.5)	0.39
Congestive heart failure	38 (17.8)	78 (21.8)	51 (17.0)	38 (18.7)	21 (20.2)	32 (23.2)	0.54
Cardiac dysrhythmia	42 (19.7)	88 (24.6)	65 (21.7)	42 (20.7)	22 (21.2)	30 (21.7)	0.80
COPD	16 (7.5)	41 (11.4)	27 (9.0)	33 (16.3)	21 (20.2)	26 (18.8)	0.0005
Psychiatric illness	20 (9.4)	52 (14.5)	43 (14.3)	33 (16.3)	11 (10.6)	18 (13.0)	0.34
Malignancy	18 (8.5)	34 (9.5)	33 (11.0)	13 (6.4)	10 (9.6)	18 (13.0)	0.38
Renal disease	5 (2.4)	16 (4.5)	14 (4.7)	11 (5.4)	4 (3.9)	3 (2.2)	0.51
Liver disease	3 (1.4)	4 (1.1)	7 (2.3)	5 (2.5)	0 (0.0)	3 (2.2)	0.51
Peptic ulcer	14 (6.6)	21 (5.9)	17 (5.7)	11 (5.4)	11 (10.6)	17 (12.3)	0.06
Rheumatic disease	4 (1.9)	6 (1.7)	1 (0.3)	5 (2.5)	3 (2.9)	3 (2.2)	0.39
Diabetes	26 (12.2)	55 (15.4)	44 (14.7)	36 (17.7)	16 (15.4)	17 (12.3)	0.65
OHCA characteristics							
Arrest in private homes	97 (45.8)	227 (64.0)	206 (69.1)	143 (70.8)	68 (66.0)	111 (81.02)	<0.0001
Bystander CPR	152 (71.7)	230 (64.3)	156 (52.2)	109 (54.0)	61 (58.7)	55 (40.2)	<0.0001
Bystander CPR in witnessed arrests	134 (75.7)	198 (67.1)	128 (54.7)	80 (58.0)	47 (67.1)	39 (44.3)	<0.0001
AED use by bystander	21 (9.9)	14 (4.0)	9 (3.0)	3 (1.5)	3 (2.9)	4 (2.9)	<0.0003
Initial shockable rhythm	147 (71.7)	232 (65.4)	176 (59.7)	99 (50.0)	54 (52.4)	71 (53.0)	<0.0001
Response time and outcome							
Response time, median (IQR)	6 (4–9)	6 (4–9)	6 (4–9)	6 (5–9)	7 (5–11)	7 (5–9)	0.007
Thirty-day survival	134 (62.9)	171 (47.8)	98 (32.7)	46 (22.7)	26 (25.0)	19 (13.8)	<0.0001
One-year survival	127 (59.6)	158 (44.1)	89 (29.7)	42 (21.2)	24 (23.1)	19 (13.8)	<0.0001
Home care data for 30-day survivors for 2008-2011 (n = 397)							
Survival in each time interval, 2008-2011	94 (64.4)	140 (50.0)	79 (32.5)	44 (25.9)	25 (27.6)	15 (12.4)	<0.0001
Patients receiving home care[a]	6 (6.4)	11 (7.9)	11 (13.9)	3 (6.8)	5 (20.0)	0 (0.0)	0.09
Median minutes/week (IQR), personal care	140 (140–140)	266 (195–332.5)	272.5 (111.5–521.5)	31 (2–60)	97 (45–125)	0 (0–0)	0.09
Median minutes/week (IQR), practical care	26.5 (20–48)	47.5 (30–68)	44 (35–57)	15 (15–15)	19 (15–23)	0 (0–0)	0.23

All results are n (%) unless otherwise specified.
EMS = emergency medical service. CPR = cardiopulmonary resuscitation. IQR = interquartile range.
[a] Among 30-day survivors.

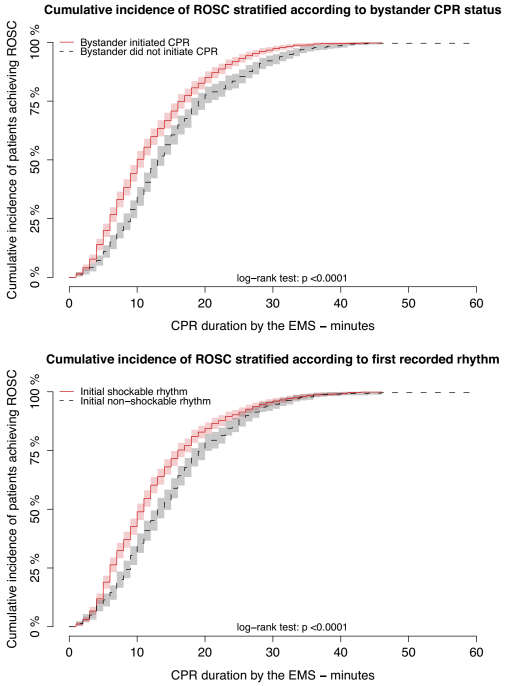

Fig. 1. Cumulative incidence to achieved ROSC according to CPR duration by the emergency medical service ($n = 1316$). The top graph shows the cumulative incidence to achieved ROSC according to CPR duration, stratified by whether bystander initiated CPR. The bottom graph shows the cumulative incidence to achieved ROSC according to CPR duration, stratified by first recorded heart rhythm. ROSC = return of spontaneous circulation. CPR = cardiopulmonary resuscitation. EMS = emergency medical service.

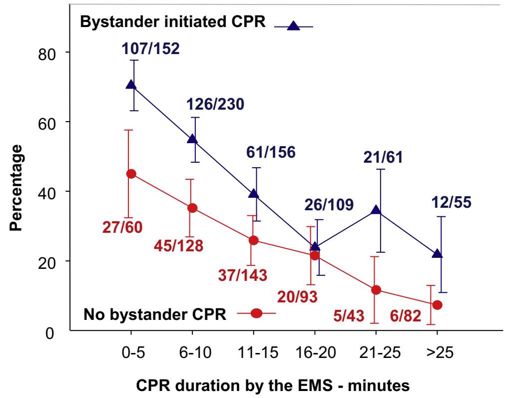

Fig. 2. Thirty-day survival related to duration of CPR by the EMS ($n = 1316$). The graph depicts 30-day survival related to CPR duration by the EMS until return of spontaneous circulation was achieved, stratified according to bystander CPR. The numbers next to each point on the figures refer to the numerator and denominator for the percentages. EMS = emergency medical service. CPR = cardiopulmonary resuscitation.

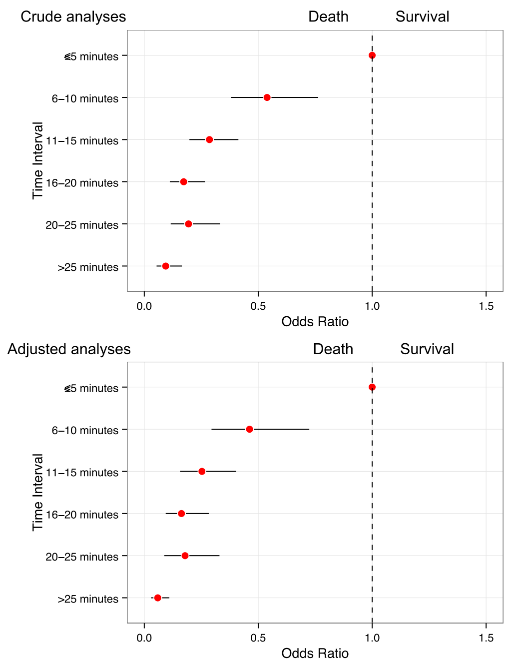

Fig. 3. Associations between 30-day survival and CPR duration time. The graphs demonstrate associations between 30-day survival and CPR duration time with ≤5 min as the reference. The top graph shows crude results and the bottom graph shows adjusted analyses. The bottom model was adjusted for: age, shockable heart rhythm, bystander use of automated external defibrillator, ambulance response times and year of arrest. CPR = cardiopulmonary resuscitation

(26/104), and 13.8% (19/138) for ≤5 min, 6–10 min, 11–15 min, 16–20 min, 21–25 min and >25 min, respectively (p-value for decreasing trend: <0.001) (Fig. 2). If bystanders initiated CPR before ambulance arrival, the corresponding 30-day survival rates were significantly higher (Fig. 2).

When stratified according to first recorded heart rhythm, the 30-day survival rates for shockable heart rhythm were 74.8% (110/147), 62.9% (146/232), 50.0% (88/176), 44.4% (44/99), 46.3% (25/54), and 22.5% (16/71) (p-value for decreasing trend: <0.0001), while the 30-day survival rates for non-shockable heart rhythm were 36.2% (21/58), 18.7% (23/123), 7.6% (9/119), 2.0% (2/99), 2.0% (1/49), and 4.8% (3/63) (p-value for decreasing trend: <0.0001), for ≤5 min, 6–10, 11–15 min, 16–20 min, 21–25 min and >25 min of CPR by the emergency medical services, respectively. Fig. 3 examines associations between 30-day survival and CPR duration time, with ≤5 min as the reference group. Compared to the ≤5 min group, survival decreased significantly with increasing CPR time in both crude and adjusted analyses.

Neurological and functional status

Fig. 4 illustrates percentages of 30-day survivors discharged to their own homes rather than being admitted to a nursing home up to one year after OHCA, and the percentages of 30-day survivors discharged without any diagnosis of anoxic brain damage up to 30

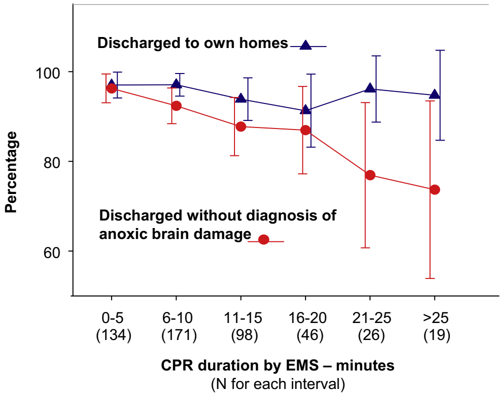

Fig. 4. Thirty-day survivors discharged to own home/without anoxic brain damage diagnosis according to duration of CPR by EMS ($n = 494$). The graph shows the rate of patients discharged to own home and without anoxic brain damage according to duration of cardiopulmonary resuscitation by the emergency medical services. The number in parenthesis under the *X*-axis refers to the total number of patients in each interval. EMS = emergency medical services. OHCA = out-of-hospital cardiac arrest. ROSC = return of spontaneous circulation.

days post discharge, according to CPR duration by the emergency medical services.

Of the 30-day survivors, the rates of patients discharged to own home showed no clear trend according to time intervals: 97.0% (130/134), 97.1% (166/171), 93.8% (92/98), 91.3% (42/46), 96.1% (25/26), and 94.7% (18/19) for CPR durations by emergency medical services of ≤5 min, 6–10 min, 11–15 min, 16–20 min, 21–25 min and >25 min, respectively (*p*-value for trend: 0.2). The rates of patients discharged without any diagnosis of anoxic brain damage showed a decreasing trend for the same time intervals: 96.3% (129/134), 92.4% (158/171), 87.8% (86/98), 87.0% (40/46), 76.9% (20/26), and 73.7% (14/19) (*p*-value for decreasing trend: <0.0001).

Supplemental Fig. 3 demonstrates the above-mentioned analyses stratified according to whether bystanders initiated CPR. No statistical differences between the bystander CPR groups were found ($p > 0.05$).

Fig. 5 shows associations between nursing home status and CPR duration with ≤5 min as the reference group for 30-day survivors. Crude and adjusted analyses showed no significant difference in nursing home status across all time interval groups.

The bottom of Table 1 shows analyses of patients who received home-care in the period 2008–2011, stratified according to CPR duration by emergency medical services. During this four-year period, 9.1% of the 30-day survivors received home care (36/397).

Discussion

This nationwide study had two major findings: (1) even though 30-day survival decreased as duration of CPR increased, patients who achieved ROSC after long durations of CPR by the emergency medical services could still achieve 30-day survival rates above 13%; (2) the majority of patients who achieved 30-day survival were able to return to their own homes rather than nursing homes, did not need home care services after discharge, and did not have a diagnosis of anoxic brain damage even when CPR duration exceeded 25 min.

Literature on prolonged pre-hospital resuscitation attempts in OHCA patients and the relation to survival outcome is limited.[6,8] A recent study evaluated the probability of survival and

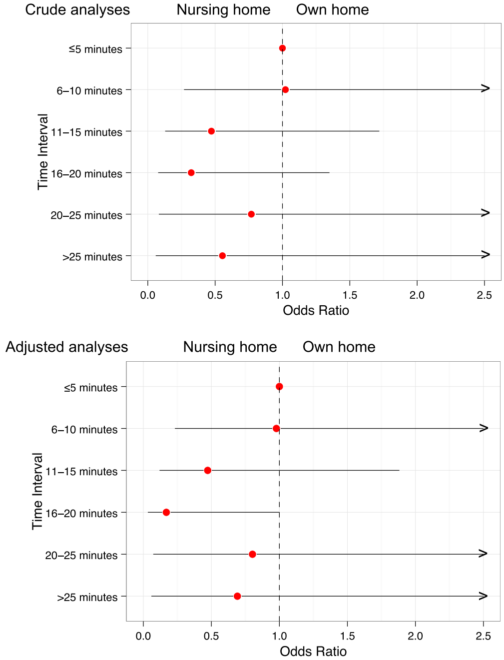

Fig. 5. Associations between nursing home status and CPR duration time in 30-day survivors. The graphs demonstrate associations between nursing home status post-discharge and CPR duration time with ≤5 min as the reference, in 30-day survivors. The top graph shows crude results and the bottom graph shows adjusted analyses. The bottom model was adjusted for: age, shockable heart rhythm, bystander use of automated external defibrillator, ambulance response times and year of arrest. CPR = cardiopulmonary resuscitation.

functional recovery associated to duration of CPR.[8] They found that by 16.1 min, 89.7% of patients with eventual modified Rankin Scale score of 0–3 had achieved ROSC. The data from the study was derived from a single site, with varying sophistication of in-hospital treatment post OHCA. The authors stated that during the same time period, they treated patients from other emergency medical service systems that displayed good functional recovery in CPR time periods exceeding 21 min. This current study has collected data from an emergency medical provider that treats OHCA nationwide rather than from a single site, thus allowing an insight into the population disparity across the country.

Older in-hospital cardiac arrest studies have previously reported that prolonged resuscitation is associated with poor survival and functional outcome.[16–18] Possibly due to these findings, there seems to be a general reluctance towards prolonged resuscitation from healthcare providers if ROSC is not achieved fairly quickly.[4] However, a recent in-hospital cardiac arrest study demonstrated that hospitals in which the median CPR time was 25 min had higher likelihood of patients achieving ROSC and subsequently surviving, compared to those hospitals with shorter CPR times.[4] However, extrapolation of these in-hospital results to OHCA cases is difficult.

In Denmark, only physicians have the authority to terminate resuscitation – the Danish Cardiac Arrest Register therefore contains many cases with long resuscitation intervals as emergency medical services are required to continue resuscitation until ROSC or hospital arrival. In our study examining ROSC patients, we observed that 20.4% of the study population achieved ROSC only after more than 25 min of CPR by the emergency medical service. Even though overall 30-day survival of the ROSC patients did decrease over time, the survival rate for time duration passing the 25-min mark remained above 13%. Additionally, bystander-initiated CPR before arrival of the emergency medical services was associated with higher chances of survival compared to those without.

Fear of severe brain damage is a prominent argument against very prolonged resuscitation. In our study, we were able to get an indication of the functional outcomes for the patients following OHCA according to duration of resuscitation efforts by examining how many survivors were admitted to nursing homes up to one year after OHCA and how many needed home care services following OHCA. Previous studies have demonstrated that these factors can serve as proxies of poor neurological and functional outcomes after out-of-hospital cardiac arrests.[19–21] The results do not indicate severe brain damage or loss of functional status as a prominent problem associated with prolonged resuscitation as at least 94.0% of surviving patients returned to private homes, and multivariate analyses showed no significant difference in rates of 30-day survivors returning to live in their own homes across all time intervals. Also, the proportion of patients who received home care up to one year after OHCA was very low across all time intervals. In Denmark, home care is a legally protected right according to the Danish Service Law and free of charge for those who need it. Therefore, taken together, these findings support the notion that the functionality and independency of the surviving patients was high even in cases with prolonged resuscitative efforts. Apart from functionality and independence measures, we also examined neurological status by observing whether the patients were diagnosed with anoxic brain damage up to 30 days post discharge. Most patients were discharged without an anoxic brain damage diagnosis. However, when the total CPR duration time by the emergency medical services exceeded 25 min, 26.3% of all surviving patients were discharged with an anoxic brain damage diagnosis.

Although various guidelines for the practical conduct of advanced resuscitative efforts are fairly standardized, recommendations on when to terminate resuscitation are less clear.[22,23] The American Heart Association Guidelines 2010 advises termination of resuscitation when all three of following conditions are fulfilled: (1) the arrest is not witnessed by the emergency medical personnel; (2) no shock is delivered before transportation to the hospital; and (3) the patient does not achieve ROSC before transportation to the hospital.[22] This termination of resuscitation prediction rule has been validated in a series of studies.[3,24–31] Considering the general hesitance towards prolonged resuscitation if ROSC is not readily achieved due to fear of severe brain damage,[4] using the termination of resuscitation predictive rules when ROSC is not achieved without a definition of a minimum resuscitation length may seem problematic. We demonstrated that a significant proportion of patients achieved ROSC only after prolonged resuscitation, with high corresponding survival rates and good functional and neurological outcome. Therefore, using the predictive rules of termination could impose the risk of prematurely terminating resuscitation for patients who could have potentially achieved ROSC and subsequently survived with good functional and neurological outcome had the resuscitative efforts lasted longer. It is therefore likely that the current recommendations are self-fulfilling prophesies (i.e. when resuscitation has more or less been given up prior to hospitalization, further resuscitative efforts are not productive). In an editorial by Cummins and Eisenberg[32] it was suggested that rules for termination of resuscitation should remain advisory, and the decision should be moderated by the full clinical picture, accounting for even a very small possibility of survival followed by continued resuscitative efforts, even when prediction rules advice termination.

The implication of the current study is that prolonged resuscitative efforts in many cases can be beneficial. The data presented are not in direct discrepancy with current guidelines, but these data highlight that longer attempts at resuscitation can save a substantial portion of patients, and guidelines should be interpreted in light of these findings.

Limitations

The observational nature of this study is the main limitation, meaning that relationships between dependent and independent variables are associations, and not cause and effect. Another important limitation is that we only present results from patients who achieved pre-hospital ROSC after prolonged resuscitation, not the total number that received prolonged resuscitation. Unless a future study is able to ensure that all patients receive prolonged resuscitation, it is not possible to estimate how many need prolonged resuscitation for one to survive without serious brain damage. Home care data was only available in the time period 2008–2011 and having the data available for all years would have yielded more complete results. Approximately one third of the patients achieving ROSC had missing data on time of ROSC and were excluded. When conducting sensitivity analysis comparing the excluded and included patients, we observed that the excluded population had higher rates of arrests outside of private homes, automated defibrillator use by a bystander, and 30-day survival. These pre-hospital cardiac arrest characteristics have been linked to higher survival and higher likelihood of neurologically intact survival and indicate that the patients with the poorest prognosis have not been excluded from this study.[15] Furthermore, it cannot be ruled out that some of the excluded cases may have achieved ROSC before the arrival of the ambulance, which may explain the higher survival.

Another limitation of this study was the lack of qualitative data, including information on the Cerebral Performance Category.[12] However, we were able to get an indication of the patients' functional status by examining diagnosis code of anoxic brain damage, combined with information on nursing home and home care. This study cannot exclude that a number of patients with severe brain damage were treated in their homes without any public help. Given that nursing homes and home care is state financed, this number is likely to be very low.

Conclusion

In this study we demonstrated that even after long intervals of resuscitation, 30-day survival and ability to return to one's home without the need for home care services remained high. These data suggest that prolonged resuscitation is not futile.

Conflicts of interest statement

Dr. Kragholm has received funding from the Laerdal Foundation. Dr. CM Hansen has received funding from the Laerdal Foundation, Trygfonden and Helsefonden. Dr. Granger has received funding from the Medtronic Foundation. Dr. Torp-Pedersen has served as a consultant for Cardiome, Merck, Sanofi and Daiichi. The remaining authors report no conflicts of interest.

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Association of Bystander Cardiopulmonary Resuscitation and Survival According to Ambulance Response Times After Out-of-Hospital Cardiac Arrest

BACKGROUND: Bystander-initiated cardiopulmonary resuscitation (CPR) increases patient survival after out-of-hospital cardiac arrest, but it is unknown to what degree bystander CPR remains positively associated with survival with increasing time to potential defibrillation. The main objective was to examine the association of bystander CPR with survival as time to advanced treatment increases.

METHODS: We studied 7623 out-of-hospital cardiac arrest patients between 2005 and 2011, identified through the nationwide Danish Cardiac Arrest Registry. Multiple logistic regression analysis was used to examine the association between time from 911 call to emergency medical service arrival (response time) and survival according to whether bystander CPR was provided (yes or no). Reported are 30-day survival chances with 95% bootstrap confidence intervals.

RESULTS: With increasing response times, adjusted 30-day survival chances decreased for both patients with bystander CPR and those without. However, the contrast between the survival chances of patients with versus without bystander CPR increased over time: within 5 minutes, 30-day survival was 14.5% (95% confidence interval [CI]: 12.8–16.4) versus 6.3% (95% CI: 5.1–7.6), corresponding to 2.3 times higher chances of survival associated with bystander CPR; within 10 minutes, 30-day survival chances were 6.7% (95% CI: 5.4–8.1) versus 2.2% (95% CI: 1.5–3.1), corresponding to 3.0 times higher chances of 30-day survival associated with bystander CPR. The contrast in 30-day survival became statistically insignificant when response time was >13 minutes (bystander CPR vs no bystander CPR: 3.7% [95% CI: 2.2–5.4] vs 1.5% [95% CI: 0.6–2.7]), but 30-day survival was still 2.5 times higher associated with bystander CPR. Based on the model and Danish out-of-hospital cardiac arrest statistics, an additional 233 patients could potentially be saved annually if response time was reduced from 10 to 5 minutes and 119 patients if response time was reduced from 7 (the median response time in this study) to 5 minutes.

CONCLUSIONS: The absolute survival associated with bystander CPR declined rapidly with time. Yet bystander CPR while waiting for an ambulance was associated with a more than doubling of 30-day survival even in case of long ambulance response time. Decreasing ambulance response time by even a few minutes could potentially lead to many additional lives saved every year.

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Key Words: cardiac arrest ■ cardiopulmonary resuscitation ■ epidemiology ■ survival

Clinical Perspective

What Is New?

- Bystander cardiopulmonary resuscitation (CPR) is associated with increased survival after out-of-hospital cardiac arrests, but not much is known about for how long CPR remains helpful.
- Bystander CPR was associated with a 2.3-fold increase in 30-day survival at 5 minutes and a 3.0-fold increase at 10 minutes. The association fell thereafter and was statistically insignificant after 13 minutes.
- Adjusted 30-day survival chances were 14.5% with bystander CPR and 6.3% without bystander CPR at 5 minutes. The corresponding figures at 10 minutes were 6.7% and 2.2%, respectively.

What Are the Clinical Implications?

- The clinical implications are related to better knowledge of potential duration of helpfulness of bystander CPR. The associations indicate a major effect during the first 5 to 10 minutes, and thereafter the absolute survival rapidly declines with or without bystander CPR.
- The study suggests that response times to advanced help of preferably <5 and at maximum 10 minutes could be used in the planning of emergency response programs, such as ambulance distribution, organization of first responders, and distribution of automated external defibrillators.

Early recognition and treatment of out-of-hospital cardiac arrest (OHCA) are well known to increase the likelihood of successful resuscitation with good neurological outcomes[1–6] without increasing the proportion of patients who need permanent care.[7] Several time factors are important for successful resuscitation after OHCA, including early bystander intervention in the form of cardiopulmonary resuscitation (CPR), defibrillation, and prompt access to advanced postresuscitation care.[4,6,7]

Bystander CPR sustains a small but crucial blood flow to vital organs that, apart from reducing the risk of brain damage, may prolong the time window for defibrillation.[8,9] Studies have shown that the sooner defibrillation is achieved, the better the chances of survival.[10,11] The 3-Phase Time-Sensitive Model regarding resuscitation after cardiac arrest underlines a need for time-sensitive ischemia/reperfusion therapy and proposes that immediate defibrillation is useful if provided within 4 minutes of the cardiac arrest.[12] However, it remains unknown to what extent bystander CPR continues to be positively associated with survival with increasing time to CPR by the emergency medical services and potential defibrillation. Such information may be useful for future planning of ambulance distributions, potential first-responder programs, and availability of automated external defibrillators.

Using data from the Danish Cardiac Arrest Registry, we assessed for how long bystander CPR was associated with 30-day survival, with duration of ambulance response time as a proxy for time from 911 call to CPR and potential defibrillation by the emergency medical services. Our primary aim was to examine the association between bystander CPR and 30-day survival as response time increased compared with patients not receiving bystander CPR. Our secondary aim was to produce individualized predicted probability of survival models for best- and worst-case scenarios (with and without bystander CPR) according to increasing response time.

METHODS

Data Source and Definitions

All OHCA patients between 2005 and 2011 were identified from the nationwide Danish Cardiac Arrest Registry. The Danish emergency medical services and the Danish Cardiac Arrest Registry have previously been described in detail.[6,13,14] Across all regions in Denmark, the emergency medical service is a 2-tier system with dispatch of basic life support ambulances staffed with ambulance technicians or paramedics and mobile emergency care units supervised by specialized anesthesiologists or paramedics. These emergency care units are sent as rendezvous with the ambulances. Denmark does not have any structured first-responder automated external defibrillator programs (police or firefighters bringing a defibrillator). In this study, we included OHCA cases handled by the largest nationwide ambulance provider in Denmark (Falck A/S). Falck A/S provided electronic data on various time intervals for each OHCA, including information on ambulance response time. We defined the duration of response time as the time from call receipt by the emergency medical services until the ambulance arrived at the site of OHCA. This time interval served as a proxy for the time to CPR and potential defibrillation by the emergency medical services. With the unique Civil Registration number provided to all residents in Denmark, we were able to collect information on age, sex, survival status, and hospital discharge diagnoses in the national administrative registries, as described previously.[6,13,14] Information on anoxic brain damage was obtained from discharge diagnoses. From Statistics Denmark, we obtained data on individuals entering and leaving nursing homes. Nursing home data have been collected since 1994 with a validated approach to secure a high degree of completion of nursing home information.[15]

Patients were categorized into OHCA of presumed cardiac cause and presumed noncardiac cause and in accordance with the Utstein guidelines. To study a more homogenous group of patients, OHCA of presumed noncardiac cause were excluded from the final study population.[16] The definition of presumed cardiac cause of arrest included cardiac disease, unexpected collapse, or unknown diseases. Other medical disorders and all traumas regardless of other diagnoses were defined as OHCA of presumed noncardiac cause (were excluded).

To calculate the number of potential lives that could be saved annually by decreasing response time, we obtained

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statistics from the latest Danish Cardiac Arrest report,[17] which reported that 3570 OHCA not witnessed by the emergency medical services took place during the latest year, of which 65.8% received bystander CPR.

Study Population

All patients ≥18 years of age with a presumed cardiac-caused OHCA for whom resuscitation was attempted were included. Inclusion and exclusion criteria are listed in detail in Figure 1. Patients who received defibrillation by a bystander were excluded because this study examined the importance of time to CPR and potential defibrillation by the emergency medical services.

Study Outcomes

The main outcome of this study was 30-day survival. No patient was lost to follow-up, and hence we have complete data for this outcome.

Statistics

Crude 30-day survival chances were computed and reported as relative frequencies (number of 30-day survivors divided by number of patients). A direct comparison of relative 30-day survival frequencies between patients with and without bystander CPR may be confounded by patient and OHCA characteristics. Therefore, the main analysis was based on a multiple logistic regression model for 30-day survival outcome according to bystander CPR and ambulance response time and further adjusted for age, sex, location of arrest (private home vs public), witnessed status, comorbidities, and year of arrest. The model was not adjusted for first recorded cardiac rhythm being shockable or nonshockable because this is an intermediate variable between bystander CPR and 30-day survival (online-only Data Supplement Figure 1). In this model, the relationship between 30-day survival chances and ambulance response time was modeled by restricted cubic splines with prespecified knots at 5, 10, 15, and 20 minutes.[18] From the logistic regression analysis, we computed 2 personalized 30-day survival chances for each patient. With "personalized 30-day survival chances," we refer to the probability that a patient with a given combination of risk factors survives the first 30 days according to our logistic regression model. For the first personalized 30-day survival chance, we standardized the data so that all patients had received bystander CPR, but we kept the actual patient and OHCA characteristics. For the second, we standardized data so that no patient had received bystander CPR, but again we kept the actual patient and OHCA characteristics. Reported were averages of personalized 30-day survival chances according to bystander CPR and ambulance response time, and ratios between the averaged 30-day survival chances for with versus without bystander CPR according to response time (g-formula[19–21]), together with 95% bootstrap confidence intervals based on 2000 bootstrap samples.

In addition to averages, we also show personalized 30-day survival chances for specific combinations of patient and OHCA characteristics: for a person having a witnessed arrest in public, no known comorbidities and being ≤65 years of age (best-case scenario), and for a person having unwitnessed arrest in a private home, one or more comorbidities and being >65 years of age (worst-case scenario). Only for these analyses of personalized 30-day survival chances in best- and worst-case scenarios was age handled as a binary variable (working age [≤65 years] vs retirement age [>65 years]).

For the purposes of descriptive statistics for Table 1, response time was divided into 5-minute intervals of 0 to 5, 6 to 10, 11 to 15, and >15 minutes. Response time was examined as a continuous variable for all other analyses.

The level of significance was set at 5%. All statistical analyses were performed using SAS, version 9.4 (SAS Institute Inc.) and R, version 3.2.2.[22]

Ethics

This study was approved by The Danish Data Protection Agency (J. ref: 2007-58-0015/local J ref: GEH-2014–017/I-Suite: 02735). Ethical approval is not required for retrospective registry-based studies in Denmark.

RESULTS

A total of 7623 patients met the inclusion criteria during the study period and comprised the final study

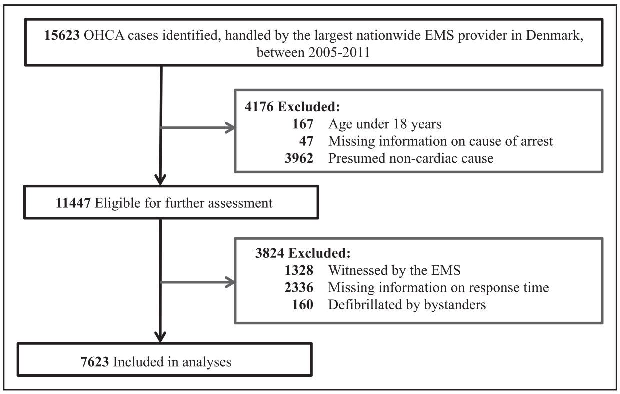

Figure 1. Flowchart showing the selection process for the study population in this study.
EMS indicates emergency medical service; and OHCA, out-of-hospital cardiac arrest.

Table 1. Patient and Arrest Characteristics According to Bystander CPR Status and Response Time Intervals

Variable	Bystander CPR				No-Bystander CPR			
	≤5 min	6–10 min	11–15 min	>15 min	≤5 min	6–10 min	11–15 min	>15 min
Count, n	848	1180	657	274	1617	1912	792	331
Median age, y (IQR)	69	67	66	67	75	74	74	72
	(59–78)	(58–77)	(58–77)	(59–76)	(65–83)	(64–81)	(65–81)	(62–81)
Male, n (%)	596	848	473	194	1057	1287	550	215
	(70.3)	(71.9)	(72.0)	(70.8)	(65.4)	(67.3)	(69.4)	(65.0)
Comorbidities, n (%)								
Ischemic heart disease (MI not included)	217	314	163	64	454	509	216	96
	(26.0)	(26.6)	(24.8)	(23.4)	(28.1)	(26.6)	(27.3)	(29.0)
Previous MI	100	134	63	32	223	228	101	45
	(11.8)	(11.4)	(10.0)	(11.7)	(13.8)	(11.9)	(12.8)	(13.6)
Heart failure	166	236	116	46	384	406	149	72
	(19.6)	(20.0)	(17.7)	(16.8)	(23.8)	(21.2)	(18.8)	(22.1)
Chronic obstructive pulmonary disease	91	140	71	34	252	314	135	41
	(10.7)	(11.9)	(10.8)	(12.4)	(15.6)	(16.4)	(17.1)	(12.4)
Cardiac arrest characteristics, n (%)								
Arrests in private homes	448	694	418	161	1178	1457	627	240
	(58.0)	(65.4)	(73.7)	(69.1)	(82.2)	(87.1)	(87.1)	(85.7)
Witnessed arrests*	548	725	408	181	730	881	375	155
	(64.7)	(61.7)	(62.5)	(66.8)	(45.2)	(46.3)	(47.4)	(47.4)
Arrest during the day	434	488	273	106	776	765	318	128
	(51.7)	(41.8)	(42.0)	(39.3)	(49.1)	(40.5)	(40.7)	(39.4)
Arrest during the evening	330	466	227	97	570	593	225	81
	(39.3)	(39.9)	(34.9)	(35.9)	(36.1)	(31.4)	(28.9)	(24.9)
Arrest during the night	75	214	150	67	234	531	237	116
	(8.9)	(18.3)	(23.1)	(24.8)	(14.8)	(28.1)	(30.4)	(35.7)
Initial shockable rhythm	393	509	244	78	410	402	104	39
	(48.2)	(44.6)	(39.2)	(31.0)	(26.6)	(22.0)	(13.6)	(12.3)
Received defibrillation by EMS	443	643	326	105	567	588	199	73
	(52.8)	(55.5)	(50.2)	(38.6)	(35.8)	(31.3)	(25.6)	(22.7)
Outcomes, n (%)								
Return of spontaneous circulation	276	319	116	31	272	213	50	22
	(33.0)	(27.2)	(17.9)	(11.3)	(17.0)	(11.3)	(6.4)	(6.7)
30-day survival	192	180	44	13	111	64	10	9
	(22.6)	(15.3)	(6.7)	(4.7)	(6.9)	(3.4)	(1.3)	(2.7)
Functional/neurological outcomes among 30-day survivors (n=623), n (%)								
Nursing home within 1 year*	4	6	0	0	6	2	1	0
	(2.1)	(3.3)	(0.0)	(0.0)	(5.4)	(3.1)	(10.0)	(0.0)
Discharged without anoxic brain damage*	177	163	38	11	97	52	8	7
	(92.2)	(90.5)	(88.4)	(84.6)	(88.2)	(81.3)	(80.0)	(77.8)

All results are n (%) unless otherwise specified.
*Non-significant *P*-value for difference across all time intervals for both bystander groups, respectively ($P>0.05$).
CPR indicates cardiopulmonary resuscitation; EMS, emergency medical services; MI, myocardial infarction; and IQR, interquartile range.

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population. The patient selection process is displayed in Figure 1.

Time-Stratified Baseline Characteristics

Table 1 depicts baseline characteristics stratified according to bystander CPR status and response time intervals. With increasing response time, patients tended to be younger and were more likely to have an OHCA during nighttime regardless of bystander CPR status. Patients who received bystander CPR were younger than those without bystander CPR and had fewer arrests during nighttime than those without bystander CPR across time intervals. Although patients were significantly less likely to receive subsequent defibrillation by the emergency medical services with increasing response time in both bystander CPR groups, patients who received bystander CPR had higher rates of subsequent defibrillation compared with patients without bystander CPR. For both bystander CPR groups, no significant statistical difference was found between rates of anoxic brain damage and discharge to nursing home across the ambulance response time groups among 30-day survivors. However, when comparing the total population of patients who survived, those who did not receive bystander CPR were more likely to be diagnosed with anoxic brain damage compared with those who received bystander CPR (12.7% vs 7.3%; P=0.02). Baseline characteristics across ambulance response time for the overall population are displayed in online-only Data Supplement Table 1.

Crude Versus Standardized 30-Day Survival Chances

Rates of 30-day survival for patients with bystander CPR for ≤5 minutes, 6 to 10 minutes, 11 to 15 minutes, and >15 minutes were 22.6% (192/848), 15.3% (180/1180), 6.7% (44/613), and 4.7% (13/274), respectively. Corresponding 30-day survival rates for patients without bystander CPR were 6.7% (111/1617), 3.4% (64/1912), 1.3% (10/792), and 2.7% (9/331), respectively. Online-only Data Supplement Figure 2 shows these crude survival chances as well as standardized survival chances according to bystander CPR and ambulance response time. The difference between the crude and standardized results indicate confounding by patient and OHCA characteristics because the magnitude of the ratio between the standardized survival chances was smaller than that of the crude survival chances.

Standardized 30-Day Survival Chances

Figure 2 displays adjusted results from the multiple logistic regression analysis standardized to a setting where all patients versus no patients had received bystander CPR according to response time. In this figure, it is observed that 30-day survival chances for both bystander CPR and no-bystander CPR decreased as response time increased: within 5 minutes, the 30-day survival chance was 14.5% (95% CI: 12.8–16.4) for bystander CPR versus 6.3% (95% CI: 5.1–7.6) for no-bystander CPR; within 10 minutes, the corresponding 30-day survival chance was 6.7% (95% CI: 5.4–8.1) versus 2.2% (95% CI: 1.5–3.1), respectively. The ratio of the standardized 30-day survival chances (g-formula) between bystander CPR and no-bystander CPR increased as response time increased: at 5 minutes, bystander CPR was associated with a 2.3 times higher 30-day survival chance after OHCA, and at 10 minutes, bystander CPR was associated with a 3.0 times higher 30-day survival chance. The association between 30-day survival and bystander CPR compared with no-bystander CPR became statistically insignificant when response time was >13 minutes (3.7% [95% CI: 2.2–5.4] for bystander CPR vs 1.5% [95% CI: 0.6–2.7] for no-bystander CPR), but bystander CPR was still associated with a 2.5 times higher 30-day survival chance.

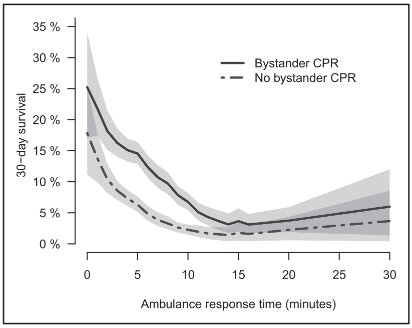

Figure 2. Standardized 30-day survival chances according to duration of response time and bystander cardiopulmonary resuscitation status.
The survival chances based on multiple logistic regression were standardized to settings where all patients versus no patients received bystander CPR according to ambulance response time. The model is adjusted for age, sex, comorbidities listed in Table 1, witnessed status, location of arrest, and year of arrest. CPR indicates cardiopulmonary resuscitation.

Online-only Data Supplement Figure 3 shows corresponding results obtained in the subpopulation of only witnessed arrests. Similar patterns were observed, although with overall higher 30-day survival chances compared with the total study population. Online-only Data Supplement Figure 4 displays corresponding results obtained in a subpopulation of only unwitnessed arrests. Overall 30-day survival chances were much lower compared with the total study population. The results were statistically insignificant, but similar patterns were observed.

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Online-only Data Supplement Figure 5 examined standardized chances of absence of new onsets of anoxic brain damage up to 30 days after the discharge from the hospital among 30-day survivors according to bystander CPR status and increasing response time. The observed results were similar, with the chances of absence of new onset of anoxic brain damage decreasing with increasing response time regardless of bystander CPR status, whereas the difference between the bystander CPR groups seemed to increase. However, the results were not statistically significant.

Additional Lives Potentially Saved Annually

Figure 3 displays the potential numbers of lives that could be saved annually in Denmark for every minute response time is shortened with the model from Figure 2 and Danish OHCA Statistics.[17] Figure 3 hence shows that by shortening response time from 10 to 5 minutes, an additional 233 lives could be saved each year. If response time was shortened from 7 (median response time in this study) to 5 minutes, an additional 119 patients could be saved each year.

Survival in Best- and Worst-Case Scenarios

Figure 4 shows predicted personalized 30-day survival chances for an individual with the best-case scenario (≤65 years of age, witnessed arrest in public, no comorbidities) and for an individual with the worst-case scenario (>65 years of age, unwitnessed arrest in a private home, one or more comorbidities) with and without bystander CPR according to response time. In the current study population, 3.6% of the population presented with the best-case scenario, whereas 11.8% of the population presented with the worst-case scenario.

In all scenarios, the personalized 30-day survival chances decreased with each increasing minute of response time, and in all scenarios, receiving bystander CPR was associated with the highest 30-day survival chances. In the best-case scenario, the 30-day survival chances within 5 minutes of response time was 54.2% if bystander CPR had been provided, whereas the chances decreased to 30.2% if no bystander CPR was provided (1.8 times higher 30-day survival chance in the bystander CPR group). By 10 minutes, the corresponding probabilities were 33.1% with bystander CPR and 12.2% with no-bystander CPR (2.7 times higher 30-day survival chances in the bystander CPR group), and by 15 minutes, the chances were 21.0% and 8.1%, respectively (2.5 times higher 30-day survival in the bystander CPR group). In the worst-case scenario, the probability of 30-day survival within 5 minutes of response time was 4.1% with bystander CPR alone and 1.5% with no bystander CPR (2.7 times higher 30-day survival in the bystander CPR group). After 10 minutes, the corresponding

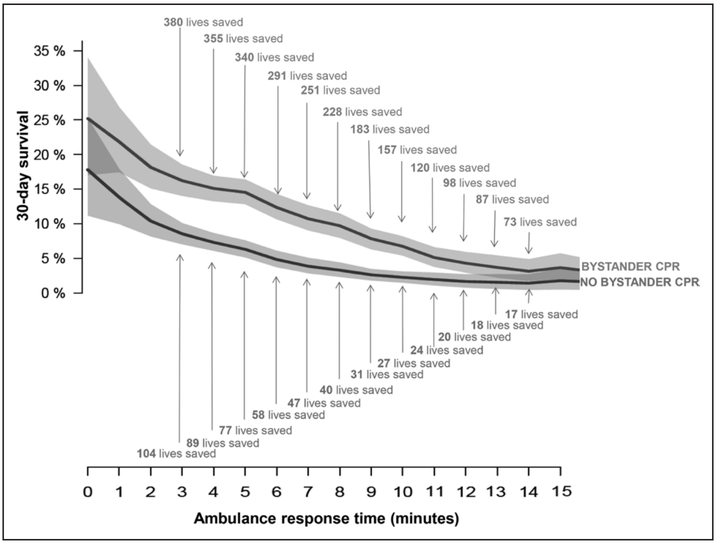

Figure 3. Potential lives saved annually if response time is deceased.
This figure is based on the adjusted logistic regression model using g-formula from Figure 2, combined with latest Danish OHCA Statistics, which reported that 3570 OHCA that were not witnessed by the emergency medical services took place during the latest year, of which 65.8% received bystander CPR. CPR indicates cardiopulmonary resuscitation; and OHCA, out-of-hospital cardiac arrest.

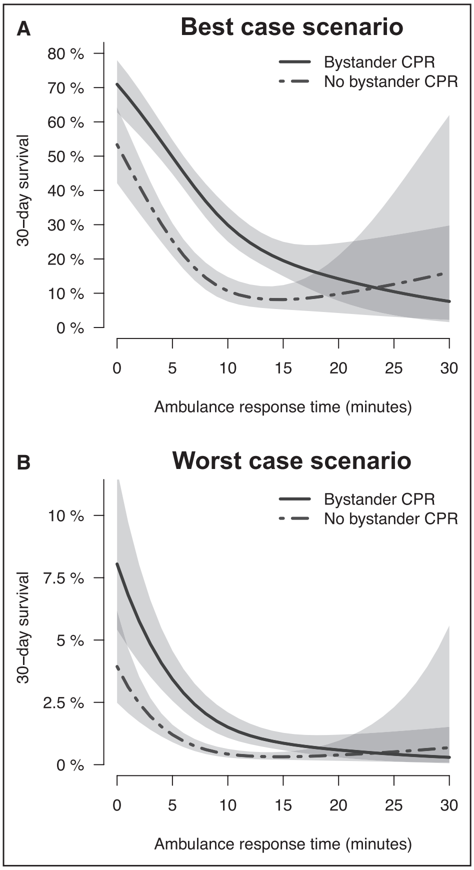

Figure 4. Thirty-day survival predictions in best- and worst-case scenarios, stratified according to bystander cardiopulmonary resuscitation status.
A, Thirty-day survival chances for an individual in a best-case scenario: having a witnessed arrest in public, no comorbidities listed in Table 1, and younger age (≤65 years).
B, Thirty-day survival chances for an individual in a worst-case scenario: having an unwitnessed arrest in a private home, one or more comorbidities listed in Table 1, and older age (>65 years). Note different Y-axis scales. CPR indicates cardiopulmonary resuscitation.

probabilities decreased to 1.7% and 0.5% (3.4 times higher 30-day survival in the bystander CPR group), and after 15 minutes, the chances were 0.9% and 0.3%, respectively (3.0 times higher 30-day survival in the bystander CPR group).

Online-only Data Supplement Figure 6 shows the best- and worst-case scenarios further stratified according to witnessed status. Similar results were obtained, although with much higher 30-day survival chances for both worst- and best-case scenarios for witnessed arrests compared with the whole population and much lower 30-day survival chances for both worst- and best-case scenarios for unwitnessed arrests. The results obtained for the unwitnessed arrests were statistically insignificant.

DISCUSSION

This study shows that bystander CPR is positively associated with 30-day survival for both short and long ambulance response times and initiation of advanced resuscitation therapy. Although the association between bystander CPR and absolute survival seemed to decline with increasing response time, the associated relative benefit in survival remained high.

Early CPR saves lives. A series of studies, including the current study, have demonstrated strong positive associations of bystander-initiated CPR and survival.[1–6] In this study, we were able to adjust for various prehospital factors while reporting predicted average 30-day survival percentages by applying causal statistics (g-formula), which showed that even when taking potential confounders into account, bystander CPR is associated with more than a 2-fold increase in 30-day survival across short and long ambulance response times. Recent years have seen a substantial focus on early CPR, and in some countries, initiatives have been implemented to increase the rate of bystander CPR.[4,6,23,24]

In our study, ambulance response time was used as a proxy for time to CPR by emergency medical services and potential defibrillation. Identifying that the absolute 30-day survival chances seem to decrease with increasing time regardless of bystander CPR status is important because it implies that, although much focus should be made on increasing the rate of bystander intervention, focus also needs to be made on identifying methods to reduce time to potential defibrillation. This goal could be achieved, for example, by decreasing ambulance response times or implementing trained first-responder programs to fully leverage the potential survival benefit of bystander CPR. Nearby trained lay or professional first responders, such as police or firefighters, would be able to provide CPR and potential defibrillation while waiting for the ambulance to arrive. This practice is in accordance with a recent study that showed higher chances of survival for patients who received bystander CPR and first responder defibrillation compared with patients who received bystander CPR and defibrillation later by the ambulance personnel.[4] In our study, we demonstrated that with increasing response time, the rates of patients who subsequently received defibrillation by the emergency medical services decreased. However, we also found that if bystander CPR was started before arrival of the emergency medical services, then the rate of patients who received subsequent defibrillation by the emergency medical service was 1.5 times higher compared with no-bystander CPR. Overall, these results are in accordance with the 3-Phase Time-Sensitive Model after cardiac arrest, which proposes that defibrillation within the first few minutes after cardiac arrest can increase survival chance >50%, but after 10 minutes, defibrillation has little incremental value.[12] It is therefore important to recognize that, apart from early CPR, prompt arrival and deployment of defibrillation is essential to increase the absolute number of OHCA survivors.

In this study, we applied Danish OHCA statistics to our model to demonstrate how many lives that could potentially be saved in Denmark for every minute ambulance response time is reduced, thereby for every minute CPR by trained rescuers and potential defibrillation arrives earlier. If they arrive even just 2 minutes earlier than the median of 7 minutes found in our study, an additional 119 patients could be saved yearly in Denmark. However, increasing ambulance density to reduce time to potential defibrillation can be a costly affair. Dispatch of nearby trained lay responders or professional first responders (police or firefighters) to assist with CPR and, most important, potential defibrillation could represent a good alternative to increase survival rates after OHCA, as other studies suggest.[4,25] A randomized controlled study from Sweden has recently examined the effect of CPR-trained mobile-dispatched laypersons.[26] The trained laypersons were dispatched if they were within 500 meters of the arrest. The median ambulance response time in their study was 8 minutes, and in 23% of the cases, the CPR-trained layperson arrived before the emergency medical services, and bystander CPR rates increased from 47.8% to 61.6% in the same time period. A similar randomized controlled study with dispatch of nearby responders with automated external defibrillators to assist with defibrillation in addition to CPR alone is warranted.

Overall, our results suggest that dispatch of nearby trained lay or professional first responders to assist with potential defibrillation apart from CPR while waiting for the ambulance is likely to save more lives every year.

When examining best- and worst-case scenarios, large variations in predicted survival percentages were observed for each of these cases as expected, with survival probability being much higher in best-case scenarios. This finding reflects how the selected prehospital factors are closely related to survival and are therefore somewhat able to predict whether the cardiac arrest patient achieves long-term survival. Notably, in both scenarios, we found that if bystander CPR is received, the 30-day survival probability is markedly increased compared with no-bystander CPR, indicating the robustness of this single factor. However, when investigating the absolute survival probability percentages between the two scenarios, absolute chances of survival in especially the worst-case scenario was particularly dependent on time regardless of bystander CPR status—if potential defibrillation is not established relatively early, then the chances of survival seem to be minimal. These results also imply the necessity of decreasing time to potential defibrillation.

Limitations

The main limitation of this study is that it is observational in nature. Hence, our data provide associations on the possible positive effect of bystander intervention on 30-day survival across several response time intervals. Also, we did not have data on several important factors that could affect survival and ambulance response time simultaneously: one important factor missing was the time for the actual collapse and duration of bystander CPR, as the current ambulance response time may not fully portray the duration of actual CPR provided by the bystander, or the duration of the cardiac arrest, before ambulance arrival. To investigate this issue, we conducted sensitivity analyses examining a subpopulation of witnessed arrests only. In this group of patients, the response time is likely to be more closely related to duration of no-flow time (duration of the cardiac arrest) and CPR (a bystander may be more likely to start CPR immediately if he or she witnessed the arrest). Although survival chances were higher across durations of ambulance response times in this subpopulation, these results did not differ from main analyses. However, it is important to note that it cannot be ruled out that bystanders may have started resuscitation before calling the emergency medical services. Other factors we did not have information on was the quality of the CPR given by the bystanders, whether they were trained in CPR and whether the CPR was telephone-assisted. Furthermore, in Denmark, high-rise buildings are rare, and we did not have any data regarding "vertical response time." Hence, our results may not be easily generalized to towns with many high-rise buildings with associated longer ambulance response times. Finally, because <1.8% of the study population had response times >20 minutes, our results have wide confidence intervals toward the long response times; the fact that the estimates increase slightly may be considered an artifact that is due to the sparse data situation in this region of the response

CONCLUSION

In this study, we demonstrated a positive association between bystander CPR and 30-day survival across ambulance response times. As ambulance response time increased, the absolute 30-day survival decreased regardless of bystander CPR status. However, the relative difference in survival was more than twice as high among patients who received bystander CPR compared

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with those who did not across all ambulance response times. Decreasing time to CPR by trained rescuers and potential defibrillation by even a few minutes could potentially lead to many additional lives saved every year. Strategies to decrease ambulance response time and implement dispatch of nearby trained lay or professional first responders for quick intervention with CPR and, importantly, potential defibrillation are likely to increase survival after OHCA.

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FOOTNOTES

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Circulation

Association of Bystander Cardiopulmonary Resuscitation and Survival According to Ambulance Response Times After Out-of-Hospital Cardiac Arrest

Shahzleen Rajan, Mads Wissenberg, Fredrik Folke, Steen Møller Hansen, Thomas A. Gerds, Kristian Kragholm, Carolina Malta Hansen, Lena Karlsson, Freddy K. Lippert, Lars Køber, Gunnar H. Gislason and Christian Torp-Pedersen

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Clinical paper

Incidence and survival outcome according to heart rhythm during resuscitation attempt in out-of-hospital cardiac arrest patients with presumed cardiac etiology☆

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ABSTRACT

Background: Knowledge about heart rhythm conversion from non-shockable to shockable rhythm during resuscitation attempt after out-of-hospital cardiac arrest (OHCA) and following chance of survival is limited and inconsistent.

Methods: We studied 13,860 patients with presumed cardiac-caused OHCA not witnessed by the emergency medical services from the Danish Cardiac Arrest Register (2005–2012). Patients were stratified according to rhythm: shockable, converted shockable (based on receipt of subsequent defibrillation) and sustained non-shockable rhythm. Multiple logistic regression was used to identify predictors of rhythm conversion and to compute 30-day survival chances.

Results: Twenty-five percent of patients who received pre-hospital defibrillation by ambulance personnel were initially found in non-shockable rhythms. Younger age, males, witnessed arrest, shorter response time, and heart disease were significantly associated with conversion to shockable rhythm, while psychiatric- and chronic obstructive pulmonary disease were significantly associated with sustained non-shockable rhythm. Compared to sustained non-shockable rhythms, converted shockable rhythms and initial shockable rhythms were significantly associated with increased 30-day survival (Adjusted odds ratio (OR) 2.6, 95% confidence interval (CI): 1.8–3.8; and OR 16.4, 95% CI 12.7–21.2, respectively). From 2005 to 2012, 30-day survival chances increased significantly for all three groups: shockable rhythms, from 16.3% (CI: 14.2%–18.7%) to 35.7% (CI: 32.5%–38.9%); converted rhythms, from 2.1% (CI: 1.6%–2.9%) to 5.8% (CI: 4.4%–7.6%); and sustained non-shockable rhythms, from 0.6% (CI: 0.5%–0.8%) to 1.8% (CI: 1.4%–2.2%).

Conclusion: Converting to shockable rhythm during resuscitation attempt was common and associated with nearly a three-fold higher odds of 30-day survival compared to sustained non-shockable rhythms.

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Introduction

Successful resuscitation following out-of-hospital cardiac arrests (OHCA) highly depends on the presenting heart rhythm, with shockable rhythms (ventricular fibrillation and pulseless ventricular tachycardia) linked to higher survival rates than initial non-shockable heart rhythms (pulseless electrical activity and asystole).[1–3]

During the past two decades, the incidence of OHCA patients presenting with shockable rhythms has decreased in several countries, and due to the link between non-shockable rhythms and poor success rates of resuscitation, the falling incidence of shockable rhythms challenges efforts to improve survival outcome after OHCA.[4–6] Yet, in some cases, first-recorded non-shockable rhythms can convert into shockable rhythms during the course of cardiopulmonary resuscitation (CPR) and advanced treatment. While previous studies indicate that converting to a shockable rhythm is linked to a better outcome than remaining in a non-shockable rhythm, little is known about which pre-hospital factors, including patient demographics (age, sex and comorbidities), that are associated with conversion to a shockable rhythm.[7–11] Furthermore, while it is well known that overall survival rates after OHCA has increased over time in several countries,[1,12,13] the temporal trend in survival for converted shockable rhythms is unknown.

Using data from the nationwide Danish Cardiac Arrest Register, we described baseline characteristics and survival associated to: (1) initial shockable rhythm, (2) conversion from initial non-shockable to shockable rhythm and (3) sustained non-shockable rhythm, and identified pre-hospital factors associated with conversion of rhythm. We also developed predictive models (best–worst case scenarios) highlighting situations giving rise to the largest and lowest survival rate for each rhythm.

Methods

Data source and definitions

All OHCA cases were identified from the nationwide Danish Cardiac Arrest Register (2005–2012). The register and the Danish emergency medical services (EMS) system and linkage to other nationwide registers has been described in detail elsewhere.[1] There are no structured first-responder automated external defibrillator programs in Denmark (police or firefighters bringing a defibrillator).

In order to examine the comorbidities of the patients, discharge diagnoses up to ten years prior to OHCA were examined in accordance with previously described methods.[14] Included cardiac comorbidities were ischemic heart disease, myocardial infarction, and heart failure. Included non-cardiac comorbidities were chronic obstructive pulmonary disease, diabetes, malignancy, renal disease and psychiatric disease. All diagnoses have been coded using the International Classification system (ICD). Before 1994, the 8th revision is applied (ICD-8), and from 1994 onwards the 10th revision is applied (ICD-10) (Supplemental Table 1).

Study population

All OHCA patients of presumed cardiac cause and ≥18 years at the time of OHCA were identified.[1] Patients defibrillated by a bystander were excluded from the study population. The first registered rhythm was defined as the presenting rhythm when the EMS arrived and connected a defibrillator. The defibrillator determined whether the rhythm was classified as shockable or not. The study population was stratified into three groups according to rhythm analysis: (1) first-recorded shockable rhythm, (2) non-shockable rhythm converted to shockable during resuscitation efforts by the EMS, and (3) sustained non-shockable rhythm. The second group, "converted to shockable rhythm", was defined as patients who initially had non-shockable rhythm at the time of EMS arrival but who subsequently received pre-hospital defibrillation from the EMS.

Study endpoints/outcomes

The primary outcome measure was 30-day survival. Secondary outcome measure was return of spontaneous circulation (ROSC) (pulse or other signs of restored circulation) at hospital arrival.

Statistics

Baseline characteristics were summarized as counts and percentages for categorical variables and as medians and interquartile range for continuous variables. In order to identify patient- and cardiac arrest characteristics associated with converting to a shockable rhythm, we analysed the subset of patients that had first-recorded non-shockable rhythms. We used multiple logistic regression with rhythm as outcome (converted shockable vs. sustained non-shockable) to investigate the following patient characteristics: age, sex, the selected comorbidities, location of arrest, witnessed status, bystander CPR, and time from recognition of arrest to rhythm analysis by the EMS. Reported were odds ratios with corresponding 95% confidence intervals. Multiple logistic regression was also performed in all patients to examine the association between heart rhythm and 30-day survival. This model was adjusted for age, sex, comorbidities, location of arrest, witnessed status, bystander CPR, time from recognition of arrest to rhythm analysis by the EMS, and year of arrest (Supplemental Fig. 1). Missing data was handled using the multiple imputations by chained equation method. Hundred imputed datasets were constructed using all covariates in Table 1, and estimates from observed and imputed datasets were compared. Temporal 30-day survival chances were reported as crude relative frequencies as well as predictions from a logistic regression model where the relationship between 30-day survival chances and calendar year was modelled by restricted cubic splines with pre-specified knots at years 2007, 2009 and 2011.[15] The analyses were repeated with ROSC as outcome instead of 30-day survival. Linear calendar time trends in data were examined by using the Cochran Armitage Trend Test. The level of statistical significance was set at 5%.

To illustrate the variation in 30-day survival for specific individuals in subgroups defined by rhythm we also report 30-day survival chances from fully adjusted logistic regression for selected specific combinations of patient- and OHCA characteristics: for a person without known comorbidities, of working age ≤65 years, with a non-residential witnessed arrest and who had received bystander cardiopulmonary resuscitation (best-case scenario), and for a person with one or more comorbidities, age >65 years, a residential unwitnessed arrest and who had not received bystander cardiopulmonary resuscitation (worst-case scenario). These results are presented as predicted 30-day survival percentages with 95% confidence intervals.

All statistical analyses were performed using SAS, version 9.4 (SAS Institute Inc., Cary, NC, USA) and R, version 3.2.3.[16]

Ethics

This study was approved by The Danish Data Protection Agency (J. ref: 2007-58-0015/local J ref: GEH-2014-017/I-Suite: 02735). Ethical approval is not required for retrospective register-based studies in Denmark.

Table 1
Baseline characteristics and crude outcome rates of OHCA patients according to presenting heart rhythm after EMS arrival, 2005–2012.

	Shockable rhythm	Converted from non-shockable to shockable rhythm	Sustained non-shockable rhythm	p-Value	Missing data
Count, no.	4181	1395	8284	–	–
Median age [IQR]	68.0 [58.0, 77.0]	71.0 [62.0, 79.0]	74.0 [65.0, 82.0]	<0.001	–
Male, no. (%)	3298 (78.9)	997 (71.5)	5121 (61.8)	<0.001	–
Out-of-hospital cardiac arrest characteristics, no. (%)					
Arrest outside private homes	1473 (38.8)	276 (21.2)	1315 (17.4)	<0.001	1199
Witnessed arrests	3134 (76.8)	751 (54.0)	3409 (41.3)	<0.001	137
Bystander provided CPR	2435 (59.6)	567 (40.8)	2936 (35.5)	<0.001	115
Median time interval[a], min [IQR]	10.0 [6.0, 14.0]	12.0 [8.0, 18.0]	13.0 [8.0, 24.0]	<0.001	1688
Comorbidity, no. (%)					
Ischemic heart disease (MI not included)	1270 (30.4)	397 (28.5)	1949 (23.5)	<0.001	–
Previous myocardial infarction	553 (13.2)	200 (14.3)	904 (10.9)	<0.001	–
Heart failure	920 (22.0)	325 (23.3)	1694 (20.4)	0.018	–
Chronic obstructive pulmonary disease	360 (8.6)	194 (13.9)	1512 (18.3)	<0.001	–
Diabetes	618 (14.8)	275 (19.7)	1464 (17.7)	<0.001	–
Malignancy	401 (9.6)	174 (12.5)	1091 (13.2)	<0.001	–
Renal disease	179 (4.3)	89 (6.4)	465 (5.6)	0.001	–
Psychiatric disease	373 (8.9)	193 (13.8)	1580 (19.1)	<0.001	–
Survival, no. (%)					
ROSC at hospital arrival	1546 (40.4)	200 (14.5)	683 (8.4)	<0.001	
30-day survival	1135 (27.1)	58 (4.2)	102 (1.2)	<0.001	–

All results are n (%) unless otherwise specified. EMS = emergency medical services. CPR = cardiopulmonary resuscitation. MI = myocardial infarction. ROSC = return of spontaneous circulation. IQR = interquartile range. Min = minutes.
[a] Estimated time from recognition of cardiac arrest to the first rhythm analysis by the EMS.

Results

During the study period, a total of 13,860 patients met the inclusion criteria and comprised the final study population. The patient selection process is displayed in detail in Fig. 1.

Of the final study population, 30.2% of the patients presented with a first-recorded shockable rhythm, 10.0% converted to a shockable rhythm from an EMS-recorded non-shockable rhythm during the pre-hospital resuscitation attempt, and 59.8% of the patients remained in a non-shockable rhythm. Thus, one-fourth of all patients who were defibrillated by the EMS started with a non-shockable rhythm at the time of EMS arrival. Supplemental Fig. 2 shows an overall decreasing trend in the prevalence of first-recorded shockable rhythms over the years (p-value for trend: 0.02).

Rhythm stratified baseline characteristics and conversion to shockable rhythm

Table 1 depicts baseline characteristics according to the rhythm groups. Patients presenting with shockable rhythms were younger, had higher rates of arrests outside of private homes, witnessed arrests, and bystander-initiated CPR, and had shorter median time interval from recognition of arrest to first rhythm analysis by the EMS. Contrary, patients with sustained non-shockable rhythms were older, had higher rates of residential arrests and non-witnessed arrests, lower rates of bystander-initiated CPR, and longer median time interval from recognition of arrest to first rhythm analysis by the EMS. Patients with converted shockable rhythms had rates in-between these two groups. In relation to comorbidity, patients who presented with shockable rhythms had higher rates of cardiac-related comorbidities (ischemic heart disease, myocardial infarction and heart failure), while patients with sustained non-shockable rhythms had higher rates of non-cardiac related comorbidities (chronic obstructive pulmonary disease, diabetes, malignancy, renal disease and psychiatric disease). Patients with converted shockable rhythms tended to have rates in-between these two groups.

Fig. 2 portrays patient- and pre-hospital related factors associated with converting from a first-recorded non-shockable rhythm to a shockable rhythm. Factors significantly associated with conversion were age ≤65 years, male sex, witnessed arrest, time interval between arrest recognition/emergency medical call and EMS arrival below 15 min, history of ischemic heart disease and previous myocardial infarction. History of chronic obstructive pulmonary disease and psychiatric disease was significantly associated with sustained non-shockable rhythm. Estimates from imputed datasets were similar (Supplemental Tables 2 and 3).

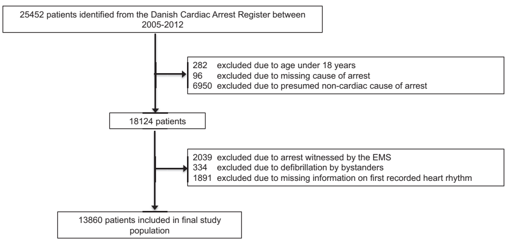

Fig. 1. Study selection process.
The figure highlights the study selection process. EMS = Emergency medical services.

Overall 30-day survival chances

During the study period 2005–2012, overall relative frequencies of ROSC patients with shockable rhythms, converted shockable rhythms and sustained non-shockable rhythms were 40.4%, 14.5% and 8.4%, respectively. Corresponding relative frequencies of 30-day survival were 27.1%, 4.2% and 2.1%, respectively. In fully adjusted models, converted shockable rhythm was significantly associated with 2.6 times higher odds of 30-day survival (CI: 1.8–3.8) compared to sustained non-shockable rhythm, while initial shockable rhythm was significantly associated with 16.4

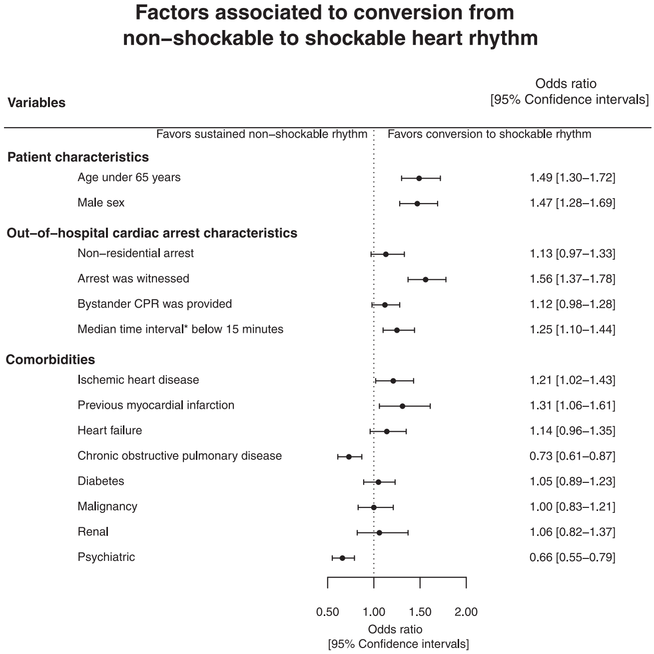

Fig. 2. Factors associated to conversion from non-shockable to shockable heart rhythm.
Patient- and pre-hospital related factors associated with converting from a first-recorded non-shockable rhythm when emergency medical services arrived, to a subsequent shockable rhythm.
*Time from recognition of arrest to first rhythm analysis by the EMS.

times higher odds of 30-day survival compared to sustained non-shockable rhythm (CI: 12.7–21.2).

Temporal ROSC and 30-day survival

Supplemental Fig. 3 portrays the relative frequencies of ROSC and 30-day survival in the study population according to calendar year between 2005 and 2012.

Fig. 3 portrays predictions of ROSC and 30-day survival chances according to calendar year using logistic regression modeled with restricted cubic splines. In these models, ROSC chances increased from 24.0% (CI: 21.8%–26.5%) to 53.1% (CI: 50.2%–55.9%) between 2005 to 2012 for patients with shockable rhythms, from 6.9% (CI: 5.7%–8.2%) to 20.8% (18.1%–23.8%) for patients with converted rhythms, and from 3.8% (CI: 3.4%–4.4%) to 15.7% (CI: 13.8%–17.8%) for patients with sustained non-shockable rhythms. Correspondingly, 30-day survival chances for patients in all three groups increased over the years: from 16.3% (CI: 14.2%–18.7%) in 2005 to 35.7% (CI: 32.5%–38.9%) in 2012 for patients with shockable rhythm; from 2.1% (CI: 1.6%–2.9%) in 2005 to 5.8% (CI: 4.4%–7.6%) in 2012 for patients with converted rhythm; and from 0.6% (CI: 0.5%–0.8%) in 2005 to 1.8% (CI: 1.4%–2.2%) in 2012 for patients with sustained non-shockable rhythm.

During the latest year (2012), the ratio between pre-hospital ROSC and 30-day survival was 1.5 for patients with shockable rhythm, 3.5 for patients with converted rhythm, and 8.7 for patients with sustained non-shockable rhythms.

Individualized 30-day survival in best- and worst-case scenarios stratified by rhythm

Fig. 4 portrays predicted personalized 30-day survival chances for an OHCA patient in a best-case scenario (age ≤65 years, non-residential witnessed arrest, no comorbidities, bystander CPR, and a median time between recognition of arrest and EMS arrival below 15 min) and for an OHCA patient with worst-case scenario (>65 years, residential unwitnessed arrest, one or more comorbidities, no bystander CPR and a median time between arrest recognition and EMS arrival 15 min or above), stratified according to the three rhythm groups. In this current study population, 2.0% presented with a best-case scenario, and 5.0% presented with a worst-case scenario. The maximum 30-day survival chance in the best-case scenario was 60.2% for shockable rhythms, 20.1% for converted to shockable rhythms, and 8.7% for patients remaining in non-shockable rhythms. The maximum 30-day survival chance in the worst-case scenario was 2.8% for shockable rhythms, 0.5% for converted to shockable rhythms, and 0.2% for patients remaining in non-shockable rhythms.

Discussion

In this nationwide study, both crude and adjusted 30-day survival rates were significantly higher for patients with converted shockable rhythms than patients with sustained non-shockable rhythms. Twenty-five percent of all patients who received pre-hospital defibrillation by the EMS were initially found with a non-shockable rhythm at the time of EMS arrival. Younger age, male

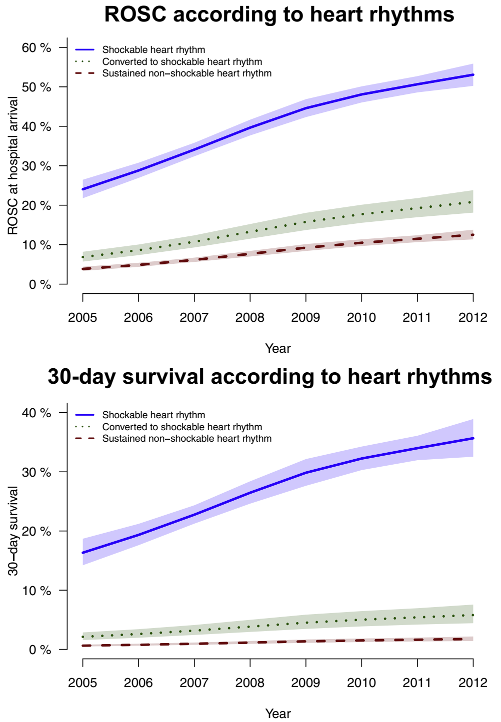

Fig. 3. Predicted ROSC and 30-day survival chances according to rhythm and calendar year.
Top figure portrays the predicted yearly development in pre-hospital ROSC chances and bottom figure portrays the predicted yearly development in 30-day survival chances of the three rhythms. The figures are based on logistic regression models using restricted cubic splines.
ROSC = return of spontaneous circulation.

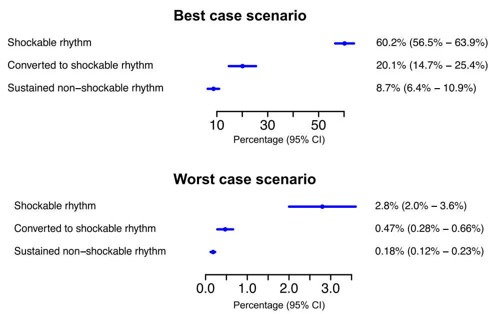

Fig. 4. Thirty-day survival chances in best- and worst case scenarios stratified by heart rhythm.
The upper panel portrays 30-day survival chances for an individual in a best-case scenario (age ≤65 years, non-residential witnessed arrest, no comorbidities, bystander CPR, median time interval below 15 min). The lower panel portrays 30-day survival chances for an individual in a worst-case scenario (>65 years, residential unwitnessed arrest, one or more comorbidities, no bystander CPR and median time interval above 15 min). In this current study population, 2.0% presented with a best-case scenario, and 5.0% presented with a worst-case scenario. Note different x-axis for the two figures.

sex, a witnessed arrest, shorter duration between arrest recognition of rhythm analysis by EMS, and a history of cardiovascular diseases were associated with conversion to a shockable rhythm, while a history of non-cardiovascular diseases was associated with sustained non-shockable rhythms.

Only a few other studies have compared patients with converted rhythms and patients with sustained non-shockable rhythms. While most studies found similar results with higher survival rates for patients who subsequently received defibrillation in the prehospital setting,[7–11] two studies found worse outcome/no difference associated with defibrillation.[15,16] One potential explanation for the differences in the previously reported studies could be found in the population of interest. While some of these studies included all-cause OHCA, some only included OHCA of presumed cardiac cause.[7–11,15,16] This indicates that underlying etiology may also have an impact on the resuscitation outcome in patients with converted rhythms. In this study we examined a population of OHCA patients of presumed cardiac cause, and found that patients who converted to a shockable rhythm were placed somewhat in-between patients who had a first-recorded shockable rhythm and patients with a sustained non-shockable rhythm in regards to pre-hospital characteristics. These pre-hospital characteristics (witnessed arrest, location outside private homes, and bystander CPR) have previously been linked to survival[17] and are therefore likely to account for some of the survival differences observed between the three groups in this study, and in previous studies. In this study, the presence of these factors also seemed to increase the possibility of rhythm conversion to a shockable rhythm from a first-recorded non-shockable rhythm. Apart from factors directly linked to the cardiac arrest, it has also been discussed that patient history of comorbidities may impact the chance of converting to a shockable rhythm as well as survival differences between different patient groups.[18] Yet, no previous study has examined differences in comorbidities in patients with shockable, converted shockable, and sustained non-shockable rhythms as a potential explanation of the differences in outcomes. We found that patients with first-recorded shockable rhythms and converted shockable rhythms were more likely to have a history of cardiovascular diseases, while patients with non-shockable rhythms were more likely to have a history of chronic obstructive pulmonary disease and psychiatric diseases. Chronic obstructive pulmonary disease has previously been linked to non-shockable rhythm and adverse survival outcomes following OHCA.[19] In this current study, cardiovascular disease seemed to serve as a predictor of conversion to shockable rhythm—a finding that could be driven by the close association between shockable rhythms and ischemic heart disease.[20]

Nevertheless, when adjusting for these important pre-hospital factors and comorbidities that may explain some of the observed differences in survival, the odds of survival of patients converting to shockable rhythm was still almost three times higher compared to patients with sustained non-shockable rhythms, while the survival of patients with first-recorded shockable rhythms had 16.4 times higher odds of surviving than patients with sustained non-shockable rhythms. In several countries survival rates after OHCA have increased, but the temporal trend in survival for converted shockable rhythms is unknown.[1,12,13] When examining temporal predictions in pre-hospital ROSC upon hospital arrival, we observed an increase for all three rhythm groups during the study period from 2005 to 2012, and when examining the 30-day survival during the same period, we observed that the relative increase in 30-day survival was lower, and also with much lower absolute 30-day survival chances compared to the chances of having a pre-hospital ROSC. While the ratio between ROSC and 30-day survival was 1.5 for patients with shockable rhythm, the corresponding ratios for patients with converted shockable rhythms and for patients with sustained non-shockable rhythm were 3.5 and 8.7, respectively. These results imply that patients with first-recorded non-shockable rhythms were a very vulnerable population even after having achieved a pre-hospital ROSC, as these patients may have had a high degree of brain damage and may have died relatively early after hospital arrival—especially those patients who did not subsequently convert to shockable rhythms. It can also be speculated that the increase in rates of pre-hospital ROSC reflects improvements made in the pre-hospital setting, while 30-day survival reflects in-hospital treatments. In-hospital treatment could potentially be more conservative for these more vulnerable patients, as physicians may evaluate that long-term prognosis for these patients could be poor. Abstention by physicians would be difficult to register, but may be a crucial factor contributing to poorer prognosis among patients initially found in non-shockable rhythms, but who achieved ROSC.

In the predicted survival models examining best-case scenarios and worst-case scenarios, we observed large variations in survival with reasonably high 30-day survival even for patients with sustained non-shockable rhythm in best-case scenarios, to 30-day survival rates below 1% for both those converting and those remaining in non-shockable rhythms in worst-case scenarios. As about 2% and 5% of the study population presented with these extremes, it can be assumed that the majority of patients will have survival rates somewhere in between. Even though the prognosis for the patients who are initially found in non-shockable rhythms may not be as positive as those patients with first-recorded shockable rhythms, the former patients can be successfully resuscitated, especially if the circumstances are favorable, as observed in this study. Based on the study results, we suggest that every patient initially found in non-shockable rhythms is given the benefit of the doubt and aggressive resuscitation is attempted until reasonable advanced life support treatment options have been exhausted, as some of these patients will convert to a shockable rhythm following resuscitation attempt with a better chance of surviving.

This study has some limitations. The main limitation of this study is its observational nature, which means that the relations between input and output variables are associations, and not causal. Secondly, the heart rhythm in this study was evaluated as the first rhythm recorded by the EMS arrival, which could inevitably be different from the very first initial rhythm after the collapse. Furthermore, conversion from a non-shockable to a shockable rhythm was confirmed indirectly by the event of defibrillation by the EMS, and could potentially lead to misclassification of the heart rhythm. However, during the study period only patients with a shockable rhythm were defibrillated, and a defibrillator determined whether the rhythm was classified as shockable or not. Defibrillation is therefore likely to be a reliable proxy of conversion.

Conclusion

Patients converting from a first-recorded non-shockable heart rhythm to a shockable heart rhythm had close to three times higher odds of achieving 30-day survival compared to patients remaining in non-shockable rhythms, even after adjusting for various patient characteristics and pre-hospital factors. ROSC and 30-day survival increased for all three rhythms during the study population. A quarter of all patients defibrillated in the pre-hospital setting were initially found in non-shockable rhythms. Younger age, male sex, a witnessed arrest, shorter duration between arrest recognition of rhythm analysis by EMS, and cardiovascular comorbidities tended to be associated with conversion to a shockable rhythm, while non-cardiovascular comorbidities were associated with sustained non-shockable rhythms.

Conflict of interest statement

Dr. Hansen is supported by The Danish Heart Foundation, and by an unrestricted grant from The Danish foundation TrygFonden. Dr. CM Hansen has received funding from the Laerdal Foundation, Trygfonden and Helsefonden. Dr. Kragholm has received funding from the Laerdal Foundation. Dr. Karlsson is supported by an unrestricted grant from The Danish foundation TrygFonden. Dr. Køber has received payment for speaking at a symposium arranged by Servier. Dr. Gislason is supported by an unrestricted clinical research scholarship from The Novo Nordisk Foundation. Dr. Torp-Pedersen has been a consultant for Cardiome, Merck, Sanofi and Daiichi.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.resuscitation.2016.12.021.

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