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

Running Title: Rajan et al.; Bystander CPR and response-time

Shahzleen Rajan, MD1; Mads Wissenberg, MD, PhD2,3; Fredrik Folke, MD, PhD1,3; Steen Møller Hansen, MD4; Thomas A. Gerds, PhD5; Kristian Kragholm, MD, PhD6; Carolina Malta Hansen, MD, PhD1,7; Lena Karlsson, MD1; Freddy K. Lippert, MD3; Lars Køber, MD, DSc8; Gunnar H. Gislason, MD, PhD9; Christian Torp-Pedersen, MD, DSc10

1Department of Cardiology, Copenhagen University Hospital Gentofte, Hellerup, Denmark; 2Department of Clinical Physiology, Nuclear Medicine and PET, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark; 3Emergency Medical Services Copenhagen, University of Copenhagen, Ballerup, Denmark; 4Department of Clinical Epidemiology, Aalborg University Hospital, Aalborg, Denmark; 5Department of Biostatistics, University of Copenhagen, Copenhagen, Denmark; 6Department of Anesthesiology & Clinical Medicine, Aalborg University Hospital, Aalborg, Denmark; 7Duke Clinical Research Institute, Duke University, Durham, NC; 8Department of Cardiology, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark; 9The National Institute of Public Health, University of Southern Denmark, Copenhagen, Denmark; 10Department of Health, Science and Technology, Aalborg University, Aalborg, Denmark

Address for Correspondence:
Shahzleen Rajan, MD
Department of Cardiology
Copenhagen University Hospital
Gentofte Kildegårdvej 28, Post 635
2900 Hellerup, Denmark
Tel: (+45) 29 71 11 65
Fax: (+45) 39 75 18 03
E-mail: shahzleen@gmail.com

Journal Subject Terms: Sudden Cardiac Death; Cardiopulmonary Arrest; Cardiopulmonary Resuscitation and Emergency Cardiac Care; Epidemiology
Abstract

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

Methods—We studied 7,623 OHCA patients between 2005-2011, identified through the nationwide Danish Cardiac Arrest Register. Multiple logistic regression analysis was used to examine the association between time from 911-call to emergency medical service arrival (response time) and survival according to whether bystander CPR was provided (yes/no). Reported are 30-day survival chances with 95% bootstrap confidence intervals.

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

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

Key-words: cardiopulmonary resuscitation; cardiac arrest; survival; epidemiology
Clinical Perspective

What is new?

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

What are the clinical implications?

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

Early recognition and treatment of out-of-hospital cardiac arrest (OHCA) are well known to increase the likelihood of successful resuscitation with good neurologic outcome without increasing the proportion of patients who need permanent care. Several time factors are important for successful resuscitation after OHCA, including early bystander intervention in the form of cardiopulmonary resuscitation (CPR) and defibrillation, as well as prompt access to advanced post-resuscitation care.

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

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

Methods

Data source and definitions

All OHCA patients between 2005 and 2011 were identified from the nationwide Danish Cardiac Arrest Register. The Danish emergency medical services and the Danish Cardiac Arrest Register have previously been described in detail.6,13,14 Across all regions in Denmark, the emergency medical service is a two-tier system with dispatch of basic life support ambulances staffed with ambulance technicians or paramedics as well as mobile emergency care units supervised by specialized anesthesiologists or paramedics. These emergency care units are sent as rendezvous with the ambulances. There are no structured first-responder automated external defibrillator programs in Denmark (police or firefighters bringing a defibrillator). In this study we included OHCA cases handled by the largest nationwide ambulance provider in Denmark (Falck A/S). Falck A/S provided electronic data on various time intervals for each OHCA, including information on ambulance response time. We defined the duration of response time as the time from call receipt by the emergency medical services till the ambulance arrived at the site of OHCA. This time interval served as a proxy for the time to CPR and potential defibrillation by the emergency medical services. Using the unique Civil Registration number provided to all residents in Denmark, we were able to collect information on age, gender, survival status, as well as hospital discharge diagnoses in the national administrative registries, as described previously.6,13,14 Information on anoxic brain damage was obtained from discharge diagnoses. From Statistics Denmark we obtained data on individuals entering and leaving nursing homes.
Nursing home data have been collected since 1994 using a validated approach to secure high degree of completion of nursing home information.15

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

In order to calculate number of potential lives that could be saved annually with decreasing response time, we obtained statistics from the latest Danish Cardiac Arrest report17, which reported that 3570 OHCA, not witnessed by the emergency medical services, took place during the latest year, of which 65.8% received bystander CPR.

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

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

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

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

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

The level of significance was set at 5%. All statistical analyses were performed using SAS, version 9.4 (SAS Institute Inc., Cary, NC, USA) and R, version 3.2.2.22

Ethics

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

Results

A total of 7,623 patients met the inclusion criteria during the study period, and comprised the final study population. The patient selection process is displayed in Figure 1.

Time stratified baseline characteristics

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

**Crude vs. standardized 30-day survival chances**

Rates of 30-day survival for patients with bystander CPR for ≤5 minutes, 6-10 minutes 11-15 minutes and >15 minutes were 22.6% (192/848), 15.3% (180/1180), 6.7% (44/613) and 4.7% (13/274), respectively. Corresponding 30-day survival rates for patients without bystander CPR were 6.7% (111/1617), 3.4% (64/1912), 1.3% (10/792) and 2.7% (9/331), respectively.

Supplemental Figure 2 shows these crude survival chances as well as standardized survival chances according to bystander CPR and ambulance response time. The difference between the crude and standardized results indicate confounding by patient- and OHCA characteristics, as the magnitude of the ratio between the standardized survival chances was smaller than that of the crude survival chances.

**Standardized 30-day survival chances**

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

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

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

**Additional lives potentially saved annually**

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

**Survival in best- and worst-case scenarios**

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

In all scenarios, the personalized 30-day survival chances decreased with each increasing minute of response time, and in all scenarios, receiving bystander CPR was associated with the highest 30-day survival chances. In the best-case scenario, the 30-day survival chances within five minutes of response time was 54.2% if bystander CPR had been provided, whereas the chances decreased to 30.2% if no bystander CPR was provided (1.8 times higher 30-day survival chance in the bystander CPR group). By 10 minutes, the corresponding probabilities were 33.1% with bystander CPR, and 12.2% with no bystander CPR (2.7 times higher 30-day survival chance in the bystander CPR group).
chances in the bystander CPR group), and by 15 minutes, the chances were 21.0% and 8.1%, respectively (2.5 times higher 30-day survival in the bystander CPR group). In the worst-case scenario, the probability of 30-day survival within five minutes of response time was 4.1% with bystander CPR alone, and 1.5% with no bystander CPR (2.7 times higher 30-day survival in the bystander CPR group). After 10 minutes, the corresponding probabilities decreased to 1.7% and 0.5% (3.4 times higher 30-day survival in the bystander CPR group), and after 15 minutes, the chances were 0.9% and 0.3%, respectively (3.0 times higher 30-day survival in the bystander CPR group).

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

**Discussion**

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

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

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

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

Overall, our results suggest that dispatch of nearby trained lay- or professional first-responders to assist with potential defibrillation apart from CPR while waiting for the ambulance is likely to save a substantial amount of more lives every year.
When examining best- and worst-case scenarios, large variations in predicted survival percentages were observed for each of these cases as expected, with survival probability being much higher in best-case scenarios. This reflects how the selected pre-hospital factors are closely related to survival, and are therefore somewhat able to predict whether the cardiac arrest patient achieves long-term survival. Notably, in both scenarios we found that if bystander CPR is received, the 30-day survival probability is markedly increased compared to no bystander CPR indicating the robustness of this single factor. However, when investigating the absolute survival probability percentages between the two scenarios, absolute chances of survival in especially the worst-case scenario was particularly dependent on time, regardless of bystander CPR status – if potential defibrillation is not established relatively early, the chances of survival seem to be minimal. These results also imply the necessity of decreasing time to potential defibrillation.

Limitations

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

Conclusions
In this study we demonstrated a positive association between bystander CPR and 30-day survival across ambulance response times. As ambulance response time increased, the absolute 30-day survival decreased regardless of bystander CPR status. However, the relative difference in survival was more than twice as high among patients who received bystander CPR compared to those who did not, across all ambulance response times. Decreasing time to CPR by trained rescuers and potential defibrillation by even a few minutes could potentially lead to many additional lives saved every year. Strategies to decrease ambulance response time as well as implementing dispatch of nearby trained lay- or professional first-responders for quick intervention with CPR and very importantly, potential defibrillation is likely to increase survival after OHCA.
Acknowledgments

We are grateful to the Danish Emergency Medical Services for their support in completing the case report forms for the Danish Cardiac Arrest Register.

Sources of Funding

The Danish foundation TrygFonden has supported this study, and had no role in the design, conduct, data collection, management, analyses or interpretation of the data, nor in preparation, review or approval of the manuscript. The Danish Cardiac Arrest Registry and the Automated External Defibrillator (AED) Network are supported by TrygFonden.

Disclosures

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


Table 1. Patient- and arrest characteristics according to bystander CPR status and response time intervals.

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

All results are n (%) unless otherwise specified.
CPR = cardiopulmonary resuscitation. IQR = Interquartile range
*Non-significant p-value for difference across all time intervals for both bystander groups, respectively (p>0.05)
Figure Legends

Figure 1. Study selection process of patients with out-of-hospital cardiac arrests.
Flowchart showing the selection process for the study population in this study.

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

Figure 3. Potential lives saved annually if response time is deceased. This figure is based on the adjusted logistic regression model using g-formula from Figure 2, combined with latest Danish OHCA Statistics, which reported that 3570 OHCA, that were not witnessed by the emergency medical services, took place during the latest year, of which 65.8% received bystander CPR.
OHCA = out-of-hospital cardiac arrest. CPR = Cardiopulmonary resuscitation.
Figure 4. Thirty-day survival predictions in best-case scenario and worst-case scenario, stratified according to bystander CPR status. The upper panel shows 30-day survival chances for an individual in a best-case scenario, having a witnessed arrest in public, no comorbidities listed in Table 1, and younger age (≤65 years). The lower panel shows 30-day survival chances for an individual in a worst-case scenario, having an unwitnessed arrest in a private home, one or more comorbidities listed in Table 1, and older age (>65 years). Note different Y-axis scales.

CPR = Cardiopulmonary resuscitation.
15623 OHCA cases identified, handled by the largest nationwide EMS provider in Denmark, between 2005-2011

4176 Excluded:
- 167 Age under 18 years
- 47 Missing information on cause of arrest
- 3962 Presumed non-cardiac cause

11447 Eligible for further assessment

3824 Excluded:
- 1328 Witnessed by the EMS
- 2336 Missing information on response time
- 160 Defibrillated by bystanders

7623 Included in analyses
Ambulance response time (minutes) vs. 30-day survival

- **No Bystander CPR**:
  - 0 minutes: 104 lives saved
  - 1 minute: 89 lives saved
  - 2 minutes: 77 lives saved
  - 3 minutes: 58 lives saved
  - 4 minutes: 47 lives saved
  - 5 minutes: 40 lives saved
  - 6 minutes: 31 lives saved
  - 7 minutes: 27 lives saved
  - 8 minutes: 24 lives saved
  - 9 minutes: 20 lives saved
  - 10 minutes: 18 lives saved
  - 11 minutes: 17 lives saved
  - 12 minutes: 18 lives saved
  - 13 minutes: 20 lives saved
  - 14 minutes: 31 lives saved
  - 15 minutes: 40 lives saved

- **Bystander CPR**:
  - 0 minutes: 380 lives saved
  - 1 minute: 355 lives saved
  - 2 minutes: 340 lives saved
  - 3 minutes: 291 lives saved
  - 4 minutes: 251 lives saved
  - 5 minutes: 228 lives saved
  - 6 minutes: 183 lives saved
  - 7 minutes: 157 lives saved
  - 8 minutes: 120 lives saved
  - 9 minutes: 98 lives saved
  - 10 minutes: 87 lives saved
  - 11 minutes: 73 lives saved
  - 12 minutes: 64 lives saved
  - 13 minutes: 58 lives saved
  - 14 minutes: 47 lives saved
  - 15 minutes: 31 lives saved
Association of Bystander Cardiopulmonary Resuscitation and Survival According to Ambulance Response-times after Out-of-Hospital Cardiac Arrest
Shahzleen Rajan, Mads Wissenberg, Fredrik Folke, Steen M. Hansen, Thomas A. Gerds, Kristian Kragholm, Carolina Malta Hansen, Lena I. M. Karlsson, Freddy K. Lippert, Lars Køber, Gunnar H. Gislason and Christian Torp-Pedersen

Circulation. published online November 22, 2016;
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2016 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/early/2016/11/22/CIRCULATIONAHA.116.024400

Data Supplement (unedited) at:
http://circ.ahajournals.org/content/suppl/2016/11/22/CIRCULATIONAHA.116.024400.DC1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org/subscriptions/
SUPPLEMENTAL MATERIAL
Supplemental Table 1: Baseline characteristics stratified according to time intervals of ambulance response time

<table>
<thead>
<tr>
<th></th>
<th>≤5 minutes (n=2469)</th>
<th>6-10 minutes (n=3095)</th>
<th>11-15 minutes (n=1452)</th>
<th>&gt;15 minutes (n=607)</th>
<th>Missing values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age</td>
<td>73 (63-81)</td>
<td>71 (62-80)</td>
<td>71 (61-79)</td>
<td>70 (61-80)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>1654 (67.0)</td>
<td>2137 (69.1)</td>
<td>1025 (70.6)</td>
<td>411 (67.7)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>671 (27.2)</td>
<td>823 (26.6)</td>
<td>380 (26.2)</td>
<td>161 (26.5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>323 (13.1)</td>
<td>362 (11.7)</td>
<td>164 (11.3)</td>
<td>77 (12.7)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>550 (22.3)</td>
<td>642 (20.7)</td>
<td>265 (18.3)</td>
<td>120 (19.8)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>COPD</td>
<td>344 (13.9)</td>
<td>455 (14.7)</td>
<td>207 (14.3)</td>
<td>75 (12.4)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Arrest in private homes</td>
<td>1630 (73.8)</td>
<td>2153 (78.7)</td>
<td>1047 (81.2)</td>
<td>403 (83.3)</td>
<td>873 (0)</td>
</tr>
<tr>
<td>Witnessed arrests</td>
<td>1279 (51.8)</td>
<td>1608 (52.2)</td>
<td>785 (54.3)</td>
<td>336 (56.1)</td>
<td>28 (0.4)</td>
</tr>
<tr>
<td>Bystander CPR</td>
<td>848 (34.4)</td>
<td>1180 (38.2)</td>
<td>657 (45.3)</td>
<td>274 (45.3)</td>
<td>12 (0.1)</td>
</tr>
<tr>
<td>Arrest during day</td>
<td>1213 (50.1)</td>
<td>1253 (41.0)</td>
<td>592 (41.3)</td>
<td>235 (39.4)</td>
<td>110* (1.4)</td>
</tr>
<tr>
<td>Arrest during evening</td>
<td>901 (37.2)</td>
<td>1059 (34.6)</td>
<td>453 (31.6)</td>
<td>178 (29.8)</td>
<td>110* (1.4)</td>
</tr>
<tr>
<td>Response time, median (IQR)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial shockable rhythm</td>
<td>803 (34.0)</td>
<td>911 (30.6)</td>
<td>349 (25.1)</td>
<td>117 (20.5)</td>
<td>327 (4.3)</td>
</tr>
<tr>
<td>Bystander CPR and received defibrillation by EMS</td>
<td>443 (52.8)</td>
<td>643 (55.5)</td>
<td>326 (50.2)</td>
<td>105 (38.6)</td>
<td>40 (1.4)</td>
</tr>
<tr>
<td>No bystander CPR, but received defibrillation by EMS</td>
<td>567 (35.8)</td>
<td>588 (31.3)</td>
<td>199 (25.6)</td>
<td>73 (22.7)</td>
<td>87 (1.9)</td>
</tr>
<tr>
<td>ROSC</td>
<td>549 (22.5)</td>
<td>534 (17.4)</td>
<td>167 (11.6)</td>
<td>53 (8.8)</td>
<td>76 (1.0)</td>
</tr>
<tr>
<td>Nursing home within one year**</td>
<td>10 (3.3)</td>
<td>8 (3.3)</td>
<td>1 (1.9)</td>
<td>0 (0.0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Discharged with anoxic brain damage**</td>
<td>22 (7.3)</td>
<td>26 (10.6)</td>
<td>5 (9.3)</td>
<td>3 (13.6)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

All results are n (%) unless otherwise specified.
CPR = cardiopulmonary resuscitation. IQR = Interquartile range. ROSC = return of spontaneous circulation.
* Combined missing value for all time periods during the day
** Among 30-day survivors
Supplemental Figure 1: Directed acyclic graph

Directed acyclic graph to identify the minimal sufficient adjustment set.
Supplemental Figure 2: Crude vs. standardized 30-day survival chances according to increasing response time intervals

This figure illustrates differences between crude and standardized 30-day survival chances for bystander CPR and no bystander CPR. Triangle points refer to no bystander CPR, while round points refer to bystander CPR. Blue lines refer to crude 30-day survival chances, while red lines refer to adjusted (standardized).

CPR = Cardiopulmonary resuscitation
Supplemental Figure 3: Sensitivity analysis: Standardized 30-day survival chances according to duration of response time and bystander CPR status in a sub-population consisting of only witnessed arrests

The survival chances based on multiple logistic regression were standardized to settings where all patients vs. no patients received bystander CPR according to ambulance response time. The result is obtained in a sub-population consisting of only witnessed arrests adjusted for age, sex, comorbidities, location of arrest and year of arrest.

CPR = Cardiopulmonary resuscitation.
Supplemental Figure 4: Sensitivity analysis: Standardized 30-day survival chances according to duration of response time and bystander CPR status in a sub-population consisting of only unwitnessed arrests

The survival chances based on multiple logistic regression were standardized to settings where all patients vs. no patients received bystander CPR according to ambulance response time. The result is obtained in a sub-population consisting of only unwitnessed arrests adjusted for age, sex, comorbidities, location of arrest and year of arrest.

CPR = Cardiopulmonary resuscitation.
Supplemental Figure 5: Standardized chances of absence of anoxic brain damage diagnosis up to 30 days post-discharge from the hospital (among 30-day survivors), according to increasing response time intervals

The chances of being discharged without diagnosis of anoxic brain damage based on multiple logistic regression were standardized to settings where all patients vs. no patients received bystander CPR according to ambulance response time. Red dots refer to bystander CPR group, while blue triangles refer to no bystander CPR group. The result is obtained for only 30-day survivors, and is adjusted for age, sex, comorbidities, location of arrest and year of arrest.

CPR = Cardiopulmonary resuscitation.
Supplemental Figure 6: Thirty-day survival predictions in best-case scenario and worst-case scenario, stratified according to bystander CPR status for witnessed arrests and unwitnessed arrests, separately

The upper left panel shows 30-day survival chances for an individual with a witnessed arrest in a best-case scenario, having a public arrest, no comorbidities listed in Table 1, and younger age (≤65 years).

The lower left panel shows 30-day survival chances for an individual with a witnessed arrest in worst-case scenario, having an arrest in a private home, one or more comorbidities listed in Table 1, and older age (＞65).

The upper right panel shows 30-day survival chances for an individual with an unwitnessed arrest in a best-case scenario, having a public arrest, no comorbidities listed in Table 1, and younger age (≤65 years).

The lower right panel shows 30-day survival chances for an individual with an unwitnessed arrest in worst-case scenario, having an arrest in a private home, one or more comorbidities listed in Table 1, and older age (＞65).

Note different Y-axis scales. CPR = Cardiopulmonary resuscitation.