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DOI (link to publication from Publisher):
10.5278/vbn.phd.med.00038

Publication date:
2015

Document Version
Publisher's PDF, also known as Version of record

Link to publication from Aalborg University

Citation for published version (APA):
Wissenberg Jørgensen, M. (2015). Out-of-Hospital Cardiac Arrest in Denmark: Bystander Intervention and Patient Survival Epidemiological Studies . Aalborg Universitetsforlag. (Ph.d.-serien for Det Sundhedsvidenskabelige Fakultet, Aalborg Universitet). DOI: 10.5278/vbn.phd.med.00038

OUT-OF-HOSPITAL CARDIAC ARREST IN DENMARK: BYSTANDER INTERVENTION AND PATIENT SURVIVAL

EPIDEMIOLOGICAL STUDIES

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MADS WISSENBERG JØRGENSEN

DISSERTATION SUBMITTED 2015

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PhD Series: Faculty of Medicine, Aalborg University

ISSN (online): 2246-1302
ISBN (online): 978-87-7112-346-3

Published by:
Aalborg University Press
Skjernvej 4A, 2nd floor
DK – 9220 Aalborg Ø
Phone: +45 99407140
aauf@forlag.aau.dk
forlag.aau.dk

Printed in Denmark by Rosendahls, 2015

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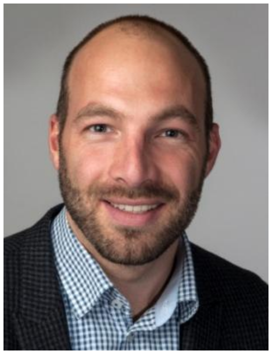
CURRICULUM VITAE



My experience with research started as a medical student. Driven by my interest in cardiovascular physiology, I contacted Professor Niels Henry Secher who is head of the Cardiovascular Research Laboratory at Rigshospitalet - Copenhagen University Hospital. He gave me a good opportunity to take part in a number of studies, one of which had to do with endurance training and how it affects brain metabolism; this became the research basis of my thesis. However, while doing clinical work, I very soon realized that the medical condition of cardiac arrest appealed to me. The combination of various aspects of cardiac arrest treatment, teamwork, and its huge impact on a patient's life, immediately caught my attention. This led me to contact Professor Christian Torp-Pedersen and Freddy Lippert, who are both involved in cardiac arrest research and the Danish Cardiac Arrest Registry. Ever since my first meeting with them, my main goal has been clear: to functionalize the Danish Cardiac Arrest Registry and do nationwide cardiac arrest studies using these unique data in combination with other nationwide registries in Denmark. So far, this goal has been achieved fairly well. The first cardiac arrest study using these data was published in the high-impact journal the *Journal of the American Medical Association* (JAMA), and resulted in much attention from both national and international media. Since this study, multiple studies have emerged using these data, and currently I am involved in more than 20 studies concerning cardiac arrest, resuscitation, and sudden cardiac death. The scientific work has further expanded to several international collaborations in the United States and Europe, including the European Registry of Cardiac Arrest (EuReCa), where I am currently positioned as the national coordinator for the Danish cardiac arrest data. From a national perspective, I am one of the lead investigators on a yearly submitted scientific national report from the Danish Cardiac Arrest Registry. These national reports have resulted in much attention on the importance of resuscitative efforts by bystanders in case of a cardiac arrest. Finally, I am involved in several registry-based studies on other medical topics.

PAPERS

This thesis is based on research carried out during my time as a PhD student at the Department of Cardiology, Gentofte Hospital, affiliated with The Institute of Health, Science and Technology, Aalborg University. The thesis includes three original papers (Appendices, Paper I, page 77; Paper II, page 96; and Paper III, page 118):

Paper I.

Wissenberg M, Lippert FK, Folke F, Weeke P, Hansen CM, Christensen EF, Jans H, Hansen PA, Lang-Jensen T, Bjerring Olesen J, Lindhardsen J, Fosbol EL, Nielsen SL, Gislason GH, Kober L, Torp-Pedersen C. Association of national initiatives to improve cardiac arrest management with rates of bystander intervention and patient survival after out-of-hospital cardiac arrest. *JAMA. 2013;310(13):1377–84.*

Paper II.

Wissenberg M, Hansen CM, Folke F, Lippert FK, Weeke P, Karlsson L, Rajan S, Søndergaard KB, Kragholm K, Christensen EF, Nielsen SL, Kober L, Gislason GH, Torp-Pedersen C. Survival after out-of-hospital cardiac arrest in relation to sex: a nationwide registry-based study. *Resuscitation. 2014;85(9):1212-8.*

Paper III.

Wissenberg M, Folke F, Hansen CM, Lippert FK, Kragholm K, Risgaard B, Rajan S, Karlsson L, Søndergaard KB, Hansen SM, Mortensen RN, Weeke P, Christensen EF, Nielsen SL, Gislason GH, Kober L, Torp-Pedersen C. Survival after out-of-hospital cardiac arrest in relation to age and early identification of patients with minimal chance of long-term survival. *Circulation. 2015;131(18):1536-45.*

SUMMARY

Multiple national initiatives have been launched in Denmark throughout the past decade to improve the management of out-of-hospital cardiac arrest (OHCA). One strategy has been to educate and train a significant proportion of the population in cardiopulmonary resuscitation (CPR), in order to increase and improve bystander resuscitation attempts. Another strategy has been to strengthen the emergency medical service system alongside updating clinical guidelines, in order to improve advanced care. The aim of the present thesis was to investigate: (1) temporal trends in resuscitative efforts by bystanders and patient survival after OHCA, following the national initiatives implemented to improve cardiac arrest management; (2) whether there were sex- and age-related differences in patient characteristics and survival during the past decade; and (3) whether it was possible at an early stage, and irrespective of patient age, to identify patients with a minimal chance of long-term survival.

A total of 21,480 patients with OHCA of a presumed cardiac cause for whom resuscitation was attempted were identified in the nationwide Danish Cardiac Arrest Registry between June 2001 and December 2011. Cardiac arrest data were subsequently linked to data from the national administrative registries using the unique and permanent Civil Registration Number that allows individual linkage of information between registries.

In Denmark, between 2001 and 2010, patient survival increased following OHCA; this increase in patient survival was associated with a concomitant increase in bystander CPR. Both measures more than doubled, and the increase was consistent in absolute numbers. In percentages, from 2001 to 2010, bystander CPR increased from 21.1% to 44.9%; survival upon hospital arrival increased from 7.9% to 21.8%; and 30-day survival increased from 3.5% to 10.8% (all $p<0.001$). The temporal increase in 30-day survival was less marked in female patients (females from 4.8% to 6.7%, versus males from 3.0% to 12.9%, in 2001 and 2010, respectively), due to female patients being associated with poorer prognostic characteristics including older age, severe comorbidities, less bystander intervention, and a lower proportion of a shockable heart rhythm. In relation to age, the temporal increase in 30-day survival was most prominent in the youngest patients aged 18–65 years (from 5.8% to 22.0%, in 2001 and 2011, respectively), in senior patients aged 66–80 years (from 2.7% to 8.4%, in 2001 and 2011, respectively), and numeric negligible in patients aged >80 years (from 1.5% to 2.0%, in 2001 and 2011, respectively). Finally, using two pre-hospital criteria, it was possible to retrospectively identify patients with 30-day survival close to none, irrespective of patient age. Out of 9499 patients, three achieved 30-day survival if they met two criteria: (1) had not achieved return of spontaneous circulation upon hospital arrival;

and (2) had not received a pre-hospital shock from a defibrillator. The three 30-day survivors were equally distributed between the three pre-selected age groups.

Taken together, the findings of the present thesis indicate that the implementation of national initiatives to improve cardiac arrest management in Denmark, including widespread CPR training, have increased patient survival; however, due to the observational study design, a causal relationship between national initiatives and increased survival remains uncertain.

DANSK RESUMÉ

Flere nationale initiativer er blevet taget i Danmark igennem de sidste 10 år for at forbedre håndteringen af hjertestop udenfor hospital (out-of-hospital cardiac arrest, OHCA). En strategi har været at uddanne og træne en stor del af befolkningen i hjertelungeredning (HLR); dette for at øge og forbedre genoplivningsindsatsen fra vidner til hjertestop. En anden strategi har været at styrke akutberedskabet sammen med opdatering af kliniske behandlingsvejledninger; dette for at forbedre den avancerede behandling. Formålet med denne afhandling var at undersøge: (1) den tidsmæssige udvikling i genoplivningsindsats ved tilskuer til hjertestop og patient overlevelse efter OHCA i forlængelse af de nationale initiativer der er blevet implementerede for at forbedre håndteringen og behandlingen af hjertestop; (2) hvorvidt der var køns og alders-relateret forskelle i patient karakteristika og overlevelse igennem de sidste 10 år; og (3) hvorvidt det var muligt, tidligt i forløbet og uanset patient alder, at identificere patienter med minimal chance for langtidsoverlevelse.

I alt blev 21.480 patienter med et formodet kardiogent udløst OHCA, hvor der blev igangsat et genoplivningsforsøg, identificeret i det landsdækkende Dansk Hjertestopregister mellem juni 2001 og december 2011. Hjertestop data blev herefter koblet sammen med data fra de landsdækkende administrative registre ved brug af det unikke og permanente CPR nummer, der tillader kobling af information mellem registre på individniveau.

I Danmark mellem 2001 og 2010, steg patient overlevelse efter OHCA; stigningen i patient overlevelse var associeret med en samtidig stigning i HLR udført af tilskuer til hjertestoppet. Begge parametre mere end fordoblede, og stigningen var konsistent i absolutte tal. I procenttal, fra 2001 til 2010, steg HLR udført af tilskuer fra 21,1 % til 44,9 %; overlevelse ved ankomst til hospital steg fra 7,9 % til 21,8 %; og 30-dages overlevelsen steg fra 3,5 % til 10,8 %, (alle p<0,001). Den tidsmæssige stigning i 30-dages overlevelse var mindre udtalt for kvinder (kvinder fra 4,8 % til 6,7 %, versus mænd fra 3,0 % til 12,9 %, i henholdsvis 2001 og 2010). Dette skyldtes at kvinder var associerede med dårligere prognostiske faktorer inklusiv en højere alder, sværere komorbiditeter, mindre intervention af tilskuer til hjertestoppet og en lavere andel med stødbar hjerterytme. I relation til alder var den tidsmæssige stigning i 30-dages overlevelse mest udtalt hos de yngste patienter mellem 18-65 år (fra 5,8 % til 22,0 %, i henholdsvis 2001 og 2011), i senior patienter mellem 66-80 år (fra 2,7 % til 8,4 %, i henholdsvis 2001 og 2011), og numerisk negligeabel for patienter over 80 år (1,5 % til 2,0 %, i henholdsvis 2001 og 2011). Endelig, ved brug af to præhospitale kriterier var det muligt retrospektivt at identificere patienter hvor chancen for 30-dages overlevelse var tæt på ikke eksisterende, dette uafhængigt af patient alder. Ud af 9499 patienter, opnåede tre 30-dages overlevelse hvis de

opfyldte to kriterier: (1) ikke havde opnået genoprettelse af spontan cirkulation ved ankomst til hospital; og (2) ikke havde modtaget et stød fra en defibrillator inden ankomst til hospital. De tre 30-dages overlevere var ligeligt fordelt mellem de tre præselekterede aldersgrupper.

Samlet set indikerer afhandlingens resultater, at de nationale initiativer der er implementeret for at forbedre håndteringen og behandlingen af hjertestop udenfor hospital i Danmark, herunder HLR træning til store dele af befolkningen, har øget patient overlevelsen. Men på grund af det observationelle studiedesign giver afhandlingen intet kausal bevis for sammenhænge mellem nationale initiativer og øget overlevelse.

ACKNOWLEDGEMENTS

I have been fortunate to be supervised by Christian Torp-Pedersen, Freddy Lippert, Gunnar Gislason, Lars Køber, and Fredrik Folke. I would like to thank my supervisors for their great supervision and support. Also, I owe many thanks to the Danish Emergency Medical Services personnel who have completed the case report forms for the Danish Cardiac Arrest Registry (these forms comprise the data on which my PhD thesis is based). Moreover, I am very grateful for the financial support I have received from TrygFonden, the Danish Heart Foundation, and the Health Insurance Foundation—without their funding, this research project would not have been possible. A special thanks goes out to my dear friend and colleague Carolina Malta Hansen, who has been supportive and helpful from the very start. We have shared many special moments, including when traveling around presenting our data here and there. In recent times I have also come to know two great Jutlanders (and Scientists) SteenMøller Hansen and Kristian Kragholm. I would like to thank them and Carolina for a great teamwork; we have had so many fruitful discussions and supported each other when needed. It is truly a great pleasure working together.

To Freddy, I owe a lot; he has always been supportive of me and believed in my project right from the beginning, making everything possible. Freddy is an extremely dedicated person and his passion for the field of resuscitation, combined with his unique ability to translate research findings into real-life practice have been very inspirational to me. Finally, he has introduced me to the large and important international resuscitation science network, and included me in his own research department; for this, I am very thankful. I also want to thank Fredrik. He has been very encouraging and has taken the time to help me when I needed most. Fredrik also has a good sense of humor and keeps up the spirit; this was great help while we sat for countless hours and coded in order to deliver data to the COSTA collaboration. We still need to do more work on that project! Taken together, many people have contributed to this PhD thesis. I cannot thank you all enough; none of you will be forgotten.

I am very grateful to be a part of the scientific framework that is skillfully and wisely led by Christian, Gunnar, and Lars. They have created an extremely stimulating and thrilling environment; a universe filled with dreams, ideas, data, manuscripts, and not least curious, dedicated, passionate, and charismatic personalities that are invigorating simply to be around. Such milieu is contagious and, indeed, very seductive; at times it feels like everything is possible, that you can make a difference through research—so many dreams, then failures, but at times victories!

As I have worked on my PhD, I have been fortunate to supervise three incredibly bright students: Shahzleen, Lena, and Sidsel. This supervisory part of research has been very satisfying and fun, providing me with training not only on the scientific level, but also on a basic human level: how to teach, motivate, and understand how people think, act, and perceive the world—which at times, can be quite different. Also, I have been fortunate not only to be involved in studies concerning cardiac arrest, but studies on other medical topics, which has been very fulfilling.

You might get lucky to meet a person in your life who has an extraordinary impact on you on multiple levels. Christian is this kind of person, and truly one of a kind, but I know he hates melodramatic elements, at least in PhD prefaces, so I will keep this part short, simple, and way too unspoken. During this project, Christian has taught me much about science and life in general—much more than this thesis could contain—which has broadened my perspective on life. I am so very grateful for this. Christian: Even though you always accuse me of not listening and instead doing exactly what I feel like, your opinion has always been important to me and I hope you will still pick up the phone when I call for advice on multiple aspects concerning science and life in general!

Research has definitely at times brought out the best in me, but at other times, the worst. For that reason, I would like to thank my girlfriend Matilde and my family and friends for always supporting me with love and understanding. Without you by my side none of this would have been possible.

Despite this being such a busy time, I love data, and I love translating data into manuscripts, so this has been, above all, an extremely fun and exciting time!

Mads Wissenberg Jørgensen,
January 2015

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BACKGROUND

Out-of-Hospital Cardiac Arrest

Cardiac arrest is an emergency medical condition characterized by the cessation of cardiac mechanical activity with the absence of circulation leading to pulselessness, loss of consciousness, and abnormal or absent breathing;[1] without immediate and decisive treatment, chances of survival are minimal.[2-4] The cessation of cardiac mechanical activity is often related to a disturbance of the electrical activity in the heart. Upon cardiac arrest, the heart rhythm can roughly be categorized as either a shockable rhythm (ventricular fibrillation or pulseless ventricular tachycardia) or a non-shockable rhythm (asystole or pulseless electrical activity). A wide range of diseases and conditions can lead to a disturbance of the electrical activity in the heart, with a subsequent risk of cardiac arrest. In this regard cardiovascular disease is the most common cause of sudden cardiac arrest in the developed world.[5] Coronary artery disease particularly dominates, but other cardiac diseases like cardiomyopathy, primary electrophysiological disorders, genetic ion-channel abnormalities, valvular and congenital heart diseases, and some other rare cardiac causes can also lead to sudden cardiac arrest.[6] Although the majority of patients experience warning signs before the arrest (typically angina pectoris and dyspnea), approximately 25% of people do not have any symptoms, which exemplifies the challenge behind predicting cardiac arrest before it happens.[7] Other typical non-cardiac diseases and conditions that can lead to cardiac arrest include: lung diseases, electrolyte imbalance, hypovolemia, trauma (accidents, violent attack, and suicide), drug overdose, suffocation, hypothermia, drowning, and electrocution.[8,9] Due to the variety of causes, cardiac arrest should be considered a condition—not a disease itself—and the common saying, "cardiac arrest is the leading cause of death" should be avoided, since cardiac arrest is an obvious consequence and inevitable part of all deaths, irrespective of the cause.

Naturally, a cardiac arrest can occur at any time and at any place; a particular subgroup is out-of-hospital cardiac arrest (OHCA). These cardiac arrest patients pose additional challenges, due to their physical location, which brings an inherent risk of delay (or altogether absence) of recognition and treatment. Since the time from initial collapse to the point at which resuscitative efforts are initiated plays a crucial role in a cardiac arrest patient's chance of survival, OHCA is not only a concern for health care professionals, but also a concern for the general public, who have the opportunity to act when witnessing a cardiac arrest.[2-4,10,11] This thesis is focused on OHCA.

Case Definition and Reporting Style

Among different regions and countries, great variations exist in calculated incidence and survival rates of OHCA.[12-17] Even though true geographical variation might exist due to differences in public health and health care systems (i.e., prevention strategies and treatment strategies) there is an inherent risk of artificial variation between regions and countries due to study-related differences in the methodology that is used (i.e., differences in OHCA case definition, population at risk, study settings, and differences in systems used to capture and subsequently record the OHCA cases).[12-17] Accordingly, both the incidence and survival rate are highly sensitive to the case definition, which can vary. For example, a definition may include all patients who die outside of a hospital, only those assessed by emergency medical services (EMS) personnel, only those for which resuscitative efforts are attempted (treated OHCA), only those with a non–EMS-witnessed arrest, only those with a presumed cardiac-caused cardiac arrest (i.e., cardiac arrest caused by cardiac disease, unexpected collapse, or unknown disease with no clear evidence of a non-cardiac cause), or only those with a shockable heart rhythm.[12,13] Also, the population at risk can vary according to various criteria, like age (can include all individuals, only those older than 18 years of age, or only those younger than 18 years of age, etc.), and the study setting can vary according to geographic characteristics and size (e.g. city vs. rural area and regional vs. national level). For these reasons, comparisons of incidences and survival rates from different studies should be done with great caution, since these measures are obviously highly sensitive to differences in methodology. In order to help overcome these challenges, the Utstein template was developed and published in 1991.[18] The Utstein template is a set of internationally recognized guidelines that encourage uniform reporting of cardiac arrest, thereby allowing for fair comparisons of OHCA findings across regions and nations.[1] Accordingly, standardized reporting minimizes the blur of artificial variation related to differences in reporting style and facilitates the comparison of a more homogenous group of patients, which is essential when trying to identify true variation in survival related to differences in community and health care system strategies to prevent and treat OHCA.

Incidence and Survival Rates of OHCA

Incidence and survival rates are common measures used when trying to understand the size and impact of a given health problem, like OHCA. In Denmark, treated OHCA affects approximately 3500 individuals annually, with an estimated incidence of approximately 62 OHCA per 100,000 person-years.[19] In North America, the incidence of treated OHCA has previously been calculated to be between 47 and 56 OHCA per 100,000 person-years.[5,12,15-17] In Europe, these figures have been reported to be a little lower (38 to 41 OHCA per 100,000 person-years).[12,14] One explanation for these disparities could be that only a small number of nationwide cardiac arrest registries exist.[20] Therefore, calculated incidence rates are often based on studies from smaller geographic areas, which are then extrapolated to estimate national levels, or even continental levels;[12-17] such extrapolation is inevitably subject to some uncertainty since the case definition, population at risk, and data collection could vary among the included studies. Furthermore, areas without cardiac arrest data might be different from areas with cardiac arrest data.

In terms of survival, a recent systematic review and meta-analysis of 142,740 adult patients with treated OHCA of a presumed cardiac cause calculated the aggregated survival rate to be 23.8% at hospital admission and 7.6% at hospital discharge.[13] The 79 included studies were conducted between 1984 and 2008; when testing temporal trends in survival at hospital discharge (in 5-year time spans), no significant change was observed.[13] In another systematic review of 67 studies, the aggregated survival rate at hospital discharge was fairly similar, and calculated to be 7.1%.[12] However, great variation was observed among the included studies in both reviews, with survival at discharge varying from 0.1% to 34%,[13] and 0.6% to 31%,[12] respectively. The large variation in survival indicates that there are important differences between the included studies with a risk of overlooking important details when analysing aggregated data; at the same time, the large variation in survival provides hope that, through systematic efforts, it is possible to increase survival after OHCA.

Although OHCA is considered a major health problem associated with poor outcomes,[12-17] several studies have shown good length and quality of life in survivors discharged from the hospital.[9,21-23] In a large study from the United States, 72% of survivors had a good or moderate cerebral performance at hospital discharge (Cerebral Performance Category [CPC] score),[9] and in a recent Dutch study, 80% of the survivors had no cerebral-cognitive impairments when assessed 6–12 months after OHCA.[23] These are important findings since they highlight that resuscitative efforts are not futile, and they attenuate the general belief that OHCA survivors are troubled with severe cognitive impairment and low quality of life.

Prognostic Factors and National Initiatives

Several factors have been identified to substantially improve the chance of survival after OHCA, including major components of the established chain-of-survival concept.[2-4,10,11,24,25] The chain-of-survival currently consists of five links which are believed to be interdependent and equally important for survival: (1) "Immediate recognition of cardiac arrest and activation of the emergency response system"; (2) "Early cardiopulmonary resuscitation (CPR) with an emphasis on chest compressions"; (3) "Rapid defibrillation"; (4) "Effective advanced life support"; and (5) "Integrated post-cardiac arrest care".[26] The third link is conditioned on the patient's heart rhythm, since only patients with a shockable rhythm can benefit from defibrillation, which may subsequently restore a pulse with return of spontaneous circulation (ROSC). Accordingly, the patient's heart rhythm is closely related to survival: patients with a shockable rhythm have much higher survival rates than those with a non-shockable rhythm. Notably, in a limited time period, the heart rhythm is somewhat dynamic and depends on several factors including: time from collapse to rhythm analysis, treatment, cause of arrest, and patient condition (age and comorbidity) i.e., shockable rhythm deteriorates to asystole with increasing time,[27-29] while early CPR seems to prolong the time patients can be found with a shockable rhythm.[29-33] Finally, studies have suggested that a non-cardiac cause of arrest, increasing patient age, and end-stage heart failure is associated with having a non-shockable heart rhythm.[34,35] Of these factors, early CPR represents an easy and direct way to help prevent and delay deterioration to a non-shockable heart rhythm.

As indicated in the chain of survival, the chance of a good outcome crucially depends on early recognition of cardiac arrest, and the application of prompt resuscitation efforts. Consequently, the chance of survival decreases dramatically for each passing minute after collapse (roughly 10% per minute) until resuscitation is initiated (i.e., CPR and/or defibrillation).[2-4,10,11,27,36,37] If early CPR is provided, then survival decreases less dramatically (roughly 3% to 4% per minute) and buys time for successful resuscitation.[27,36] However, in the case of OHCA, receiving early resuscitative efforts can be challenging, as the time from cardiac arrest recognition to EMS arrival can be long,[2,8,38] leaving bystanders in a uniquely critical position to potentially impact patient prognosis through intervention before EMS arrival.[2-4,15,18] Accordingly, discharge survival rates have been reported to be 2–3 times higher in patients who received bystander CPR, and discharge survival rates as high as 49–75% have been reported in patients that have received an early shock from a bystander using an automatic external defibrillator (AED).[33,39-45] Overall, these findings reveal a major potential for bystanders to improve patient survival following OHCA and the importance of early resuscitative efforts from bystanders is already well recognized.[8,10,11,13,33,39-45] Unfortunately, several studies have also shown that only a minority of cardiac arrest victims receive bystander resuscitation efforts.[9,12,13,15,43,46] Education, training, and guidance of the public in resuscitation may provide one solution to change such tendency, as initiatives of this kind seem to increase the willingness of bystanders to act in case of a cardiac arrest.[8,10,11,46-53] Consequently, there has been a growing focus on community approaches to increase and improve resuscitative efforts from bystanders with education and training of citizens on the first three links in the chain of survival.[11,54,55] And although survival remains low,[12,13] there is some evidence that public efforts to improve pre-hospital and in-hospital handling can result in improved survival following OHCA.[8,47,48,56,57]

A low frequency of bystander CPR (<20%) and low 30-day survival (<6%) were identified nearly ten years ago in Denmark.[19] These findings led to several national initiatives to strengthen bystander resuscitation attempts and advance care. These strategies included: (1) implementation of mandatory resuscitation training in elementary schools (since January 2005) and when acquiring a driver's license (since October 2006), combined with a rise in voluntary first aid training;[58] (2) free distribution of approximately 150,000 CPR self-instruction training kits between 2005 and 2010;[59] (3) nationwide improvement of telephone guidance from emergency dispatch centers to bystanders witnessing a cardiac arrest, including the addition of healthcare professionals at dispatch centers (starting in 2009); (4) a large increase in the number of AEDs located outside of hospitals (approximately 15,000 were in place by 2011);[60] (5) efforts to improve advanced care with updates of clinical guidelines,[4,25] including the introduction of therapeutic hypothermia in Denmark (starting from 2004), and a growing focus on early revascularization; and (6) overall strengthening of the EMS system with training of the ambulance personnel, implementation of paramedics, and mobile emergency care units staffed with either specialized anesthesiologists or paramedics dispatched as rendezvous with basic life support ambulances. Despite these nationwide efforts, it was unknown prior to this project whether there had been changes in resuscitation attempts by bystanders and changes in patient survival.

Sex and Age

A number of studies have shown significant sex-related differences in pre-hospital patient characteristics, with female sex being associated with poor prognostic factors, including a lower frequency of witnessed arrest, bystander CPR, and shockable heart rhythm.[61-69] Nonetheless, female sex has been associated with improved survival upon hospital arrival,[61-63,65,68,69] as well as improved 30-day survival/survival at discharge in the reproductive age[64,66,67] and at all ages.[63,65] Some have proposed that female sex hormones may be the underlying factor for such findings.[63-67] However, there are still factors incompletely understood or not yet even identified that influence survival.[2,70] Consequently, more data are needed, and before this project, little was known about cardiac arrest patients' comorbidity in relation to sex and subsequent survival. This parameter could vary according to sex and influence the chances of survival following OHCA.

Another central aspect is patient age. Aging influences multiple physiological processes and with increasing age, there is an escalated susceptibility to contract diseases and critical illness, including conditions like cardiac arrest.[71-73] Accordingly, increasing age is associated with a concomitant increase in OHCA incidence, as well as a low chance of survival following OHCA.[8,47,48,56,57,72-76,77-81] Despite this lower chance of survival, several studies have reported that resuscitative efforts in older patients or in nursing homes are not futile, underlining that patient age alone does not seem to be a good parameter for denying a patient resuscitative efforts.[74-76,82,83] Yet it has been widely debated whether or not it is possible, a priori, to define a specific patient group where a resuscitation attempt is considered futile.[77-81] Such early identification of patients with minimal chance of survival could be helpful in the complex and difficult decision-making process regarding when to terminate a resuscitation attempt.

Objectives

Utilizing the Danish nationwide registries, we sought to evaluate community-based care relative to OHCA in Denmark and clarify whether there have been changes in resuscitation attempts by bystanders and changes in patient survival during a decade where major efforts have been taken to improve cardiac arrest management (i.e., improve bystander resuscitation attempts and advance care). Also, in order to improve the understanding and focus future national strategies for cardiac arrest management, it was important to know how patient-related and cardiac arrest-related characteristics, as well as patient survival, were reflected with regard to patient sex and age, and whether it is possible to identify patients with minimal chance of long-term survival.

The major efforts and major resources taken to improve cardiac arrest management in Denmark make this investigation of public relevance, and inspired the body of work leading to this thesis.

The present thesis focuses on analyses of presumed cardiac-caused OHCA in Denmark from 2001–2011 and has the following aims:

1. To investigate rates of bystander intervention and patient survival, between 2001 and 2010—a period where several national initiatives were taken to increase and improve bystander resuscitation attempts and improve advanced care.

2. To investigate whether there were sex-related differences in patient characteristics and crude survival between 2001 and 2010, as well as examine the association between sex and survival when taking patient characteristics (including comorbidity) into account in multivariable analyses.

3. To investigate age-related differences in patient characteristics and survival between 2001 and 2011.

4. To investigate whether pre-hospital criteria can be used to identify patients with minimal chance of 30-day survival, irrespective of age.

METHODS

Definition and Recording of OHCA

The Danish Cardiac Arrest Registry has existed since June 2001, and is a complete nationwide registry containing information on OHCA events.[84] A patient is included in the Danish Cardiac Arrest Registry when a clinical condition of cardiac arrest outside of a hospital results in a resuscitation attempt by either EMS personnel or a bystander; this OHCA definition excludes patients with late signs of death where resuscitation attempts are not initiated. The capture of OHCA cases is close to complete since: (1) EMS is activated for all severe clinical emergencies in Denmark (including cardiac arrests); and (2) EMS is required to fill out a case report form for every OHCA, thereby forming the Danish Cardiac Arrest Registry. For the current thesis, we included information on date; time; location of arrest (private home vs. outside private home); whether the collapse was non-, bystander-, or EMS-witnessed; whether the bystander initiated CPR and/or defibrillated the patient using an AED located outside hospital; first observed heart rhythm (shockable or non-shockable rhythm); whether EMS personnel defibrillated the patient; time interval, an estimate from recognition of OHCA to rhythm analysis by EMS (time for recognition of OHCA was estimated based on the time the EMS call was received, as well as on a subsequent interview of the caller led by the EMS personnel at the scene); and whether the patient had achieved survival (ROSC) upon arrival at the hospital.

To study and compare a more homogenous group of patients, we categorized cardiac arrests into presumed cardiac cause and presumed non-cardiac cause, as recommended by the Utstein template.[1] This categorization was conducted using diagnosis codes from death certificates and discharge diagnoses from all Danish hospitals. Events with diagnosis codes containing cardiac disease, unexpected collapse, or unknown disease, were defined as a cardiac cause of arrest. Events with diagnosis codes of other medical disorders (i.e., absence of diagnoses mentioned above) were defined as a non-cardiac cause. Trauma including various accidents, violent attack, and attempted suicide were together with drug overdose defined as non-cardiac causes, regardless of other diagnoses.

Data from Nationwide Administrative Registries in Denmark

Denmark holds nationwide and complete administrative registries on a wide range of health care-related variables.[85] Data exist on an individual level in the registries, and individual-level linkage of information between the nationwide registries is possible due to the unique and permanent Civil Registration Number, which is assigned to each Danish resident. This number is used in all interactions with Danish government agencies, including all contacts with the tax-funded public health care system, and ensures that the administrative registries are close to complete.[85]

This thesis was based on a database consisting of data from the Danish Cardiac Arrest Registry and data from selected national administrative registries (described below). The database was accessed through secure servers placed at Statistics Denmark (Office for National Statistics). Statistics Denmark encrypted the Civil Registration Number to ensure anonymity.

Information on sex, age, civil status, and vital status including date of death occurrence (all deaths are registered within 14 days of occurrence) was obtained from the **Danish Civil Registration System**.[86] Discharge diagnosis codes, as well as admission and discharge dates from all Danish hospitals, were obtained from the **Danish National Patient Registry**.[87] Each hospital admission is registered with one main discharge coding diagnosis and, if appropriate, one or more secondary diagnoses. These data are assumed to be complete because hospital departments are reimbursed based on diagnostic and procedural registration. To investigate patients' comorbidities, discharge diagnoses were examined up to ten years prior to OHCA. Also, new onset of anoxic brain damage in 1-year survivors was examined. A new onset was defined as: (1) patients diagnosed with anoxic brain damage during the period from hospital discharge (following OHCA) to 30 days post-discharge; and (2) no history of anoxic brain damage up to five (Paper I) or ten years (Paper II and Paper III) before the cardiac arrest. Information on patients' pharmacotherapy was obtained from the **Danish Registry of Medicinal Product Statistics** (the national prescription registry) and drug use was examined up to 180 days prior to OHCA. Each drug dispensing is registered according to an international classification of drugs system, the Anatomical Therapeutic Chemical (ATC) classification system.[88] The capture of drug use is close to complete due to every pharmacy being required to register all dispensed drug prescriptions since the national healthcare system in Denmark partially reimburses drug expenses.[89] Diagnosis codes from death certificates with immediate, contributory, and underlying causes of death were obtained from the **National Causes of Death Registry**.[90] All deaths should be included in the registry since the doctor declaring the individual's death is obligated to complete the death certificate; hence these data ought to be complete since such registration is mandatory by law.

All diagnosis codes are registered according to the International Classification of Diseases (ICD) system; before 1994, the 8th revision (ICD-8) was used, and from 1994 to the present, the 10th revision (ICD-10) was used.

Study Design

All three studies comprising this thesis are nationwide registry-based data analyses. Inclusion and exclusion criteria were the same for each study except for patient age, which varied according to the individual study aim, as described below. The participants in the studies were identified through the Danish Cardiac Arrest Registry.

Study Setting

The three studies were conducted in Denmark which occupies 43,000 square kilometers, and includes rural, suburban, and urban areas. The study period was from June 1, 2001 to December 31, 2010 in Paper I and Paper II; and from June 1, 2001 to December 31, 2011 in Paper III. The Danish population increased during the period from 5,355,000 in June 2001 to 5,581,000 in January 2012, together with an increase in overall life expectancy (for newborn babies) from 76.9 years in 2001 to 79.9 years in January 2012.[91]

In Denmark, the EMS system consists of basic life support ambulances staffed with ambulance technicians or paramedics, and mobile emergency care units staffed with specialized anesthesiologists or paramedics. The mobile emergency care units are dispatched as rendezvous with basic life support ambulances and have gradually increased in number during the study period. Throughout the study period, treatment has been given according to the latest guidelines on resuscitation and emergency cardiovascular care.[3]

Study Population

Paper I. National initiatives to improve bystander intervention and patient survival after OHCA

Using data from the nationwide Danish Cardiac Arrest Registry (2001─2010), we identified 19,468 patients (all ages) with a presumed cardiac-caused OHCA for whom CPR was attempted.

Paper II. OHCA in relation to sex

Using data from the nationwide Danish Cardiac Arrest Registry (2001─2010), we identified 19,372 patients $\geq$12 years old with a presumed cardiac-caused OHCA for whom CPR was attempted. The cut-off at 12 years of age was decided according to the sex differentiation that occurs at puberty with the rise in sex hormone levels and subsequent development of phenotypic secondary sex characteristics, as done before.[13]

Paper III. OHCA in relation to age and identification of patients with minimal chance of survival

Using data from the nationwide Danish Cardiac Arrest Registry (2001─2011), we identified 21,480 patients $\geq$18 years old with a presumed cardiac-caused OHCA for whom CPR was attempted. The patients were then divided into pre-selected age groups in different ways, with the primary age groups being: “working-age patients” aged 18–65 years; “early-senior patients” aged 66–80 years; and “late-senior patients” aged >80 years. The cut-off levels in age groups were decided according to stages of life that roughly reflect the physiologic reserve and the functional capacity of individuals. Hence, working-age roughly reflects one level of functioning in society with the capability of having a job, and with increasing age, a gradual transition to the senior lifestyle and functioning. To acknowledge that aging represents a continuum with a gradual decrease in physiologic reserve and functioning throughout life, the study’s main outcome measure was also tested in shorter age intervals.

Main Outcome Measures

The main outcome measures consisted of temporal trends in bystander CPR, bystander defibrillation, and survival upon arrival at the hospital, at 30 days, and at 1 year; overall, and in relation to sex and pre-selected age groups.

Ethics

The studies included in this thesis were approved by the Danish Data Protection Agency (reference no. 2007-58-0015; local reference no. GEH-2014-017; I-suite.no. 02735). Patients were anonymized as the Civil Registration Numbers were encrypted. In Denmark, ethical approval is not required for retrospective registry-based studies.

Statistical Analyses

To test for differences between groups, we used a Chi-square test for binary variables and a Wilcoxon rank-sum test for continuous variables; for more than two groups, we used the Kruskal-Wallis test for continuous variables. To test for temporal changes, a Wilcoxon rank-sum test was used for binary variables in Paper I and Paper II, while logistic regression models were used in Paper III, Spearman rank correlation coefficients were used for continuous variables (calendar year was treated as a continuous variable). Poisson regression analyses were used to test for temporal changes in absolute incidence of OHCA (Paper I and Paper III) and survivors (Paper I and Paper III). Furthermore, joinpoint regression analyses were used to test if any joinpoints were statistically significant with a change in slope for temporal trends in bystander CPR and survival rates (Paper I). The Cochran–Armitage test was used to test for trends in binary variables according to age groups. When calculating percentages and medians, we only included observations with data for the covariate involved in the calculation. In order to test whether missing data could introduce bias, we applied the multivariate imputation by chained equations

(MICE) method. Using MICE, missing values from each variable were imputed.[92] The imputed values were predicted using information from all patient-related and cardiac arrest-related variables in the dataset. Overall, ten imputed datasets (complete datasets with observed and imputed values) were generated from the existing dataset (incomplete dataset containing missing values). Estimates were then calculated from the imputed datasets and combined using multiple imputed pooled analyses. Afterwards, estimates from the existing dataset were compared with estimates from the imputed datasets.

In Paper I, the association between pre-hospital factors and 30-day survival were investigated using both univariable and multivariable logistic regression analyses; the latter adjusted for age and sex. Logistic regression analyses were also used in Paper II to examine the association between patient sex and 30-day survival. Multivariable analyses were adjusted for cardiac arrest-related and patient-related characteristics, including comorbidities. Covariates for multivariable models were selected prior to analysis, and included those pre-hospital factors considered most relevant. Model assumptions were tested and found to be valid unless otherwise addressed. Associations are presented as calculated odds ratios (ORs) with 95% confidence intervals (CIs). Missing data were in logistic regression analyses handled by MICE in order to minimize bias and avoid reducing statistical power.[92] A two-sided p-value <0.05 was considered statistically significant. Data management and analyses were performed using: SAS, version 9.2 (SAS Institute Inc., Cary, NC, USA); R, version 2.15.2 (R Development Core Team); and Joinpoint Regression program, version 4.0.1 (National Cancer Institute at the National Institutes of Health, USA).

RESULTS

This section presents a brief summary of the main findings of the three studies constituting this thesis. The structure is the same for each paper: a short introduction explaining the clinical importance of the study question, followed by the objective, study design, setting, population, main outcome measures, results, and finally, conclusions and relevance. The main tables and figures are included. Detailed description and supplemental results can be viewed in the Appendix section.

Paper I: Association of National Initiatives to Improve Cardiac Arrest Management with Rates of Bystander Intervention and Patient Survival after Out-of-Hospital Cardiac Arrest

Importance: OHCA is a major health problem associated with poor outcomes. Early recognition and intervention is critical for patient survival. Bystander CPR is one factor among many associated with improved survival.

Objective: To examine temporal changes in bystander resuscitation attempts and survival during a 10-year period where several national initiatives were taken to increase bystander resuscitation and improve advanced care.

Design, Setting, and Participants: Patients with OHCA for whom resuscitation was attempted were identified between 2001 and 2010, in the nationwide Danish Cardiac Arrest Registry. Of 29,111 cardiac arrest patients, we excluded those with arrests of a presumed non-cardiac cause (n=7,390) and arrests witnessed by EMS (n=2,253), leaving a final study population of 19,468 patients.

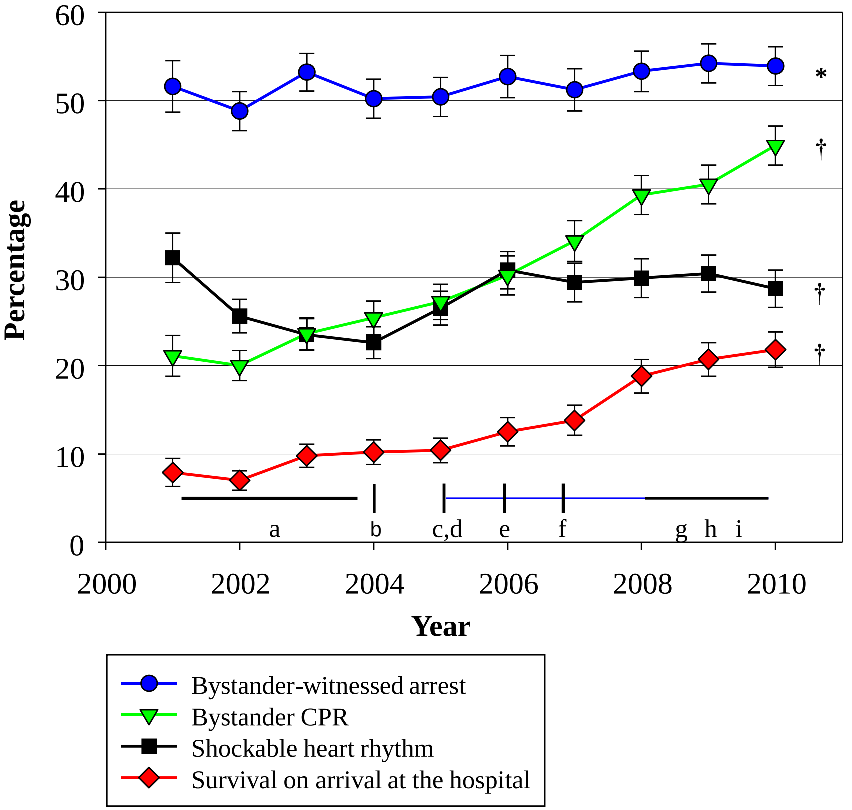
Main Outcome and Measures: Main outcome measures included temporal trends in bystander CPR, bystander defibrillation, survival upon hospital arrival, 30-day survival, and 1-year survival.

Results: The median age was 72 years (1st-3rd quartiles [Q1-Q3] 61–80) and 67.4% were male. Bystander CPR increased significantly during the study period, from 21.1% in 2001 to 44.9% in 2010, $p<0.001$ (Figure 1), defibrillation by bystander remained low, although a small increase was observed (1.1% in 2001 to 2.2% in 2010, $p=0.003$). More patients had achieved survival on hospital arrival (7.9% in 2001 to 21.8% in 2010, $p<0.001$). Also, 30-day survival increased from 3.5% in 2001 to 10.8% in 2010 ($p<0.001$), as well as 1-year survival (2.9% in 2001 to 10.2% in 2010, $p<0.001$; Figure 2). In patients with a shockable rhythm, 30-day survival increased from 10.5% in 2001 to 32.0% in 2010; and in those with a non-shockable rhythm from 0.5% in 2001 to 2.4% in 2010 ($p<0.001$). Despite a decrease in the incidence of OHCA during the study period from 40.4 to 34.4 per 100,000 persons in 2001 and 2010, respectively ($p=0.002$), the absolute incidence of survivors increased significantly, $p<0.001$ (Supplementary Figure 1, page 71-72). Throughout the study period, the increase in 30-day survivors was achieved mainly among patients who had received bystander CPR (Supplementary Figure 2, page 73). For the entire study period, bystander CPR was positively associated with 30-day survival regardless of witnessed status: 30-day survival for non-witnessed cardiac arrest was 4.3% with bystander CPR and 1.0% without (OR 4.38, CI 3.17–6.06; Table 1); for witnessed arrest, the figures were 19.4% and 6.1% (OR 3.74, CI 3.26–4.28).

Conclusion and Relevance: In Denmark between 2001 and 2010, there was an increase in survival following OHCA that was associated with a concomitant increase in bystander CPR. Due to the co-occurrence of other related initiatives, a causal relationship between the increase in bystander CPR and the increase in survival remains uncertain.

Figure 1

Bystander-Witnessed Arrest, Bystander CPR, Shockable Heart Rhythm as First Recorded Rhythm, and Survival on Arrival at the Hospital, Denmark, 2001-2010



a) about 175,000 first aid certificates distributed annually (2001-2004)
b) introduction of therapeutic hypothermia (starting 2004)
c) mandatory education in resuscitation in elementary schools (January 2005)
d) distribution of about 150,000 CPR self-instruction training kits (2005-2010)
e) new guidelines for resuscitation (November 2005)
f) mandatory resuscitation course when acquiring a driver's license (October 2006)
g) increase to about 300,000 first aid certificates distributed annually (2008-2010)
h) introduction of healthcare professionals at dispatch centers (starting 2009)
i) throughout the study period:
1) a large increase in number of AEDs located outside hospitals (approximately 15,000 in 2011)
2) implementation of paramedics, and mobile emergency care units staffed with anesthesiologists
*p=0.001; †p<0.001

Figure 2

Long-Term Survival Following Out-of-Hospital Cardiac Arrest, 2001-2010

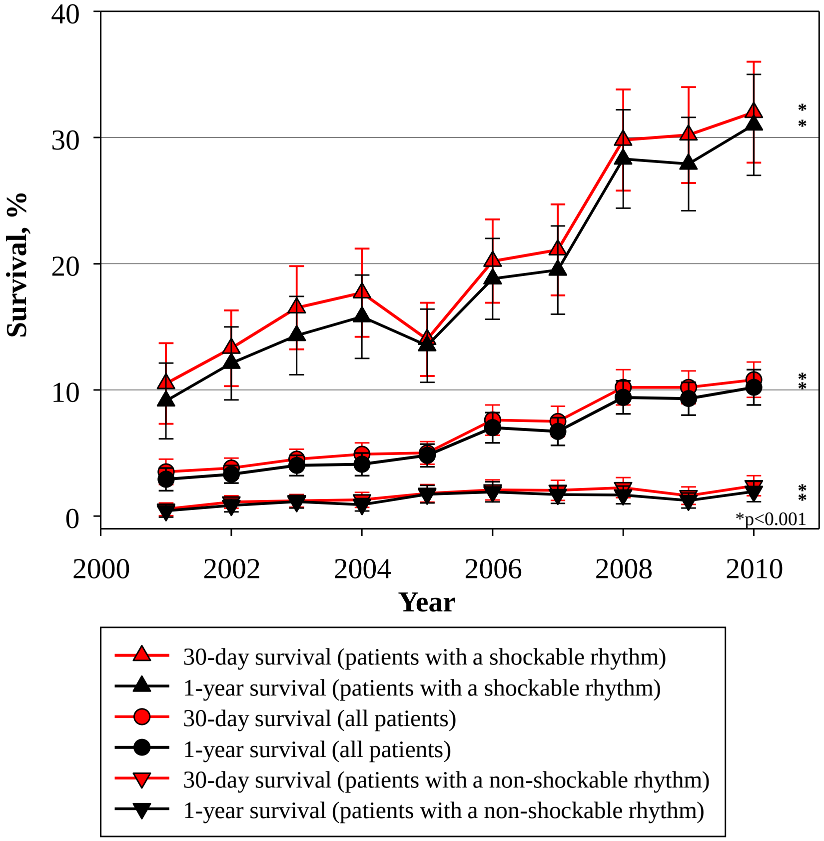


Table 1

Association Between Prehospital Factors and 30-Day Survival for the Entire Study Period

Factor	No.	Crude 30-d Survival, % (95% CI)	OR (95% CI)			
					Imputed Data Sets[a]	
			Unadjusted	Adjusted[b]	Unadjusted	Adjusted[b]
Sex						
Women	6357	4.4 (3.9-4.9)	0.54 (0.47-0.62)	0.66 (0.57-0.76)[c]	0.54 (0.47-0.62)	0.66 (0.57-0.76)[c]
Men	13 111	7.9 (7.4-8.4)				
Age, per 10 additional years	19 468	NA	0.70 (0.67-0.72)	0.70 (0.68-0.72)[d]	0.70 (0.67-0.72)	0.70 (0.68-0.72)[d]
Cardiac arrest in private home						
No	4203	15.2 (14.1-16.3)	4.04 (3.57-4.56)	3.33 (2.94-3.78)	3.98 (3.51-4.51)	3.31 (2.91-3.76)
Yes	12 083	4.3 (3.9-4.6)				
Bystander-witnessed arrest						
Yes	9474	11.3 (10.7-12.0)	7.28 (6.13-8.66)	7.38 (6.20-8.79)	7.12 (5.99-8.47)	7.24 (6.08-8.63)
No	8763	1.7 (1.5-2.0)				
Bystander CPR overall						
Yes	5621	14.3 (13.4-15.2)	4.88 (4.32-5.52)	3.92 (3.45-4.44)	4.77 (4.22-5.40)	3.79 (3.34-4.31)
No	12 654	3.3 (3.0-3.6)				
Bystander CPR in nonwitnessed arrest						
Yes	1874	4.3 (3.4-5.2)	4.38 (3.17-6.06)	3.48 (2.50-4.84)	4.38 (3.17-6.06)	3.47 (2.50-4.84)
No	6858	1.0 (0.8-1.3)				
Bystander CPR in witnessed arrest						
Yes	3709	19.4 (18.1-20.7)	3.74 (3.26-4.28)	2.98 (2.59-3.42)	3.73 (3.26-4.27)	2.98 (2.59-3.42)
No	5730	6.1 (5.4-6.7)				
AED use by bystander						
Yes	241	27.8 (22.1-33.5)	5.93 (4.44-7.91)	4.42 (3.28-5.95)	6.13 (4.53-8.29)	4.51 (3.31-6.14)
No	17 398	6.1 (5.8-6.5)				
Shockable heart rhythm						
Yes	4981	21.0 (19.9-22.2)	15.9 (13.7-18.5)	14.0 (12.0-16.3)	16.0 (13.8-18.6)	14.0 (12.0-16.3)
No	13 058	1.7 (1.4-1.9)				
Estimated time interval, 1 additional min from recognition of OHCA to rhythm analysis by EMS	16 074	NA	0.97 (0.96-0.97)	0.97 (0.96-0.97)	0.97 (0.96-0.99)	0.97 (0.96-0.99)
Estimated time interval >10 min from recognition of OHCA to rhythm analysis by EMS						
Yes	8565	3.8 (3.4-4.2)	0.35 (0.31-0.40)	0.35 (0.30-0.40)	0.40 (0.35-0.47)	0.40 (0.35-0.47)
No	7509	10.0 (9.3-10.7)				

Abbreviations: AED, automated external defibrillator; CPR, cardiopulmonary resuscitation; EMS, emergency medical services; NA, not applicable; OHCA, out-of-hospital cardiac arrest; OR, odds ratio.

[a] In the analysis using imputed data sets missing value for information on prehospital factor was imputed. Therefore, these analyses correspond to entire study population (n = 19 468), except for subanalysis on nonwitnessed (n = 8763) and witnessed (n = 9474) arrest.

[b] Adjusted for sex and age.

[c] Adjusted only for age.

[d] Adjusted only for sex.

Paper II:
Survival after Out-of-Hospital Cardiac Arrest in Relation to Sex: A Nationwide Registry-based Study

Importance: Crude survival following OHCA has increased between 2001 and 2010 in Denmark, a period during which several national initiatives were taken to improve cardiac arrest management, yet it remains unknown whether temporal changes in survival were different between the sexes.

Objective: To examine sex-related differences in patient characteristics and survival during a 10-year study period.

Design, Setting, and Participants: Patients with OHCA for whom resuscitation was attempted were identified between 2001 and 2010, in the nationwide Danish Cardiac Arrest Registry. Of 29,111 patients with cardiac arrests, we excluded patients aged <12 years (n=214), arrests of a presumed non-cardiac cause (n=7,276), and arrests witnessed by EMS personnel (n=2,249), leaving a final study population of 19,372 patients.

Main Outcome and Measures: Main outcome measures included sex-related differences in comorbidity, bystander CPR, first recorded heart rhythm, and survival during a 10-year study period.

Results: One-third were female patients, with a median age of 75 years (Q1–Q3; 65–83). Compared to males, females were five years older and were more likely to have severe comorbidities (e.g., chronic obstructive pulmonary disease [16.5% vs. 12.8%], Supplementary Table 1, page 69), and were less likely to have arrest outside of the home (18.7% vs. 29.4%), receive bystander CPR (25.9% vs. 32.9%), and have a shockable rhythm as the first-recorded heart rhythm (17.2% vs. 32.6%), all p<0.001. The estimated median time-to-rhythm analysis by EMS personnel was similar between the sexes (females 11 minutes [Q1–Q3; 6–19], and males 11 minutes [Q1–Q3; 7–18]). During the study period, bystander CPR rates increased for both sexes (p<0.001), yet compared to males, CPR rates were lower in female patients (Figure 3). When examining the first and last study year, the increase in survival upon hospital arrival was comparable between the sexes; however, female patients tended to have lower survival rates during the study period. Thirty-day crude survival increased, but the increase was less pronounced in female patients (4.8% in 2001 to 6.7% in 2010) compared to males (3.0% in 2001 to 12.9% in 2010), p<0.001 (Figure 4). The lower 30-day survival rate in females was consistent in patients with a non-shockable rhythm, but not in patients with a shockable rhythm

(Supplementary Figure 3, page 74). Finally, multivariable logistic regression analyses showed that the sex-related differences in pre-hospital factors were important for the lower 30-day survival in females. Consequently, in fully adjusted models, there was no significant difference in 30-day survival between sexes in patients with a non-shockable rhythm (OR 1.00; 95% CI 0.72–1.40), while female sex was positively associated with 30-day survival in patients with a shockable rhythm (OR 1.31; 95% CI 1.07–1.59) (Figure 5). The multivariable analyses were rhythm-stratified, due to a significant interaction between sex and heart rhythm. There was no significant interaction between sex and calendar year. In Figure 5, separate analyses in two age groups are also presented: 12–50 years of age (roughly reflecting the age of endogenous hormone production in females), and >50 years of age (roughly reflecting the postmenopausal age of females).

Conclusions and Relevance: The temporal increase in 30-day crude survival was more marked in males due to poorer prognostic characteristics in females, which among other factors, included a lower proportion of bystander CPR and a lower proportion of shockable rhythm. In a fully adjusted model, female sex was positively associated with 30-day survival in patients with a shockable rhythm. This study may help to understand sex-related differences in survival after OHCA, as well as draw attention to cardiac arrest recognition and bystander intervention in females in case of a collapse.

Figure 3

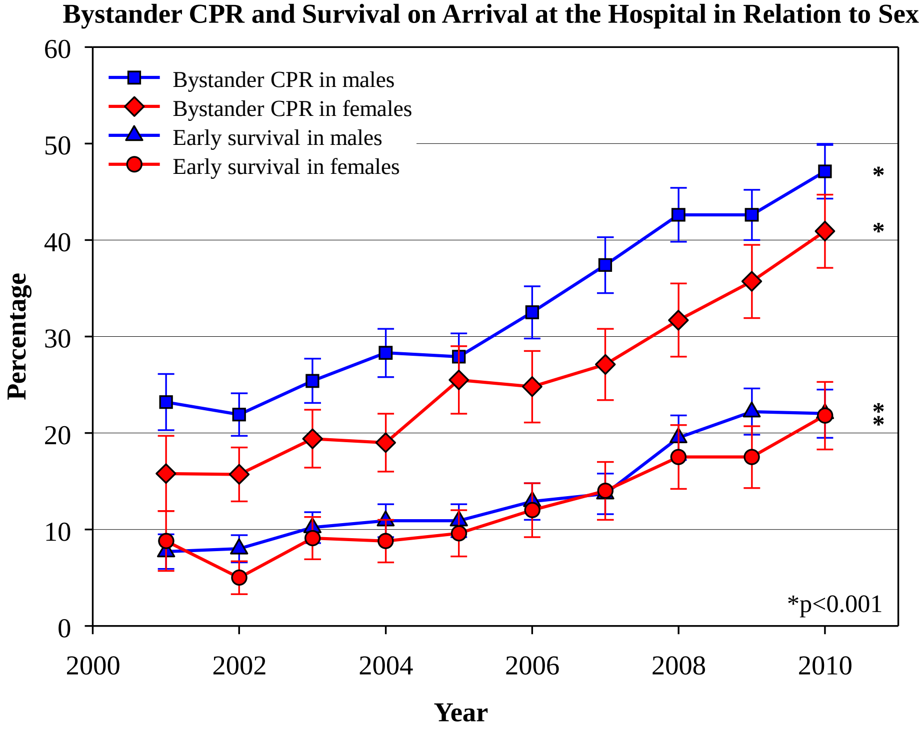

Bystander CPR and Survival on Arrival at the Hospital in Relation to Sex
Bystander CPR in males
Bystander CPR in females
Early survival in males
Early survival in females
Percentage
Year
0
10
20
30
40
50
60
2000
2002
2004
2006
2008
2010
*
*
*
*
*p<0.001

Figure 4

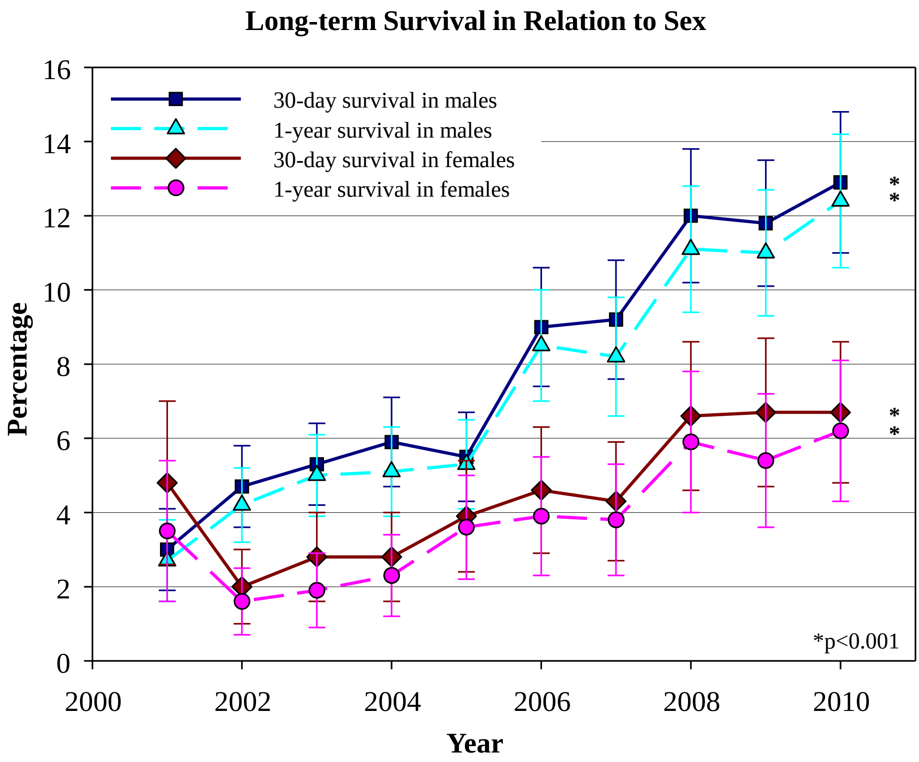
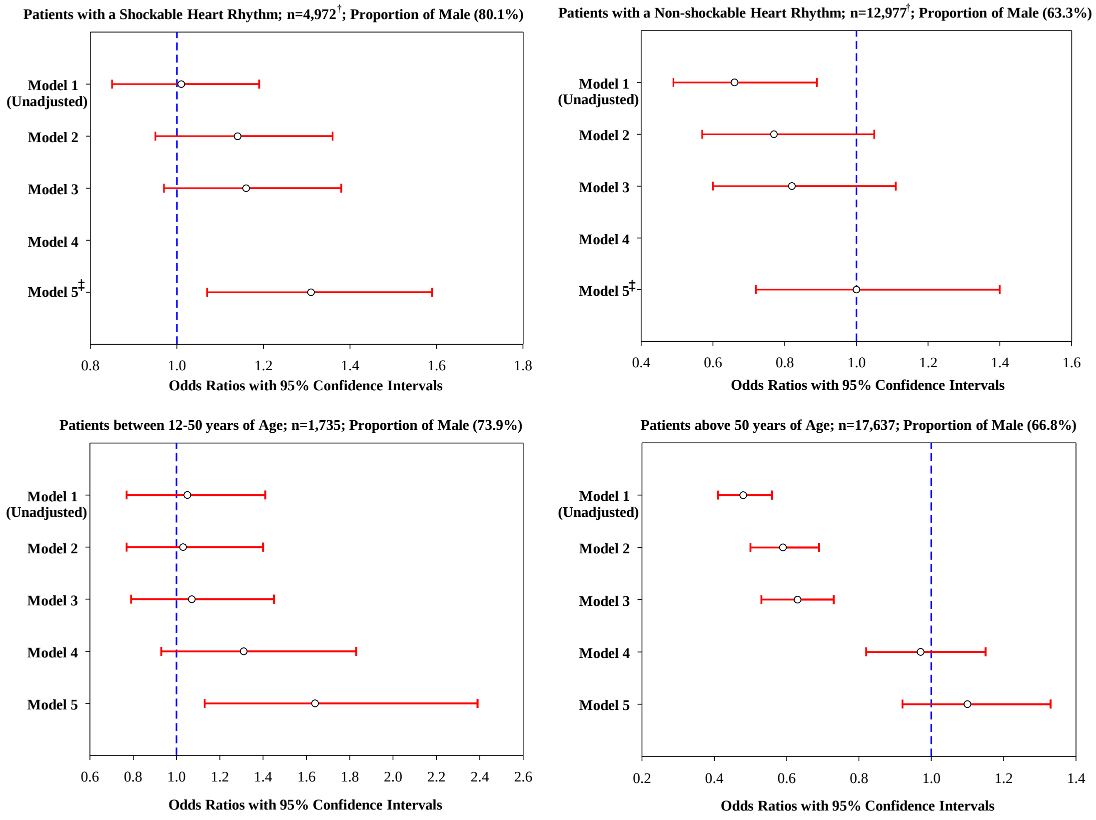

Long-term Survival in Relation to Sex
30-day survival in males
1-year survival in males
30-day survival in females
1-year survival in females
Percentage
16
14
12
10
8
6
4
2
0
2000
2002
2004
2006
2008
2010
Year
*
*
*
*
*p<0.001

Figure 5

Logistic Regression Analysis of Association Between Sex and 30-day Survival*
reference group: male patients (blue line)



*Analyses with imputed datasets. Odds ratio >1.00 indicates that female sex is positively associated with 30-day survival.
Model 2: Adjusted for age.
Model 3: Adjusted for age and comorbidities: MI, ischemic heart disease (MI excluded), cardiac dysrhythmia, heart failure, cerebral vascular disease, peripheral vascular disease, diabetes, COPD, and malignancy.
Model 4: Adjusted for age and comorbidities listed in Model 3 and first recorded heart rhythm.
Model 5: Adjusted for factors listed in Model 4 and calendar-year, civil status, location of arrest, witnessed status, whether bystander CPR and bystander defibrillation were initiated, and time interval from recognition of OHCA to rhythm analysis by emergency medical service.
†Only patients with observed information on first recorded heart rhythm were included in these analyses (n=1,423 patients were excluded due to missing data).
‡Adjusted for factors listed in Model 5 except for first recorded heart rhythm.
CI indicates confidence interval; COPD, chronic obstructive pulmonary disease; CPR, cardiopulmonary resuscitation; MI, myocardial infarction; OHCA, out-of-hospital cardiac arrest.

Paper III:
Survival after Out-of-Hospital Cardiac Arrest in Relation to Age and Early Identification of Patients with Minimal Chance of Long-term Survival

Importance: In Denmark between 2001 and 2010 survival after OHCA has increased, yet the impact of patient age on changes in survival remains unknown. Older patient age is associated with poor survival; early identification of patients with minimal chance of 30-day survival could be helpful regarding when to terminate resuscitative efforts.

Objective: To examine age-related differences in survival during an 11-year study period and identify patients with a minimal chance of 30-day survival.

Design, Setting, and Participants: Patients with OHCA for whom resuscitation was attempted were identified between 2001 and 2011, in the nationwide Danish Cardiac Arrest Registry. Of 32,757 patients with cardiac arrests, we excluded patients aged <18 years (n=348), arrests of a presumed non-cardiac cause (n=8,607), and arrests witnessed by EMS personnel (n=2,536), leaving a final study population of 21,480 patients. Patients were then divided into three pre-selected age groups: "working-age patients" aged 18–65 years (33.7%), "early-senior patients" aged 66–80 years (41.5%), and "late-senior patients" aged >80 years (24.8%).

Main Outcome and Measures: Main outcome measures included temporal changes in ROSC upon arrival at the hospital and 30-day survival according to pre-selected age groups, and 30-day survival rates in patients considered to have a minimal chance of 30-day survival.

Results: Characteristics in working-age patients, early-senior patients, and late-senior patients were as follows: witnessed arrest 53.8%, 51.1%, and 52.1%; bystander CPR 44.7%, 30.3%, and 23.4%; median time-to-rhythm analysis by EMS personnel 11 minutes, 11 minutes, and 12 minutes; shockable rhythm as a first-recorded heart rhythm 36.7%, 26.5%, and 17.9%; and pre-hospital shock from a defibrillator 54.7%, 45.0%, and 33.8%, respectively, all $p<0.05$. Comorbidity and use of medicine is displayed in Supplementary Table 2 (page 70). Patients who had achieved ROSC upon hospital arrival increased over time: working-age patients 12.1% (2001) to 34.6% (2011); early-senior patients 6.4% (2001) to 21.5% (2011); and late-senior patients 4.0% (2001) to 15.0% (2011), all $p<0.001$ (Figure 6). Furthermore, 30-day survival increased: working-age patients 5.8% (2001) to 22.0% (2011), $p<0.001$; and early-senior patients 2.7% (2001) to 8.4% (2011) $p<0.001$; while late-senior patients only experienced a minor increase 1.5% (2001) to 2.0%

(2011), p=0.01 (Figure 7). A similar tendency was observed when stratifying patients into shorter age intervals (Supplementary Figure 4, page 75), as well as when stratifying patients according to the first recorded heart rhythm (Supplementary Figure 5, page 76). Consequently, 30-day survival rate in those late-senior patients who had achieved ROSC upon hospital arrival decreased significantly over time, while 30-day survival was without any significant change over time in working-age and early-senior ROSC patients (Figure 8). Three out of 9499 patients achieved 30-day survival if they met two criteria: (1) had not achieved ROSC upon hospital arrival; and (2) had not received a pre-hospital shock from a defibrillator. The three 30-day survivors were equally distributed with one survivor in each of the pre-selected age groups: working-age patients 1/2683 (0.04%), early-senior patients 1/4047 (0.02%), and late-senior patients 1/2769 (0.04%).

Conclusions and Relevance: All three age groups experienced a large temporal increase in ROSC upon arrival at the hospital, but the temporal increase in 30-day survival was most prominent in the young. Using only two pre-hospital criteria, it was possible to retrospectively identify patients with almost no chance of 30-day survival irrespective of age; this may be helpful in the decision-making process regarding when to terminate resuscitative efforts.

Figure 6

Bystander CPR and ROSC on Arrival at the Hospital Following Out-of-Hospital Cardiac Arrest, 2001–2011

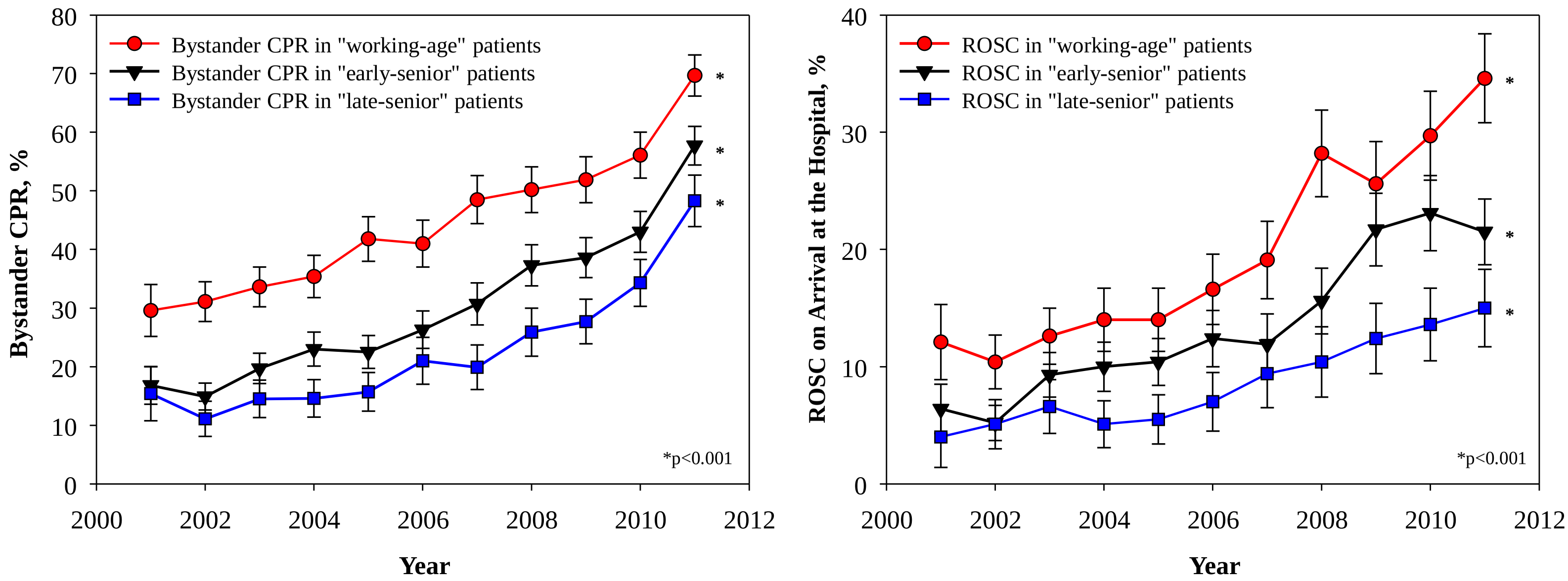
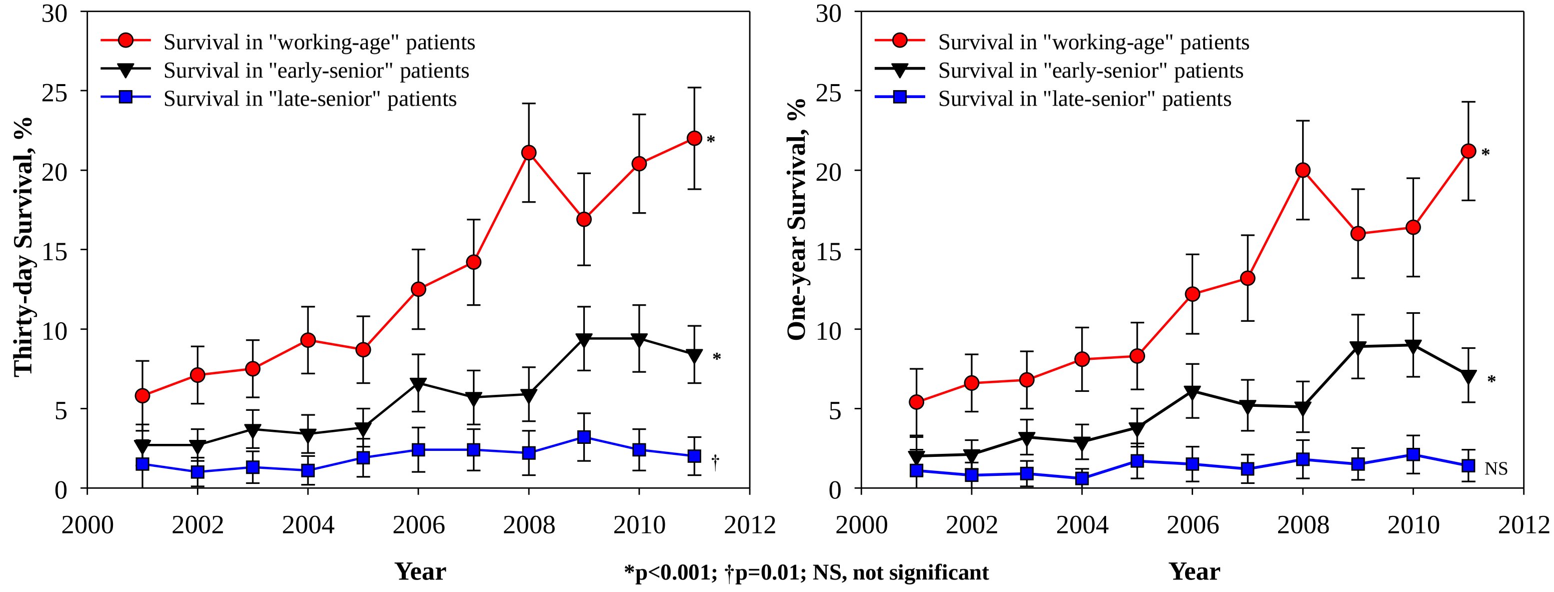


Figure 7

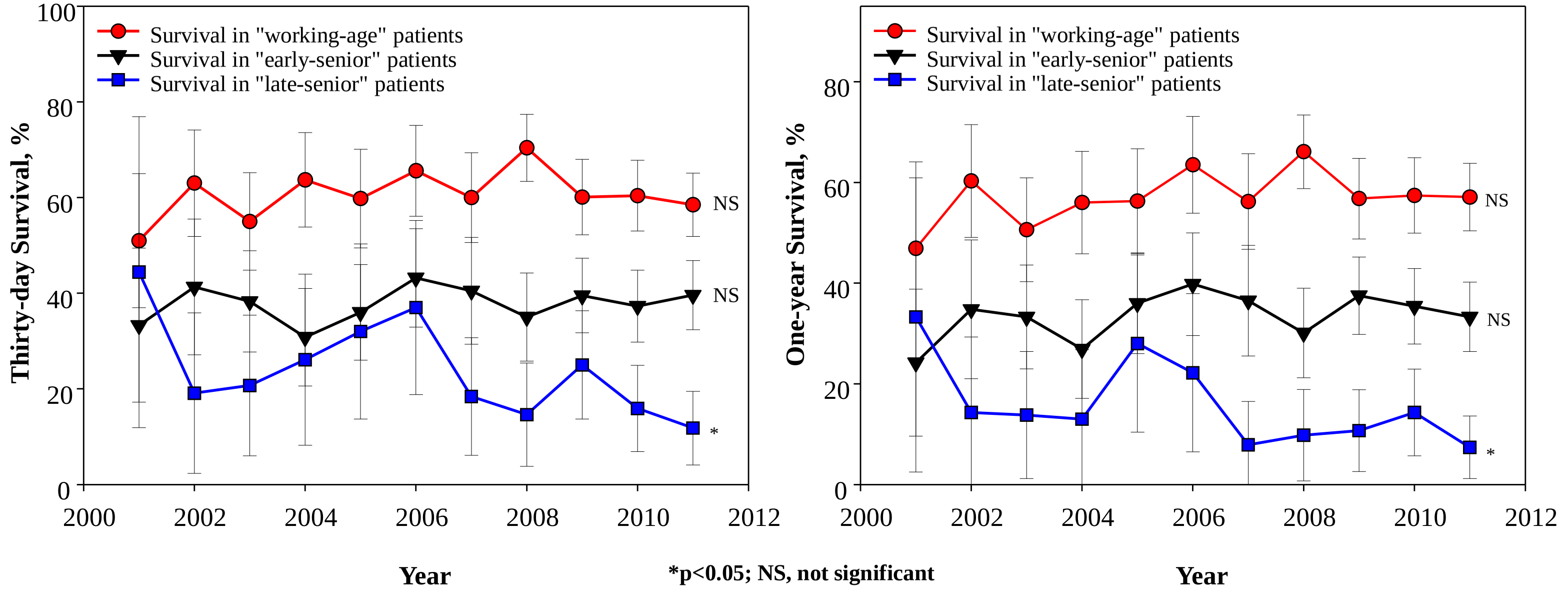
Thirty-day Survival and 1-year Survival Following Out-of-Hospital Cardiac Arrest, 2001–2011



***p<0.001; †p=0.01; NS, not significant**

Figure 8

Thirty-day and 1-year Survival in ROSC Patients, 2001–2011



***p<0.05; NS, not significant**

DISCUSSION

In this thesis, we investigated temporal trends in bystander resuscitation attempts and patient survival during a 10-year period where several national initiatives were implemented to improve cardiac arrest management in Denmark. We used a registry-based approach; from the nationwide Danish Cardiac Arrest Registry we identified about 20,000 patients with a presumed cardiac-caused OHCA where resuscitation was attempted. Our studies showed a temporal increase in bystander CPR and patient survival following OHCA; percentages of both measures more than doubled and the increase was consistent in absolute numbers.

The temporal increase in survival on hospital arrival was comparable between males and females; however, the increase in 30-day survival was more marked in male patients due to poorer prognostic characteristics in females. All age groups experienced a large temporal increase in survival on arrival at the hospital, yet the increase in 30-day survival was most prominent in the youngest and numerically negligible in patients aged >80 years; a similar tendency was observed when stratifying patients into shorter age intervals. Finally, using only two pre-hospital criteria, it was possible to identify patients with 30-day survival close to none, irrespective of patient age.

Paper I generally indicates that the national initiatives taken to increase and improve bystander resuscitation attempts have had a positive impact on cardiac arrest management in the pre-hospital setting, with an increase in patient survival. During the period studied, there have also been changes in hospital management of cardiac arrest survivors, which may have contributed to improved long-term survival. In fact, some of the improvements could be due to increased attention on treatment of ROSC patients following the various initiatives. For instance, the introduction of therapeutic hypothermia in Denmark changed practice; current national guidelines recommend that prognostication of ROSC patients, selected for therapeutic hypothermia, should not be performed until > 72 hours after rewarming.[93] Hence, it is recommended that neurologic evaluation followed by decision-making regarding continuation or withdrawal of therapy should be postponed to 96 hours after initiation of therapeutic hypothermia. This recommendation also includes cases that are initially considered to have a poor prognosis. Consequently, such systematic regimen, with treatment efforts for a minimum of 96 hours in an intensive care unit, could help ensure that care is not interrupted prematurely. Such change in attitude in treatment of ROSC patients may, in itself, have contributed to improved long-term survival.

The large temporal increase in bystander CPR shown in Paper I is most likely due to the overall growing level of attention to bystander resuscitation in

Denmark, including a rise in both mandatory and voluntary first aid training, with an estimate of more than 15% of the Danish population having taken CPR courses between 2008 and 2010.[58] This figure is based on the number of first aid certificates distributed from organizations conducting first aid courses in Denmark; it is estimated that the number of Danish citizens who completed CPR training increased from approximately 175,000 citizens annually between 2001 and 2004, to approximately 300,000 citizens annually between 2008 and 2010 (~5% of the overall population annually).[58] In addition, a significant proportion of children were trained in elementary schools. The distribution of about 150,000 CPR training kits between 2005 and 2010[59] could also have made an impact and contributed to widespread CPR training, as previous studies have shown that, on average, such training kits are used by 2.5 persons and are equally effective in teaching laypersons basic life-support as compared to a 6-hour first aid course with an instructor.[94,95] The training kits and contents have been described in detail elsewhere.[94] Taken together, it appears that widespread education and training on resuscitation in the Danish population have increased the awareness and attention on resuscitative efforts in case of a cardiac arrest, indicating that the sum of the initiatives has made an early impact on bystander CPR rates. Other studies also support the concept that systematic educational and training efforts can increase bystander CPR rates.[8,10,11,46-53]

In relation to survival, the large temporal increase in bystander CPR in conjunction with the large temporal increase in patients that had achieved survival upon hospital arrival, is a strong indicator of improvements made in pre-hospital settings. Thirty-day survival and 1-year survival also increased, which likely reflects improvements in both pre-hospital and in-hospital settings, including the strengthening of the EMS system and advanced care. As a result, the reason for increased survival is probably multifactorial and is most likely related to improvements in each of the links in the chain of survival,[2-4,24,25] as well as other factors that influence survival.[70] This notion is supported by the observation that 30-day survival increased among patients with and without bystander CPR. Consequently, bystander CPR was only one important factor among many associated with good outcomes. Yet survival rates remained low for patients without bystander CPR, and the large increase in 30-day survivors over time was primarily observed in patients who had received bystander CPR. Our study design does not allow any conclusion to be drawn related to which specific factors have contributed most to the increase in survival over time, but the very parallel time course for the increase in bystander CPR and survival, together with the largely positive association between bystander CPR and survival, may suggest a positive effect of increasing bystander CPR rates on survival, although this cannot be confidently concluded with the observational data presented. Nevertheless, these findings are supported by other studies within this field and strengthen the notion that a causal relationship exists between an increase in bystander resuscitative efforts and an increase in patient survival.[8,47,48,54-57]

Paper II took the findings in Paper I into consideration and further examined the temporal increase in bystander resuscitation attempts and patient survival in relation to patient sex. This study demonstrated how OHCA cases were fairly different in relation to sex with significant sex-related difference in patient characteristics. Accordingly, female patients were more likely to: (1) be older than male patients; (2) have more severe comorbidities; (3) have a cardiac arrest in a private home; (4) not receive bystander CPR; and (5) have a non-shockable rhythm as the first recorded heart rhythm. These findings are in agreement with a variety of other epidemiological studies demonstrating poorer prognostic characteristics in females;[61-69] however, the present finding that sex-related differences in comorbidities added to the lower survival in females is a new insight. From this perspective, female patients were more likely to have a history of chronic obstructive pulmonary disease, cancer, and psychiatric illness, while male patients more frequently had a history of cardiovascular disease. The sex-related differences in comorbidities were also reflected in the use of medicine. Hence, female patients were more likely to use bronchial dilators, systemic corticosteroids, analgesics, and psychiatric medication including sedatives/anxiolytics. Taken together, with poor prognostic characteristics being associated with female sex, it was not a surprise that 30-day and 1-year crude survival remained lower in females compared to males. By performing multivariable logistic regression analyses, we demonstrated how the sex-related differences in patient characteristics were important for lower crude survival in females. As a result, when taking the differences in patient characteristics into account in fully adjusted models, there was no longer survival difference between the sexes among patients with a non-shockable rhythm, while female sex was positively associated with survival among patients with a shockable rhythm. Other studies have also shown female sex to be associated with improved survival,[61-69] especially in patients of reproductive age.[64,66,67] Some researchers have suggested that female sex hormones could be the underlying factor for such a finding.[63-67] This notion is supported by animal studies, in which the endogenous estrogen production in females has been demonstrated to be neuroprotective[96] and cardioprotective.[97] Also, myocardial remodeling appears to be more favourable in females after injury to the myocardium.[98] In our study, the strongest positive association between female sex and 30-day survival was found in patients between 12 and 50 years of age (fully adjusted models) and supports the notion that female sex hormones could be a positive factor associated with survival. However, our study design does not allow us to conclude further on this subject, and other factors, like specific cause of arrest, could be of importance.

An interesting finding was that bystander CPR rates were nearly 10% lower in female patients—even in the subset of cases with witnessed arrest, and the difference being even larger in witnessed arrest outside of a private home (Supplementary Material in Paper II). One possible explanation for this finding could be that bystanders, to a higher extent, associate male collapses with cardiac arrest, whereas female collapses are associated with more benign conditions like syncope, thereby risking a delay (or total absence) of cardiac arrest recognition in females in case of a collapse. However, more studies, including qualitative studies of how bystanders think and act in the case of cardiac arrest, are needed to confirm this notion. If confirmed, such lack of knowledge in cardiac arrest recognition should be addressed in CPR training.

Paper III showed how the temporal increase in long-term survival was less pronounced with increasing age, and practically failed in patients older than 80 years. The patients' pre-arrest condition (physiologic reserve and comorbidity) could be an explanation of why long-term survival remained low in late-senior patients. With more than a three-fold increase in the number of patients who had achieved ROSC upon hospital arrival over time, it is very likely that the long-term survival potential in these additional ROSC patients have been lower, leading towards little to no temporal change in 30-day and 1-year survival in late-senior patients. This notion is supported by the overall decreasing trend of initial shockable rhythm in admitted ROSC patients over time (Supplementary Material in Paper III). In relation to this, the fairly stable proportion of ROSC patients achieving 30-day and 1-year survival over time in working-age and early-senior patients (despite a tripling of the numbers of admitted ROSC patients with a likely increase in poor ROSC patients over time) could be interpreted as an improvement and may involve factors both prior to and after hospitalization. This notion is also supported by the temporal decrease in rates of anoxic brain damage in working-age survivors (Figure 7 in Paper III), which generally must be considered an encouraging finding. The even lower rate of anoxic brain damage in senior survivors was not surprising since this probably reflects how these senior patients were more susceptible to critical illness with a higher risk of dying during hospitalization, therefore only leaving a few, but good-conditioned, long-term survivors. Notably, other studies support the notion that most older-aged OHCA survivors are in acceptable health.[74,82,83,99]

An interesting secondary finding was the large increase in bystander CPR rates in the last year of the study period (2011). The observed increase in bystander CPR rates during the entire study period probably reflects the sum of all initiatives that have been taken to increase resuscitative efforts from bystanders, including widespread CPR training.[100] However, in recent years there has been an increasing focus on the employment of healthcare professionals at emergency dispatch centers in order to improve the telephone-assisted resuscitation guidance to the alarm caller. The employment of healthcare professionals was introduced in 2009, but was first fully implemented on a nationwide scale in May 2011; therefore, this specific initiative could have contributed to the large increase in bystander CPR rates in 2011.

Clinicians are sometimes faced with the dilemma of whether to continue or terminate resuscitative efforts. These complicated decisions are often made within seconds or minutes, and are frequently based solely on a clinician's prediction of survival outcome in the individual suffering a cardiac arrest. Survival prediction can be very complex and difficult to determine. In order to overcome these challenges and to standardize the decision-making process, it has been extensively investigated and discussed whether it is possible, early in the process, to identify patients where a resuscitation attempt is considered futile.[77-81] Several proposals have emerged, with one suggestion being the TOR rule by Verbeek et al.[80] This TOR rule is based on three pre-hospital criteria: (1) "there has been no ROSC"; (2) "no shock has been given"; and (3) "the arrest was not witnessed by EMS personnel."[80] Inspired by this rule, we retrospectively selected patients to be considered for TOR if two criteria were fulfilled: (1) no ROSC upon hospital arrival; and (2) no pre-hospital shock from a defibrillator. The third criterion by Verbeek et al. was already fulfilled, since the EMS-witnessed arrests were excluded in this study; this is an important aspect which overall ensures a reasonable amount of time to use a defibrillator or achieve ROSC in the pre-hospital setting. Taken together, these criteria identified patients with no chance of 30-day survival fairly well, irrespective of patient age. The three out of 9499 patients who did survive the criteria illustrate how it is always possible to construct or observe a scenario where following a guideline can be questionable, and demonstrates the obvious limitations related to extrapolation from group findings to individual cases. Even though TOR guidelines should never overrule clinical judgment or replace efforts to improve handling and treatment in the uttermost vulnerable cases, knowledge concerning cardiac arrest patients with minimal chance of survival may be useful in the decision-making process regarding when to terminate a resuscitation attempt.

Incidence Rates and Case Definition

In the three studies constituting this thesis, the incidence of treated OHCA of a presumed cardiac cause was about 36 per 100,000 person-years and is fairly close to the corresponding calculated mean incidence in Europe, which is estimated to be 35 per 100,000 person-years.[12] Therefore, major underreporting seems unlikely, even though we observed a decrease in the incidence of cardiac arrests over time. This decline could be due to improvements in primary and secondary prevention in Denmark, where the overall annual mortality rate is decreasing,[101] including the incidence and mortality rate of patients with first time acute myocardial infarction.[102] Such reduction in incidence and mortality could have made an impact since our study, as well as previous studies, have shown that the majority of OHCA are of a presumed cardiac cause.[8,9] On the other hand, the number of OHCA patients (all-cause) only constitutes approximately 6% of all deaths[98] (each year around 55,000 persons die in Denmark).[101] Consequently, OHCA represents only a small fraction of all deaths and must be considered a highly combined event conditioned on multiple factors, in order to fulfill the definition (cardiac arrest located outside of a hospital, and a resuscitation attempt). Hence, fulfilling the definition is closely related to several factors like the patient's pre-arrest medical condition (including do not attempt resuscitation order), civil status, location of cardiac arrest, whether people are present nearby or arrive shortly after collapse, and whether people recognize the cardiac arrest and act with an alarm call. All of these factors could differ over time and add to the variation in OHCA incidence, since they are key elements for whether EMS is attending, whether resuscitative efforts are given, and as a result, whether the OHCA event is registered. Another important aspect is a possible delay in the delivery of case reports to the registry, which naturally leads to a decline in incidence of cardiac arrests, particularly with regard to the last year of the study period.

There is a risk of reporting bias in most studies, and particular temporal trend studies are sensitive to changing in reporting over time, with risk of an increasing underreporting of patients with the best or poorest outcomes over time. As a result, both the numerator and denominator are of importance when assessing temporal trends. To adjust for the possibility that the increased survival percentages over time could be driven by changes in reporting (increased underreporting of patients with poorest outcomes over time), we performed separate analyses focusing only on changes in absolute numbers of survivors (numerator) as dependent on population size (denominator), which did not change the main findings (Supplementary Figure 1, page 71-72). Therefore, we did not find any indication that the observed increase in survival over time was driven by changes in reporting.

OHCA comprised a low number of all deaths in Denmark, and several scenarios could account for this finding: patients who survived the OHCA event; patients with in-hospital cardiac arrest (not related to a prior OHCA); and patients with a "do not resuscitate order", i.e., terminally ill patients who are expected to die and prefer to die at home with no attempt of resuscitation. In addition, having an unexpected cardiac arrest alone without an attempt of resuscitation, combined with the OHCA definition (i.e., demands an attempt of resuscitation) could also be a central explanation for why OHCA only represents a small fraction of all deaths. In this way, many people probably die alone in private homes and are then found afterwards with obvious late signs of death. In these individuals, a resuscitation attempt is not performed, nor are they registered in the Danish Cardiac Arrest Registry. This scenario could also explain the lower incidence of reported female patients in our studies, since Danish females older than 60 years are more likely to live alone without a partner compared to males older than 60 years.[101] Further research is needed to illuminate this aspect more thoroughly, including data on inside hospital deaths versus outside hospital deaths.

Putting it All Together

Several national initiatives have been taken during the last decade in Denmark to improve cardiac arrest management, including widespread CPR training of the Danish population,[58,59] strengthening of the EMS system, and improvements in advanced care.[58,59] During the same time period, ROSC upon hospital arrival more than doubled, irrespective of patient sex and pre-selected age groups, together with more than a two-fold increase in bystander CPR rates. These findings generally indicate that the national initiatives taken to improve cardiac arrest management have had a positive impact in the pre-hospital setting for both female and male patients, as well as in the pre-selected age groups. The large temporal increase in long-term survival (overall, more than a three-fold increase) may also indicate that the national initiatives have made a positive impact on cardiac arrest management in the in-hospital setting. The temporal increase in long-term survival was less marked in female patients and numerically negligible in patients aged >80 years. One explanation for this could be that both females and older patients were associated with poorer prognostic characteristics. As a result, it is likely that the overall sex- and age-specific differences in pre-hospital factors have made male patients and the youngest patients more prone to benefit from improvements made in cardiac arrest management and subsequent survival, leading to improvements over time being more pronounced in these patient groups.

Notably, epidemiological studies such as ours cannot establish causality, but in a field of research with few randomized trials, we find it important to report these observational data which indicate that national initiatives taken to improve cardiac arrest management have increased patient survival. Along with other recent studies in this field, the current data provide further evidence that, even though OHCA is a devastating medical condition associated with a poor prognosis, systematic efforts to improve cardiac arrest management can have an impact on patient survival following a cardiac arrest.

Strengths and Limitations

This nationwide study has been possible to conduct due to the unique Danish civil registration number which makes individual-level linkage of data between nationwide registries possible. Most studies report on smaller geographical areas[12-17] and nationwide cardiac arrest studies are relatively rare,[20] but obviously of great importance for the external validation of the study, when extrapolating results to nationwide implications. Consequently, by using nationwide registries with a large sample size, we minimized the risk of selection bias due to differences in geographic and demographic factors. However, there are several important limitations that need to be addressed. First, the main limitation is that our studies are observational in nature; therefore, the relationship between variables represent associations—not causal relationships. Also, the national initiatives overlapped in time, and while data are suggestive of a positive effect of national initiatives including CPR training, the findings are largely ecological, and although supportive, they offer no direct causal link between initiatives and outcomes. Second, there is a risk of selection bias in relation to bystander intervention, so one could speculate that the largely positive association between bystander intervention (CPR and AED use) and survival is partly due to a higher degree of bystander intervention in patients with the best chance of survival even before intervention is initiated. For example, bystander CPR is positively associated with having a witnessed collapse, which is associated with a shorter response time, meaning that patients receiving bystander CPR more often also have the advantage of earlier recognition and faster EMS arrival. Such bias would lead to an overestimate of the association between bystander intervention and survival. This being said, we performed separate analyses and found that bystander CPR was positively associated with 30-day survival in both patients with a witnessed and a non-witnessed arrest. This is an important finding and suggests that the beneficial effects of bystander CPR are not entirely driven by earlier recognition of cardiac arrest with earlier alarm call and, therefore, faster arrival of EMS. Third, we were only able to analyze a limited number of covariates without data on several important factors including: the quality of CPR given; whether CPR was dispatcher-assisted; and detailed information on advanced treatment including therapeutic hypothermia, revascularization, etc. Accordingly, it was not possible to test whether these factors were different in relation to calendar year, patient sex, and patient age, and therefore, not possible to take these factors into account. In addition, our outcomes data was limited to simple information on short- and long-term survival (survival upon arrival at the hospital, 30-day survival, and 1-year survival) since we did not have qualitative data on more advanced outcome measurements, such as functional outcome and quality of life, including standardized neurological outcomes scores like the Cerebral Performance Category (CPC) score.[1] Overall, this must be considered an important limitation, yet we used discharge diagnosis codes to report new onset of anoxic brain damage in 1-year survivors. Rates with anoxic brain damage were relatively low, and could reflect that: (1) one-year survivors represent a favorable group of patients with fairly good neurological outcome; and (2) only patients with major cognitive impairment were coded with anoxic brain damage. The second notion could be an explanation of the low rates of brain damage in late-senior patients, since they might be subject to less aggressive neurological examination and testing. Nevertheless, other studies have shown good length and quality of life in survivors discharged from the hospital overall supporting the former notion: that only a minor proportion of long-term survivors after OHCA suffer from major cerebral-cognitive impairments.[9,21-23] Fourth, we initially excluded approximately 10% of the cardiac arrest patients, due to invalid or missing Civil Registration Number. Paper III (Supplementary Figure 5 and Supplementary Figure 6) showed how these missing data did not seem to affect the temporal changes in survival systematically, since the proportion of these patients with an invalid or missing Civil Registration Number was stable over time, nor were these patients associated with lower ROSC rates compared to patients with a valid Civil Registration Number. Moreover, a number of patients had missing data for the cardiac arrest-related variables; however, comparing estimates from the existing dataset (incomplete dataset containing missing data) with estimates from the imputed datasets (complete datasets with both observed and imputed data) did not change our main findings. Consequently, we did not find any indication that missing data influenced our main conclusions. Finally, despite the fact that data collection was consecutive, the more detailed and accurate decisions concerning the study design were conducted retrospectively. Nevertheless, the Danish Cardiac Arrest Registry was in place before the national initiatives described in this thesis were introduced.

Conclusion

The studies in the present thesis contribute novel and valuable information to the field of cardiac arrest. In Denmark, between the years of 2001 and 2011, several national initiatives were taken to improve cardiac arrest management. In the same period, there was a large increase in bystander CPR and patient survival following OHCA. The temporal increase in 30-day survival was more marked in male patients, due to poorer prognostic characteristics in females such as older age, severe comorbidities, less bystander intervention, and a lower proportion of a shockable rhythm. In relation to age, the temporal increase in 30-day survival was most prominent in the youngest, and was numerically negligible in patients aged >80 years. Finally, using only two pre-hospital criteria, it was possible to identify patients with a 30-day survival rate close to none, irrespective of patient age. This may be helpful in the decision-making process about when to terminate resuscitative efforts.

Although our study design does not allow us to determine how much each initiative has actually led to the changes observed, it is reassuring that the sum of the initiatives seems to have made an impact on patient survival, indicating that systematic national efforts to improve cardiac arrest management can result in improvement; however, because these data are observational, a causal relationship remains uncertain.

Implications and Future Research

The present findings encourage continued efforts to improve cardiac arrest management, with the ultimate goal of increasing survival after OHCA and improving the quality of life in survivors.

Even though there was a large increase in the number of bystanders who provided CPR, many cardiac arrest patients did not receive resuscitative efforts before ambulance arrival, and there is still a large potential to increase the use of AEDs located outside of the hospital. To further improve survival after OHCA, future strategies should focus on strengthening each of the links in the chain of survival with:

(1) Continued efforts to guide, educate, and train the population in resuscitative efforts. One strategy could be to: a) implement CPR and AED training as a permanent and systematic element (class scheduled) for elementary, middle, and high schools; and b) strengthen widespread CPR and AED training in the working-age population and among senior citizens through an increase in regular public courses, which could include web-based teaching in sports halls, senior centers, yearly training programs at work, etc.

(2) Continued efforts to increase the dissemination of AEDs placed outside of the hospital together with AED registration to the Public Access Defibrillation program "hjertestarter.dk"; the latter to ensure a quick easy guide to the nearest available AED in case of cardiac arrest, as well as enable strategic placement of AEDs at places with high risk of OHCA and at places with long EMS response intervals. Implementation of first responder programs could also be important tools to increase accessibility and use of public AEDs.

(3) Continued efforts to strengthen advanced treatment (in both pre- and in-hospital settings) and post-resuscitation care, including rehabilitation of survivors; this through research with updates of clinical guidelines, together with frequent and systematic education and training of the health care personnel.

(4) Continued efforts to systematically collect cardiac arrest data, as well as data related to various initiatives and interventions. Knowledge concerning changes over time and possible impact of efforts is important in order to be able to target the most appropriate future initiatives and interventions.

Looking to the future, we need more studies. In particular, we need more studies to answer: (1) Do continuous efforts to educate and train the population in resuscitative efforts increase bystander CPR rates further? And how will further increases in bystander CPR rates effect patient survival? Also, will improved AED dissemination translate into increased AED use, and how this will effect survival outcome?; (2) How are the changes over time reflected in different patient groups and different geographic locations in Denmark, and which patient characteristics and geographic characteristics might explain differences in improvement over time?; and (3) Do similar public initiatives in other countries and regions, with potentially different population densities, comorbidities, public health, and health care systems, encourage similar changes in bystander CPR and patient survival?

Taken together, we need to understand how initiatives that are implemented to improve cardiac arrest management are actually associated with changes in survival overall, and in relation to different settings and patient groups. Improving the understanding of these relationships might help optimize available resources and tailor efforts to improve cardiac arrest management in the best way, so ultimately, more lives can be saved.

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APPENDICES

Supplementary Tables

Supplementary Table 1

Treatment at hospital up to 10 years before cardiac arrest and patient's pharmacotherapy up to 180 days before cardiac arrest.

	Female $n = 6318$	Male $n = 13{,}054$	p-Value[*]	All Patients $n = 19{,}372$
Comorbidity, n (%)				
Peripheral vascular disease	595 (9.4)	1447 (11.1)	<0.001	2042 (10.5)
Cerebral vascular disease	790 (12.5)	1628 (12.5)	0.94	2418 (12.5)
Ischemic heart disease (MI excluded)	1286 (20.4)	3709 (28.4)	<0.001	4995 (25.8)
Myocardial infarction	675 (10.7)	1842 (14.1)	<0.001	2517 (13.0)
Cardiac dysrhythmia	1124 (17.8)	2562 (19.6)	0.002	3686 (19.0)
Heart failure	1248 (19.8)	2813 (21.6)	0.004	4061 (21.0)
Diabetes	883 (14.0)	1982 (15.2)	0.03	2865 (14.8)
COPD	1040 (16.5)	1672 (12.8)	<0.001	2712 (14.0)
Malignancy	742 (11.7)	1399 (10.7)	0.03	2141 (11.1)
Renal disease	208 (3.3)	585 (4.5)	<0.001	793 (4.1)
Liver disease	139 (2.2)	252 (1.9)	0.21	391 (2.0)
Peptic ulcer	617 (9.8)	1022 (7.8)	<0.001	1639 (8.5)
Rheumatic disease	241 (3.8)	245 (1.9)	<0.001	486 (2.5)
Psychiatric illness	1090 (17.3)	1584 (12.1)	<0.001	2674 (13.8)
Pharmacotherapy, n (%)				
Antithrombotic agents	2572 (40.7)	5932 (45.4)	<0.001	8504 (43.9)
Cholesterol lowering drugs	1101 (17.4)	3196 (24.5)	<0.001	4297 (22.2)
Calcium inhibitors	1265 (20.0)	2375 (18.2)	0.002	3640 (18.8)
Beta-blockers	1541 (24.4)	3523 (27.0)	<0.001	5064 (26.1)
ACEi/ARB	1970 (31.2)	4827 (37.0)	<0.001	6797 (35.1)
Diuretics	3195 (50.6)	5366 (41.1)	<0.001	8561 (44.2)
Digoxin	873 (13.8)	1890 (14.5)	0.22	2763 (14.3)
Anti-angina medication	732 (11.6)	1689 (12.9)	0.008	2421 (12.5)
Glucose lowering medication	785 (12.4)	1779 (13.6)	0.02	2564 (13.2)
Bronchial dilators	1377 (21.8)	2172 (16.6)	<0.001	3549 (18.3)
Corticosteroids (systemic)	829 (13.1)	1141 (8.7)	<0.001	1970 (10.2)
Antidepressants	1593 (25.2)	1683 (12.9)	<0.001	3276 (16.9)
Sedatives/anxiolytics	2239 (35.4)	2713 (20.8)	<0.001	4952 (25.6)
Anti-psychotic medication	752 (11.9)	720 (5.5)	<0.001	1472 (7.6)
Analgesics[a]	3198 (50.6)	4394 (33.7)	<0.001	7592 (39.2)

ACEi indicates angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; COPD, chronic obstructive pulmonary disease; MI, myocardial infarction; SD, standard deviation.

[*] Test for differences between the sexes. A p-value <0.05 was considered to be statistically significant.

[a] Including nonsteroidal anti-inflammatory drugs (NSAIDs), other analgesics, antipyretics, and opioids.

Supplementary Table 2

Discharge Diagnoses from Hospital up to 10 Years before Cardiac Arrest and Patient's Use of Medicine up to 180 Days before Cardiac Arrest

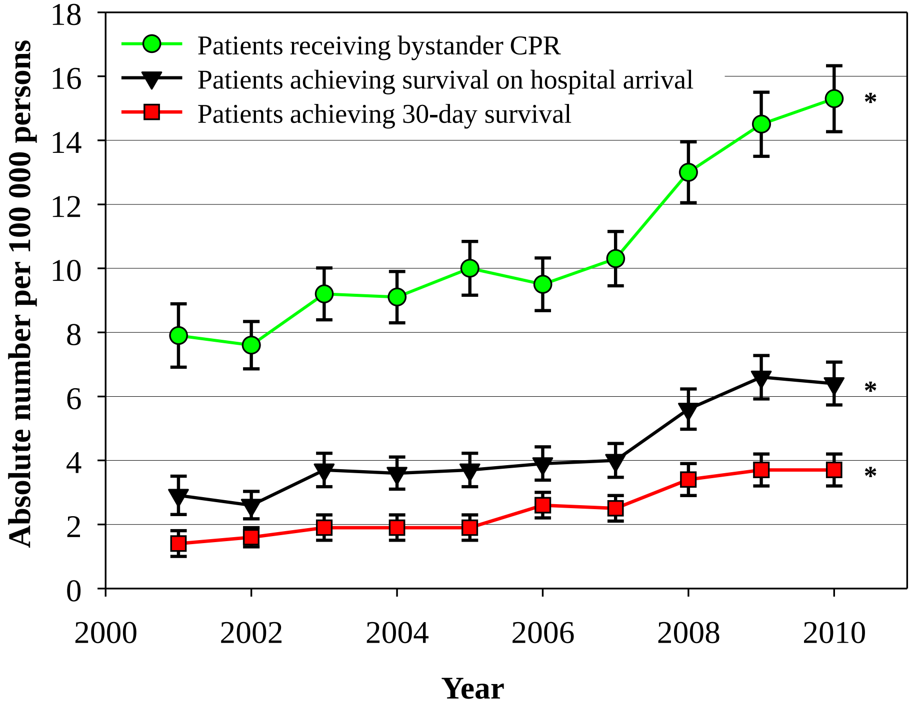
	Working-Age* n=7,227	Early-Senior* n=8,919	Late-Senior* n=5,334	p-value†	All patients n=21,480
Comorbidity, n (%)					
Peripheral vascular disease	501 (6.9)	1,205 (13.5)	610 (11.4)	<0.001	2,316 (10.8)
Cerebral vascular disease	516 (7.1)	1,280 (14.4)	913 (17.1)	<0.001	2,709 (12.6)
Ischemic heart disease (MI excluded)	1,312 (18.2)	2,641 (29.6)	1,603 (30.1)	<0.001	5,556 (25.9)
Myocardial infarction	631 (8.7)	1,232 (13.8)	904 (17.0)	<0.001	2,767 (12.9)
Cardiac dysrhythmia	732 (10.1)	1,902 (21.3)	1,543 (28.9)	<0.001	4,177 (19.5)
Heart failure	949 (13.1)	2,075 (23.3)	1,507 (28.3)	<0.001	4,531 (21.1)
Diabetes	1,041 (14.4)	1,540 (17.3)	708 (13.3)	<0.001 0.28 (trend)	3,289 (15.3)
COPD	575 (8.0)	1,665 (18.7)	816 (15.3)	<0.001	3,056 (14.2)
Malignancy	476 (6.6)	1,127 (12.6)	814 (15.3)	<0.001	2,417 (11.3)
Renal disease	234 (3.2)	422 (4.7)	270 (5.7)	<0.001	926 (4.3)
Liver disease	261 (3.6)	154 (1.7)	29 (0.5)	<0.001	444 (2.1)
Peptic ulcer	490 (6.8)	762 (8.5)	555 (10.4)	<0.001	1,807 (8.4)
Rheumatic disease	93 (1.3)	275 (3.1)	169 (3.2)	<0.001	537 (2.5)
Psychiatric illness	1,275 (17.6)	1,013 (11.4)	752 (14.1)	<0.001	3,040 (14.2)
Dementia	56 (0.8)	301 (3.4)	447 (8.4)	<0.001	804 (3.7)
Pharmacotherapy, n (%)					
Antithrombotic agents	1,909 (26.4)	4,606 (51.6)	3,057 (57.3)	<0.001	9,572 (44.6)
Cholesterol lowering drugs	1,468 (20.3)	2,669 (29.9)	920 (17.3)	<0.001 0.03 (trend)	5,057 (23.5)
Calcium inhibitors	989 (13.7)	1,926 (21.6)	1,170 (21.9)	<0.001	4,085 (19.0)
Beta-blockers	1,532 (21.2)	2,638 (29.6)	1,602 (30.0)	<0.001	5,772 (26.9)
ACEi/ARB	2,069 (28.6)	3,686 (41.3)	1,901 (35.6)	<0.001	7,656 (35.6)
Diuretics	1,926 (26.7)	4,257 (47.7)	3,357 (62.9)	<0.001	9,540 (44.4)
Digoxin	468 (6.5)	1,368 (15.3)	1,159 (21.7)	<0.001	2,995 (13.9)
Anti-angina medication	439 (6.1)	1,183 (13.3)	1,038 (19.5)	<0.001	2,660 (12.4)
Glucose lowering medication	934 (12.9)	1,410 (15.8)	607 (11.4)	<0.001 0.08 (trend)	2,951 (13.7)
Bronchial dilators	949 (13.1)	2,052 (23.0)	966 (18.1)	<0.001	3,967 (18.5)
Corticosteroids(systemic)	421 (5.8)	1,130 (12.7)	609 (11.4)	<0.001	2,160 (10.1)
Antidepressants	1,048 (14.5)	1,544 (17.3)	1,129 (21.2)	<0.001	3,721 (17.3)
Sedatives/anxiolytics	1,478 (20.5)	2,358 (26.4)	1,555 (29.2)	<0.001	5,391 (25.1)
Anti-psychotic medication	650 (9.0)	610 (6.8)	369 (6.9)	<0.001	1,629 (7.6)
Analgesics‡	2,284 (31.6)	3,633 (40.7)	2,593 (48.6)	<0.001	8,510 (39.6)

*Patients were divided into three pre-selected age groups: working-age-patients aged 18–65 years; early-senior-patients aged 66–80 years; and late-senior-patients aged >80 years.
†Chi-square test for differences between the age groups. In addition, the Cochran–Armitage test was used to test for trends in binary variables according to age groups. P-value for trend is indicated if different from Chi-square test. A p-value <0.05 was considered to be statistically significant.
‡Including NSAIDs, other analgesics, antipyretics, and opioids.
Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; COPD, chronic obstructive pulmonary disease; MI, myocardial infarction; NSAIDs, nonsteroidal anti-inflammatory drugs; SD, standard deviation

Supplementary Figures

Supplementary Figure 1a

Bystander CPR, Survival on Arrival at the Hospital, and 30-day Survival, 2001-2010

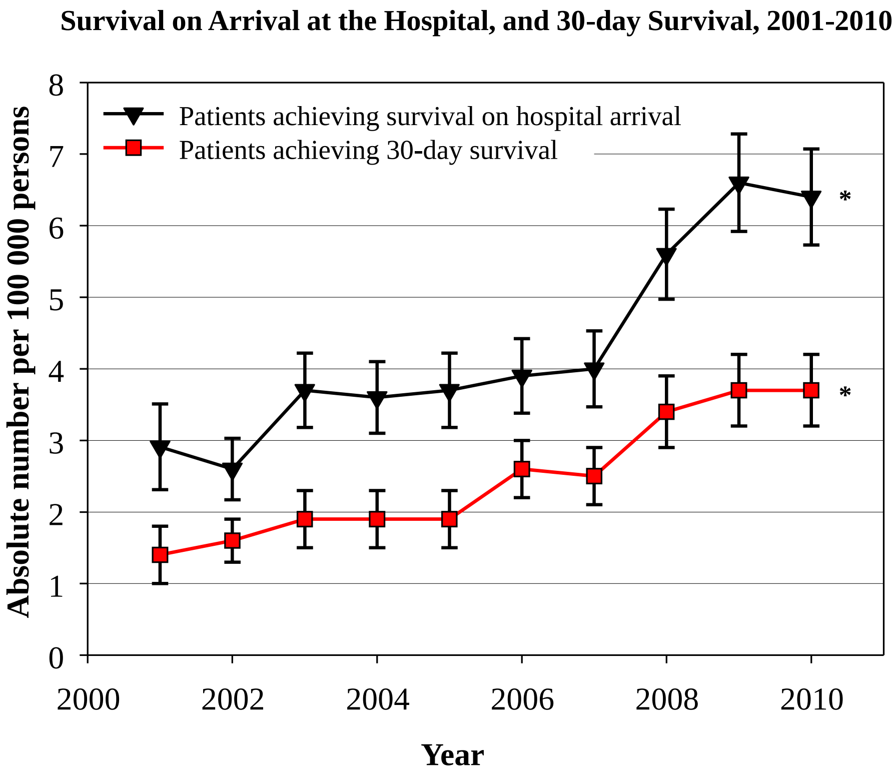


Bystander CPR, Survival on Arrival at the Hospital, and 30-day Survival, 2001-2010

Temporal trends in numbers of patients receiving bystander CPR and achieving survival on hospital arrival and 30-day survival. Changes over time were tested; a two-sided p-value <0.05 was considered to be statistically significant.

*p<0.001

Supplementary Figure 1b



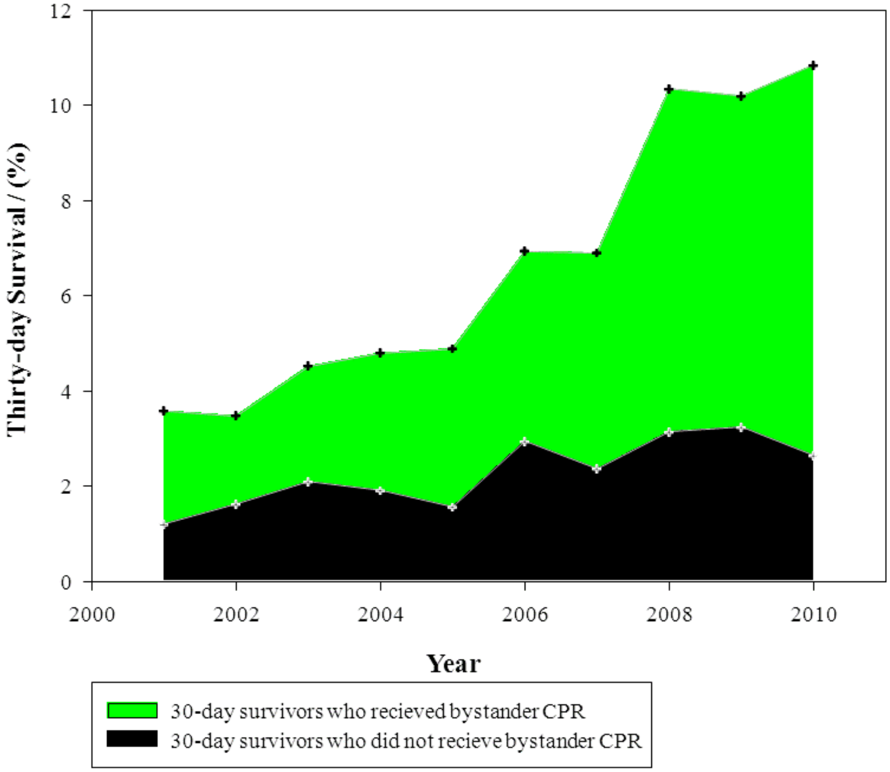
Survival on Arrival at the Hospital, and 30-day Survival, 2001-2010

Temporal trends in numbers of patients achieving survival on hospital arrival and 30-day survival. Changes over time were tested; a two-sided p-value <0.05 was considered to be statistically significant.

*p<0.001

Supplementary Figure 2

Proportion of patients who had received bystander CPR among 30-day survivors



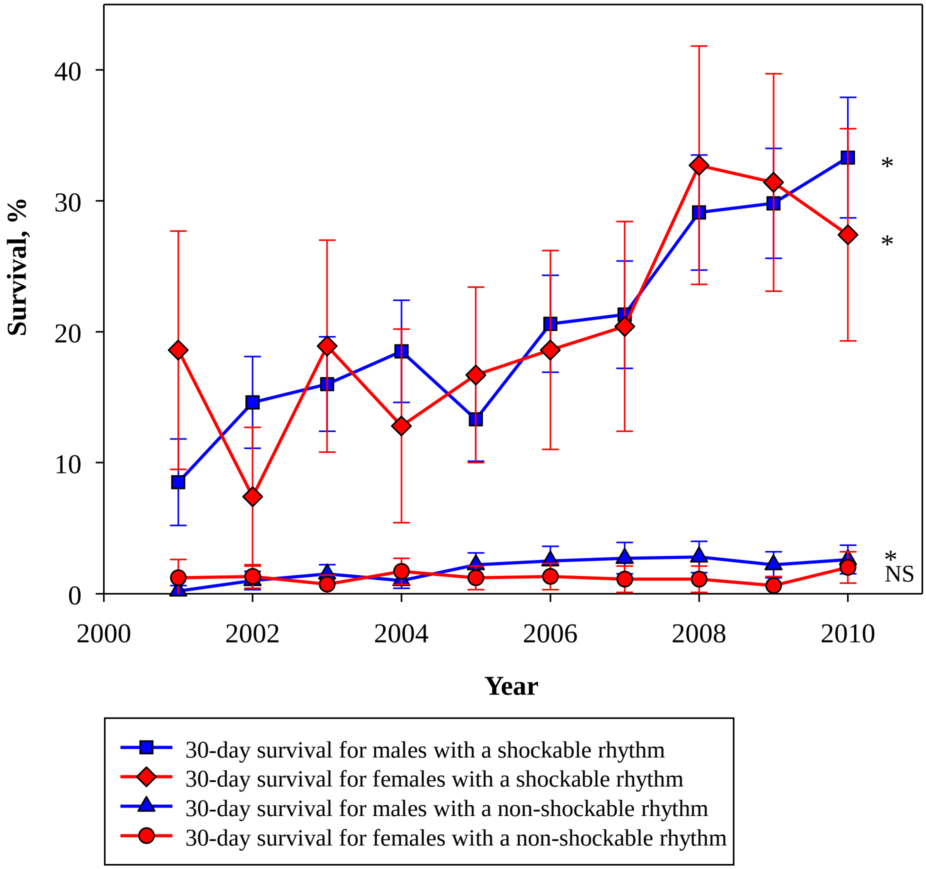
Proportion of patients who had received bystander CPR among 30-day survivors

Percentage of patients achieving 30-day survival according to calendar year with survivors stratified according to whether bystander CPR was given. Patients with missing data for whether bystander CPR was given were excluded in the analysis (n=1193 [6.1%]).

Abbreviations: CPR, cardiopulmonary resuscitation

Supplementary Figure 3

Thirty-day Survival in Relation to Sex and First Recorded Heart Rhythm



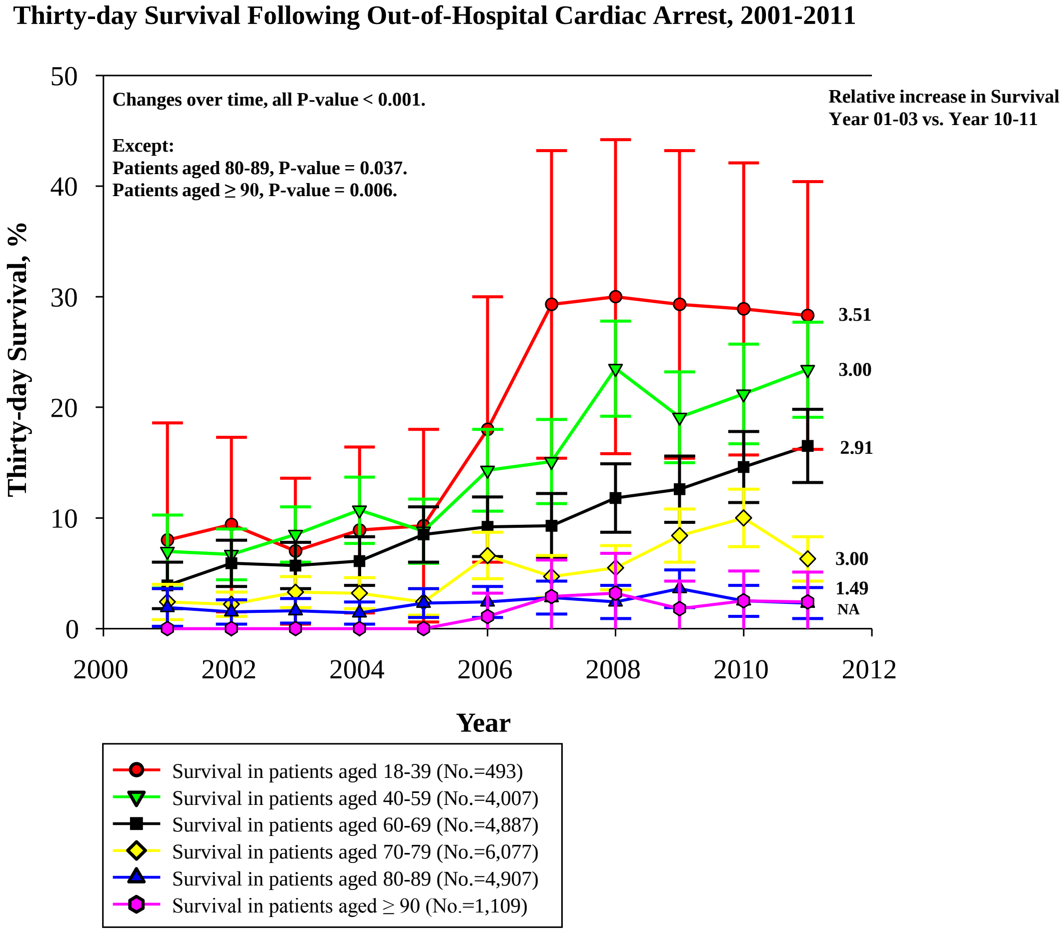
Thirty-day Survival in Relation to Sex and First Recorded Heart Rhythm

Temporal trends in proportions of patients achieving 30-day survival for patients with: (1) a shockable rhythm; and (2) a non-shockable rhythm, respectively, according to sex. Changes over time were tested; a two-sided p-value <0.05 was considered to be statistically significant.

Abbreviations: NS, not significant

*p<0.001

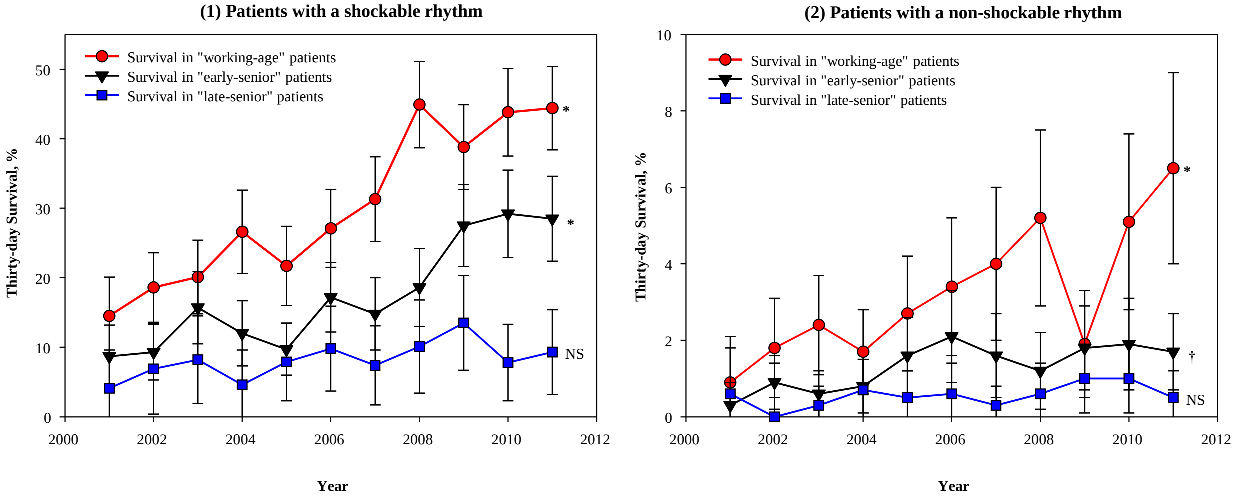
Supplementary Figure 4



Thirty-day Survival Following Out-of-Hospital Cardiac Arrest, 2001-2011
Temporal trends in proportions of patients achieving 30-day survival according to age group. Changes over time were tested a two-sided p-value <0.05 was considered to be statistically significant. Relative increase in survival (year 01-03 vs. year 10-11) is indicated on the right side of the figure.

Supplementary Figure 5

Thirty-day Survival in Relation to First Recorded Heart Rhythm, 2001–2011



Thirty-day Survival in Relation to First Recorded Heart Rhythm, 2001–2011

Temporal trends in proportions of patients achieving 30-day survival for patients with: (1) a shockable rhythm; and (2) a non-shockable rhythm, respectively, according to age group. Changes over time were tested; a two-sided p-value <0.05 was considered to be statistically significant.

Abbreviations: NS, not significant

*p<0.001

†p<0.01

Original Investigation

Association of National Initiatives to Improve Cardiac Arrest Management With Rates of Bystander Intervention and Patient Survival After Out-of-Hospital Cardiac Arrest

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IMPORTANCE Out-of-hospital cardiac arrest is a major health problem associated with poor outcomes. Early recognition and intervention are critical for patient survival. Bystander cardiopulmonary resuscitation (CPR) is one factor among many associated with improved survival.

OBJECTIVE To examine temporal changes in bystander resuscitation attempts and survival during a 10-year period in which several national initiatives were taken to increase rates of bystander resuscitation and improve advanced care.

DESIGN, SETTING, AND PARTICIPANTS Patients with out-of-hospital cardiac arrest for which resuscitation was attempted were identified between 2001 and 2010 in the nationwide Danish Cardiac Arrest Registry. Of 29 111 patients with cardiac arrest, we excluded those with presumed noncardiac cause of arrest (n = 7390) and those with cardiac arrests witnessed by emergency medical services personnel (n = 2253), leaving a study population of 19 468 patients.

MAIN OUTCOMES AND MEASURES Temporal trends in bystander CPR, bystander defibrillation, 30-day survival, and 1-year survival.

RESULTS The median age of patients was 72 years; 67.4% were men. Bystander CPR increased significantly during the study period, from 21.1% (95% CI, 18.8%-23.4%) in 2001 to 44.9% (95% CI, 42.6%-47.1%) in 2010 ($P < .001$), whereas use of defibrillation by bystanders remained low (1.1% [95% CI, 0.6%-1.9%] in 2001 to 2.2% [95% CI, 1.5%-2.9%] in 2010; $P = .003$). More patients achieved survival on hospital arrival (7.9% [95% CI, 6.4%-9.5%] in 2001 to 21.8% [95% CI, 19.8%-23.8%] in 2010; $P < .001$). Also, 30-day survival improved (3.5% [95% CI, 2.5%-4.5%] in 2001 to 10.8% [95% CI, 9.4%-12.2%] in 2010; $P < .001$), as did 1-year survival (2.9% [95% CI, 2.0%-3.9%] in 2001 to 10.2% [95% CI, 8.9%-11.6%] in 2010; $P < .001$). Despite a decrease in the incidence of out-of-hospital cardiac arrests during the study period (40.4 to 34.4 per 100 000 persons in 2001 and 2010, respectively; $P = .002$), the number of survivors per 100 000 persons increased significantly ($P < .001$). For the entire study period, bystander CPR was positively associated with 30-day survival, regardless of witnessed status (30-day survival for nonwitnessed cardiac arrest, 4.3% [95% CI, 3.4%-5.2%] with bystander CPR and 1.0% [95% CI, 0.8%-1.3%] without; odds ratio, 4.38 [95% CI, 3.17-6.06]). For witnessed arrest the corresponding values were 19.4% (95% CI, 18.1%-20.7%) vs 6.1% (95% CI, 5.4%-6.7%); odds ratio, 3.74 (95% CI, 3.26-4.28).

CONCLUSIONS AND RELEVANCE In Denmark between 2001 and 2010, an increase in survival following out-of-hospital cardiac arrest was significantly associated with a concomitant increase in bystander CPR. Because of the co-occurrence of other related initiatives, a causal relationship remains uncertain.

JAMA. 2013;310(13):1377-1384. doi:10.1001/jama.2013.278483

Author Audio Interview at jama.com

Supplemental content at jama.com

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Resuscitation xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Resuscitation

journal homepage: www.elsevier.com/locate/resuscitation

Clinical Paper

Survival after out-of-hospital cardiac arrest in relation to sex: A nationwide registry-based study☆

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ARTICLE INFO

Article history:
Received 17 February 2014
Received in revised form 7 May 2014
Accepted 5 June 2014

Keywords:
Cardiac arrest
Resuscitation
Sex
Survival

ABSTRACT

Aim: Crude survival has increased following an out-of-hospital cardiac arrest (OHCA). We aimed to study sex-related differences in patient characteristics and survival during a 10-year study period.
Methods: Patients ≥12 years old with OHCA of a presumed cardiac cause, and in whom resuscitation was attempted, were identified through the Danish Cardiac Arrest Registry 2001–2010. A total of 19,372 patients were included.
Results: One-third were female, with a median age of 75 years (IQR 65–83). Compared to females, males were five years younger; and less likely to have severe comorbidities, e.g., chronic obstructive pulmonary disease (12.8% vs. 16.5%); but more likely to have arrest outside of the home (29.4% vs. 18.7%), receive bystander CPR (32.9% vs. 25.9%), and have a shockable rhythm (32.6% vs. 17.2%), all $p < 0.001$. Thirty-day crude survival increased in males (3.0% in 2001 to 12.9% in 2010); and in females (4.8% in 2001 to 6.7% in 2010), $p < 0.001$.

Multivariable logistic regression analyses adjusted for patient characteristics including comorbidities, showed no survival difference between sexes in patients with a non-shockable rhythm (OR 1.00; CI 0.72–1.40), while female sex was positively associated with survival in patients with a shockable rhythm (OR 1.31; CI 1.07–1.59). Analyses were rhythm-stratified due to interaction between sex and heart rhythm; there was no interaction between sex and calendar-year.
Conclusions: Temporal increase in crude survival was more marked in males due to poorer prognostic characteristics in females with a lower proportion of shockable rhythm. In an adjusted model, female sex was positively associated with survival in patients with a shockable rhythm.

1. Introduction

Major efforts have been launched in many countries throughout the past decade to improve bystander resuscitation attempts and advance care following out-of-hospital cardiac arrest (OHCA).[1–7] In parallel, patient survival has increased[1–6] and in Denmark survival rates have approximately tripled during the past decade and was associated with a concomitant increase in bystander cardiopulmonary resuscitation (CPR).[1] Nevertheless, it remains unknown whether efforts to improve survival have different impact on male and female patients. Dissimilarities may exist, as a number of studies have shown sex-related differences in survival outcomes after OHCA.[8–16] Accordingly, female sex has been associated with improved survival upon hospital arrival,[8–10,12,15,16] as well as improved 1-month survival/survival at discharge in the

☆ A Spanish translated version of the summary of this article appears as Appendix in the final online version at http://dx.doi.org/10.1016/j.resuscitation.2014.06.008.

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http://dx.doi.org/10.1016/j.resuscitation.2014.06.008
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Survival After Out-of-Hospital Cardiac Arrest in Relation to Age and Early Identification of Patients With Minimal Chance of Long-Term Survival

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Background—Survival after out-of-hospital cardiac arrest has increased during the last decade in Denmark. We aimed to study the impact of age on changes in survival and whether it was possible to identify patients with minimal chance of 30-day survival.

Methods and Results—Using data from the nationwide Danish Cardiac Arrest Registry (2001–2011), we identified 21 480 patients ≥18 years old with a presumed cardiac-caused out-of-hospital cardiac arrest for which resuscitation was attempted. Patients were divided into 3 preselected age-groups: working-age patients 18 to 65 years of age (33.7%), early senior patients 66 to 80 years of age (41.5%), and late senior patients >80 years of age (24.8%). Characteristics in working-age patients, early senior patients, and late senior patients were as follows: witnessed arrest in 53.8%, 51.1%, and 52.1%; bystander cardiopulmonary resuscitation in 44.7%, 30.3%, and 23.4%; and prehospital shock from a defibrillator in 54.7%, 45.0%, and 33.8% (all $P<0.05$). Between 2001 and 2011, return of spontaneous circulation on hospital arrival increased: working-age patients, from 12.1% to 34.6%; early senior patients, from 6.4% to 21.5%; and late senior patients, from 4.0% to 15.0% (all $P<0.001$). Furthermore, 30-day survival increased: working-age patients, 5.8% to 22.0% ($P<0.001$); and early senior patients, 2.7% to 8.4% ($P<0.001$), whereas late senior patients experienced only a minor increase (1.5% to 2.0%; $P=0.01$). Overall, 3 of 9499 patients achieved 30-day survival if they met 2 criteria: had not achieved return of spontaneous circulation on hospital arrival and had not received a prehospital shock from a defibrillator.

Conclusions—All age groups experienced a large temporal increase in survival on hospital arrival, but the increase in 30-day survival was most prominent in the young. With the use of only 2 criteria, it was possible to identify patients with a minimal chance of 30-day survival. **(*Circulation*. 2015;131:1536-1545. DOI: 10.1161/CIRCULATIONAHA.114.013122.)**

Key Words: age ■ heart arrest ■ resuscitation ■ survival

During the past decade, major efforts have been taken to improve cardiac arrest management (ie, to improve bystander resuscitation attempts and advanced care).[1–8] In the same time period, survival after out-of-hospital cardiac arrest (OHCA) has increased in many countries, indicating that, although OHCA is a devastating medical condition associated with a poor prognosis, systematic efforts can result in improvement.[1–6] Aging influences multiple physiological processes; with increasing age, there is an increasing susceptibility to contract diseases and critical illness, including conditions such as cardiac arrest.[1,9–11] Accordingly, aging is associated with a concomitant increase in OHCA incidence and a low chance of survival.[1–6,10–14] To improve and focus future strategies for cardiac arrest management, it is important to know how changes in survival are reflected in different age groups and whether it is possible to identify patients with minimal chance of survival.

Clinical Perspective on p 1545

Received September 3, 2014; accepted February 20, 2015.

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The online-only Data Supplement is available with this article at http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIRCULATIONAHA.114.013122/-/DC1.

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Circulation **is available at http://circ.ahajournals.org** **DOI: 10.1161/CIRCULATIONAHA.114.013122**

SUMMARY

Cardiac arrest is an emergency medical condition characterized by the cessation of cardiac mechanical activity; without immediate and decisive treatment, a victim's chances of survival are minimal. Out-of-hospital cardiac arrest is a particular arrest subgroup that poses additional challenges, due to the victim's physical location, which brings an inherent risk of delay (or altogether absence) of recognition and treatment of cardiac arrest. A low frequency of bystander cardiopulmonary resuscitation and low 30-day survival after out-of-hospital cardiac arrest were identified nearly ten years ago in Denmark. These findings led to several national initiatives to strengthen bystander resuscitation attempts and advance care. Despite these nationwide efforts, it was unknown prior to this project whether these efforts resulted in changes in resuscitation attempts by bystanders and changes in patient survival following out-of hospital cardiac arrest; utilizing the Danish nationwide registries, we sought to answer these questions. Moreover, in order to further improve understanding and target future national strategies for cardiac arrest management, we examined whether there were sex- and age-related differences in patient characteristics and survival, and whether it was possible to identify patients with minimal chance of long-term survival.

ISSN (online): 2246-1302
ISBN (online): 978-87-7112-346-3

AALBORG **UNIVERSITY PRESS**