Survival After Out-of-Hospital Cardiac Arrest in Relation to Age and Early Identification of Patients with Minimal Chance of Long-Term Survival

Running title: Wissenberg et al.; Survival after OHCA According to Age

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Abstract

Background—Survival following out-of-hospital cardiac arrest (OHCA) 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 OHCA for which resuscitation was attempted. Patients were 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%). Characteristics in working-age-patients, early-senior-patients, and late-senior-patients: witnessed arrest 53.8%, 51.1%, and 52.1%; bystander CPR 44.7%, 30.3%, and 23.4%; and pre-hospital shock from a defibrillator 54.7%, 45.0% and 33.8%, all p<0.05. Between 2001 and 2011, return of spontaneous circulation (ROSC) upon hospital arrival increased: working-age-patients from 12.1% to 34.6%; early-senior-patients 6.4% to 21.5%; and late-senior-patients 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; while late-senior-patients only experienced a minor increase 1.5% to 2.0%, p=0.01. Overall, three out of 9499 patients, achieved 30-day survival if they met two criteria: had not achieved ROSC upon hospital arrival; and had not received a pre-hospital 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. Using only two criteria, it was possible to identify patients with minimal chance of 30-day survival.

Key words: heart arrest, resuscitation, aging, survival
During the past decade, major efforts have been taken to improve cardiac arrest management (i.e., improve bystander resuscitation attempts and advanced care). In the same time period, survival following 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. Aging influences multiple physiological processes; with increasing age, there is an increasing susceptibility to contract diseases and critical illness, including conditions like cardiac arrest. Accordingly, aging is associated with a concomitant increase in OHCA incidence and a low chance of survival.

To improve and to 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.

In parallel with national initiatives to improve cardiac arrest management in Denmark, survival has approximately tripled between 2001 and 2010. However, the impact of patients’ age on temporal changes in survival remains unknown. To address this question, we studied age-related differences in patient characteristics and survival during an 11-year study period. Additionally, we examined whether it was possible to use pre-hospital criteria to identify patients with a very low chance of 30-day survival, irrespective of age, as this knowledge could be helpful in the decision-making process regarding when to terminate a resuscitation attempt.

Methods

Study Setting and Population

This study was conducted in Denmark from June 1, 2001 to December 31, 2011. The Danish population constitutes approximately 5.6 million inhabitants. In Denmark, the emergency medical service (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. Throughout the study period, treatment was given according to the latest guidelines on resuscitation and emergency cardiovascular care.\(^7\)

**Definition and Recording of OHCA**

A patient was included in the Danish Cardiac Arrest Registry when a clinical condition of cardiac arrest outside of a hospital resulted in a resuscitation attempt by either EMS personnel or a bystander; therefore, the definition of OHCA excluded patients with late signs of death where resuscitation attempts were not initiated. The capture of OHCA cases is close to complete since:

1. EMS is activated for all severe clinical conditions 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 study, we included information on date; time; location of arrest (outside private home vs. inside private home); whether the collapse was non-, bystander-, or EMS-witnessed; whether the bystander initiated cardiopulmonary resuscitation (CPR) and/or defibrillated the patient using an automatic external defibrillator (AED) located outside hospital; first observed heart rhythm (shockable rhythm [ventricular fibrillation or pulseless ventricular tachycardia] or non-shockable rhythm [asystole or pulseless electrical activity]); 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 return of spontaneous circulation (ROSC) upon arrival at the hospital.

To study and compare a more homogenous group of patients, we categorized cardiac
arrests into presumed non-cardiac cause and presumed cardiac cause of arrest, as recommended by the Utstein template,\textsuperscript{16} and as done previously.\textsuperscript{1} The categorization was conducted using diagnosis codes from death certificates and discharge diagnoses from 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.

Patients with: age <18 years; a presumed non-cardiac cause of arrest; and an EMS-witnessed arrest, were excluded from the final study population (Figure 1). 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. To acknowledge that aging represents a continuum with a gradual decrease in physiologic reserve and functioning throughout life, 30-day survival was also tested in shorter age intervals. Also, a smoothing spline transformation was conducted to display the overall pattern in 30-day survival rates at each age level, which illustrated a non-linear relationship (Figure 2).

To try and identify patients with a minimal chance of long-term survival, irrespective of age, we tested the 30-day survival rate among patients with a non-shockable rhythm; this was inspired by our earlier study\textsuperscript{1} in which the first recorded heart rhythm appeared to be one of the strongest pre-hospital factors associated with 30-day survival. Furthermore, inspired by the termination of resuscitation (TOR) rule by Verbeek et al.,\textsuperscript{17} we tested 30-day survival rate in patients who met two criteria: (1) had not achieved ROSC upon hospital arrival; and (2) had not
received a shock from a defibrillator in the pre-hospital setting.

Data from Nationwide Administrative Registries in Denmark

In Denmark, each resident is assigned a unique and permanent Civil Registration Number that allows individual linkage of information between nationwide registries. This number is used in all interactions with the Danish government agencies including all contacts with the single-payer tax-funded public health care system and ensures that the administrative registries are close to complete.

Information on age, sex, vital status, and civil status were obtained from the Civil Registry. Discharge diagnosis codes, provided by physicians, as well as admission and discharge dates from all Danish hospitals, were obtained from the Danish National Patient Registry. To investigate patients’ comorbidity, discharge diagnoses were examined up to ten years prior to OHCA. In addition, new onset of anoxic brain damage in 1-year survivors was examined. New onset was defined as: (1) patients diagnosed with anoxic brain damage during the period from hospital discharge to thirty days post-discharge; and (2) no history of anoxic brain damage up to ten years before the cardiac arrest. Diagnosis codes from death certificates were obtained from the National Causes of Deaths Registry. All diagnosis codes are registered according to the International Classification of Diseases (ICD) system. To add information to the patients’ comorbidity status we also included information on the patients’ pharmacotherapy from The Danish Registry of Medicinal Product Statistics up to 180 days before the OHCA. Drugs are classified according to the Anatomical Therapeutic Chemical (ATC) system. All administrative registries have been described in detail elsewhere.\(^\text{18}\)

Endpoints

The main outcome measures were ROSC upon hospital arrival and 30-day survival, according to
pre-selected age groups.

**Statistics**

To test for differences between the pre-selected age groups, we used a Chi-square test for binary variables and the Kruskall-Wallis test for continuous variables. In addition, the Cochran–Armitage test was used to test for trends in binary variables according to age groups. Logistic regression models were used to test for temporal changes in binary variables, while Poisson regression analyses were used to test for temporal changes in OHCA incidences and numbers of 30-day survivors. When calculating percentages and medians, only observations with data for the covariate involved in the calculation were included. A number of patients had missing data for the cardiac arrest-related variables (Table 1). In order to test whether missing data could introduce bias into the study we applied multivariate imputation by chained equations (MICE) method. Using MICE, missing values were imputed using information from all variables in Table 1 and Supplemental Table 1 and ten imputed datasets were constructed (complete datasets with observed and imputed values). We then compared estimates from the original dataset (incomplete dataset containing missing data) with estimates from the imputed datasets. A two-sided p-value <0.05 was considered statistically significant. Data management and analyses were carried out using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA); and R, version 2.15.2 (R Development Core Team).

**Ethics**

This study was approved by the Danish Data Protection Agency (2007-58-0015, local ref.nr. GEH-2014-017, I-Suite.nr. 02735). In Denmark, ethical approval is not required for retrospective registry-based studies.
Results

Patient-related Characteristics

The final study population comprised 21,480 patients (Figure 1). The numbers of arrests in working-age-patients, early-senior-patients, and late-senior-patients were as follows: n=7,227 (33.7%), n=8,919 (41.5%), and n=5,334 (24.8%), respectively (Table 1); the average incidence rate was 19.7, 143.4, and 258.6 OHCA per 100,000 persons per year (with the background population being on average between 2001 and 2011: 3,461,617 residents aged 18–65 years; 587,959 residents aged 66–80 years; and 194,921 residents aged >80 years),15 respectively (Supplemental Figure 1); median age was 57 years (25th–75th percentile 50–62), 73 years (25th–75th percentile 69–76), and 85 years (25th–75th percentile 82–88), respectively; and male sex constituted 75.0%, 69.2%, and 54.3%, respectively.

The distribution of comorbidities and use of medicine differed between the age groups (Supplemental Table 1). Roughly, all disease frequencies, including cardiovascular disease and cancer, were higher with increasing age group. A few exceptions were observed: liver disease and psychiatric illness were more frequent in working-age-patients; and chronic obstructive pulmonary disease, diabetes and peripheral vascular disease were more frequent in early-senior-patients.

Cardiac Arrest-related Characteristics

With increasing age group, patients were less likely to: have an arrest outside of the home (34.4% vs. 24.1% vs. 21.0%); receive bystander CPR (44.7% vs. 30.3% vs. 23.4%); have a shockable rhythm as a first-recorded heart rhythm (36.7% vs. 26.5% vs. 17.9); and receive a pre-hospital shock from a defibrillator by either a bystander or EMS personnel (54.7% vs. 45.0% vs. 33.8%), all p<0.001. The proportions of patients having a witnessed collapse and the estimated
median time interval from recognition of cardiac arrest to rhythm analysis by EMS were fairly similar between age groups (53.8% vs. 51.1% vs. 52.1%) and (11 minutes vs. 11 minutes vs. 12 minutes), respectively. All cardiac arrest-related characteristics stratified by age group are shown in Table 1.

Temporal Changes in Resuscitative Efforts by Bystander

During the study period, there was an increase in bystander CPR rates in all age groups (Figure 3). Nevertheless, CPR rates remained lower in early-senior-patients and late-senior-patients compared to working-age-patients. This pattern was consistent when analyzing only bystander-witnessed arrests (Supplemental Figure 2). Overall, bystander defibrillation remained limited and decreased with increasing age group (2.5% vs. 1.4% vs. 0.6%, p<0.001). Only working-age-patients and early-senior-patients experienced a significant increase in bystander defibrillation over time (working-age-patients 1.2% in 2001 to 4.2% in 2011; and early-senior-patients 1.2% in 2001 to 3.7% in 2011, p<0.001).

Temporal Changes in ROSC and Long-term Survival

A temporal increase in ROSC upon hospital arrival was observed in each age group with ROSC rates being the highest in working-age-patients and lowest in late-senior-patients throughout the study period (Figure 3). A temporal increase in 30-day and 1-year survival was most pronounced in working-age-patients followed by early-senior-patients (Figure 4), while the increase was numeric smaller in late-senior-patients. A similar tendency was observed when stratifying patients into shorter age intervals (Supplemental Figure 3), as well as when stratifying patients according to the first recorded heart rhythm (Figure 5). Also, temporal changes in absolute numbers of 30-day survivors (numerator) as dependent on population size (denominator) were tested and showed a similar pattern (Figure 6). The relative increase in 30-
day survival (2001–2003 vs. 2010–2011) was 3.04 (95% CI 2.51-3.68) in working-age-patients; 2.88 (95% CI 2.20-3.76) in early-senior-patients; and 1.81 (95% CI 0.96-3.42) in late-senior-patients.

**Long-term Survival in ROSC Patients**

Thirty-day and 1-year survival in those patients who had achieved ROSC upon hospital arrival are depicted in Figure 7. In those ROSC patients, 30-day and 1-year survival was without any significant change over time in working-age-patients and early-senior-patients, while a significant decrease was observed in late-senior-patients. In relation to first recorded heart rhythm, rates of shockable rhythm showed a decreasing trend over time in ROSC patients (Supplemental Figure 4) that was significant for late-senior-patients and early-senior-patients, but insignificant for working-age-patients.

**New Onset of Anoxic Brain Damage in 1-Year Survivors**

Overall, 9.8% of the 1-year survivors were diagnosed with anoxic brain damage during the period from hospital discharge to 30 days post-discharge. The corresponding numbers in working-age-patients, early-senior-patients, and late-senior-patients were as follows: 11.0%; 8.7%; and 1.4%, respectively, p=0.02 for differences and p=0.01 for age trend. Rates of anoxic brain damage decreased significantly over time in working-age-patients (p=0.003) (Figure 8), while no significant change over time was observed in early-senior-patients and late-senior-patients (p=0.96 and p=0.25, respectively).

**Patients with 30-Day Survival Close to None**

Out of 14,301 patients with a non-shockable rhythm as the first recorded heart rhythm, 238 patients (1.7%) achieved 30-day survival. Non-shockable rhythm appeared to be a fairly strong predictor for not achieving 30-day survival in late-senior-patients (30-day survival = 0.6%
corresponding to 22 patients), but was less strong in early-senior-patients (30-day survival = 1.3% corresponding to 80 patients) and in working-age-patients (30-day survival = 3.2% corresponding to 136 patients).

In addition, we tested 30-day survival in patients who met two criteria: (1) had not achieved ROSC upon hospital arrival; and (2) had not received a pre-hospital shock from a defibrillator. Using only the first criterion, 53 out of 16,444 patients (0.3%) achieved 30-day survival. Using only the second criterion, 103 out of 10,385 patients (0.99%) achieved 30-day survival. Using both criteria, three out of 9,499 patients achieved 30-day survival during the entire study period of 10.6 years (corresponding to 0.03%). 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%).

Other Analyses
If the above mentioned criteria [(1) and (2)] were fulfilled, a similar pattern was observed when patients with a presumed non-cardiac cause were included (a total of 28,861 patients); five out of 13,799 patients who fulfilled the two criteria achieved 30-day survival (corresponding to 0.04%). The distribution of the five 30-day survivors according to age group was as follows: working-age-patients 3/4885 (0.06%); early-senior-patients 1/5396 (0.02%); and late-senior-patients 1/3518 (0.03%).

Regarding missing data, the association between pre-selected age groups and (1) receiving bystander CPR and (2) achieving ROSC on arrival at the hospital were similar between the original dataset with missing data and the imputed datasets (Supplemental Table 2). Also, the association between 1-year increase in calendar year and (1) receiving bystander CPR and (2)
achieving ROSC on arrival at the hospital were similar between the original dataset and the imputed datasets (Supplemental Table 2).

Regarding patients who were excluded from the study due to missing Civil Registration Number: the excluded proportion (10.7% in Figure 1) was fairly stable over time (Supplemental Figure 5), and the proportion of these patients achieving ROSC was fairly similar to ROSC rates in patients with valid Civil Registration Number (Supplemental Figure 6).

**Discussion**

Our study had three major findings. First, a large increase in patients who had achieved ROSC upon hospital arrival was observed in each of the three age groups. Second, working-age-patients and early-senior-patients experienced a large increase in 30-day survival, while late-senior-patients only experienced a minor increase in 30-day survival; a similar tendency was observed when stratifying patients into shorter age intervals. Finally, two criteria could be used to identify patients with close to no chance of 30-day survival, irrespective of age: (1) no ROSC upon hospital arrival; and (2) no pre-hospital shock from a defibrillator.

**Age-related Differences**

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.\(^1\)

During the same time period, ROSC upon hospital arrival roughly tripled in each age group together with a three-fold increase in bystander CPR rates, which generally indicates that the national initiatives taken to improve cardiac arrest management have had a positive impact on all age groups in the pre-hospital setting. During the study period there have also been changes in
hospital management of cardiac arrest survivors which may have contributed to the improved long-term survival.1,7,8

The temporal increases in long-term survival were less pronounced with increasing age and practically failed in patients greater than 80 years old. The patients’ pre-arrest condition (physiologic reserve and co-morbidity) could be an explanation of why long-term survival remained low in late-senior-patients. With more than a three-fold increase in the numbers 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 has 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. 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 supported by the temporal decrease in rates of anoxic brain damage in working-age survivors, which generally must be considered a very 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 high-aged OHCA survivors are in acceptable health.12,19-21

Clinicians are at times faced with the dilemma of whether to continue or to 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 for 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 widely debated whether it is possible, a priori, to define a specific patient group where a resuscitation attempt is considered futile.\textsuperscript{17, 22-25} Several proposals have emerged, with one suggestion being the TOR rule by Verbeek et al.\textsuperscript{17} The 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.”\textsuperscript{17} Inspired by this rule, we retrospectively selected patients and tested 30-day survival if two criteria were fulfilled: (1) no ROSC upon hospital arrival; and (2) no pre-hospital shock from a defibrillator. Overall, these two criteria identified patients with no chance of 30-day survival fairly well, and irrespective of patient age. The third criterion by Verbeek was already fulfilled as the EMS-witnessed arrests were excluded in this study; this is an important aspect which overall insures a reasonable amount of time to use a defibrillator or achieve ROSC in the pre-hospital setting. The three 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, they could be useful in the decision-making process regarding when to terminate a resuscitation attempt.

Regarding the use of first recorded heart rhythm vs. status of defibrillation as a selecting criterion: overall, 28\% of the patients had a shockable rhythm as the first recorded heart rhythm, while 46\% received a pre-hospital shock from a defibrillator. This illustrates how having a non-
shockable rhythm can be a dynamic condition with chance of conversion to a shockable rhythm during treatment. The criterion “did not receive a pre-hospital shock from a defibrillator” acknowledges this aspect, whereas “did not have a shockable rhythm as the first recorded heart rhythm” does not; this might explain why the former criterion is favorable.

Limitations

Our study has several important limitations. The main limitation is the observational study design, thus the relationship between variables represents associations and they offer no direct causal link between factors. Also, while the data are suggestive of a positive effect of national initiatives, these findings are also associations. The fact that a series of national initiatives, including widespread CPR training, seem to have changed the habits of a western nation and increased the number of people who are able and willing to perform resuscitation can most likely be used by other countries. Similar, information on the age-related differences in survival and the identification of patients with minimal chance of 30-day survival can most likely be translated to other countries. Nonetheless, setting-related characteristics are important for the external validation of this study and differences in systems of care including ambulance response time and advanced post resuscitation care are likely to influence outcomes. Nevertheless, we believe that these study findings can be translated to densely populated communities with a possibility of bystander intervention, and where an ambulance is likely to be fairly close by.

We did not have qualitative data on more advanced outcome measures, and no data on neurologic outcome scores such as the Cerebral Performance Category score, yet we used discharge diagnosis codes to assess neurologic outcome. Importantly, the rate of new onset of anoxic brain damage in 1-year survivors was relatively low and even decreased over time in working-age-patients. These low rates of brain damage could be reflective of how: (1) one-year
survivors are a favorable group of patients; and/or (2) only patients with major anoxic brain damage are coded. The second notion could be an explanation of the low rates of brain damage in late-senior-patients, as they might be subject to less aggressive neurological examination and testing. Nevertheless, other studies support the first notion by demonstrating that OHCA survivors have a fairly good length and quality of life.\textsuperscript{26-28}

Over time there was a small decrease in the incidence of OHCA among working-age-patients and early-senior-patients (\textit{Supplemental Figure 1}). The cardiac arrest definition was the same throughout the study period and as a result the case definition should not affect temporal trends within the study population. But to adjust for the possibility that the increased survival percentages over time could be driven by increasingly underreporting of patients with poorest outcomes we tested temporal changes in absolute numbers of 30-day survivors for each age group. These analyses did not change the main findings so overall we did not find any indication that the increase in survival was driven by changes in reporting.

Overall, 10.7\% of the cardiac arrest patients were excluded from the study due to invalid or missing Civil Registration Number (individual-level linkage of information between the nationwide registries was impossible without the Civil Registration Number). This number includes tourists and other foreigners without permanent residence in Denmark. As data are missing, we cannot be completely certain that this has not affected the absolute number of 30-day survivors who survived with the two criteria: (1) had not achieved ROSC upon hospital arrival; and (2) had not received a pre-hospital shock from a defibrillator. However, we find it highly unlikely that 30-day survivors with missing Civil Registration Number should be related to surviving the extreme scenario where only three out of 9,499 patients achieved 30-day survival. Moreover, missing data on Civil Registration Number should not affect the temporal
changes in survival systematically nor the age-related differences in survival, as the proportion
with invalid or missing Civil Registration Number was stable over time and each Danish resident
is assigned a Civil Registration Number and included in the administrative registries used,
irrespective of age. Also, patients with invalid or missing Civil Registration Number were not
associated with lower ROSC rates compared to patients with valid Civil Registration Number.

Finally, a number of patients had missing data for the cardiac arrest-related variables;
however, comparing estimates from the original 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. Hence, we did not find any indication that
missing data influenced our main conclusions.

Conclusions
Our nationwide OHCA study focused on the impact of patient’s age on changes in survival
during an 11-year study period. The increase in ROSC upon hospital arrival was observed
irrespective of patient age, while the increase in 30-day and 1-year survival was most prominent
in patients aged 18–80 years, and little to no change was observed in patients aged >80 years.
These findings indicate that the national initiatives taken to improve cardiac arrest management
had an impact on short-term survival for all age groups, but improvements in cardiac arrest
management had hardly any impact on long-term survival for patients aged >80 years. Finally,
using only two criteria upon arrival at the hospital, it was possible to identify patients who had
almost no chance of 30-day survival; this could be helpful in the decision-making process
regarding when to terminate a resuscitation attempt.
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Conflict of Interest Disclosures: Dr Lippert is serving as a board member for TrygFonden. Dr Køber has received payment for speaking at a symposium arranged by Servier. Dr. Gislason is supported by an independent research scholarship from the Novo Nordisk Foundation. Dr Torp-Pedersen is serving as a consultant for Cardiome, Merck, Sanofi, and Daiichi and has received grants or grants pending from Bristol-Myers Squibb. No other authors have disclosures.

References:


Table 1. Demographic and Cardiac Arrest-Related Characteristics* Stratified by Age Group†

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Working-Age n=7,227</th>
<th>Early-Senior n=8,919</th>
<th>Late-Senior n=5,334</th>
<th>p-value‡</th>
<th>All patients n=21,480</th>
<th>Missing data n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex, n (%)</td>
<td>5,417 (75.0)</td>
<td>6,170 (69.2)</td>
<td>2,894 (54.3)</td>
<td>&lt;0.001</td>
<td>14,481 (67.4)</td>
<td>0‡</td>
</tr>
<tr>
<td>Median age, y (25th–75th percentile)</td>
<td>57 (50-62)</td>
<td>73 (70-77)</td>
<td>85 (83-89)</td>
<td>-</td>
<td>72 (62-80)</td>
<td>0‡</td>
</tr>
<tr>
<td>Male age</td>
<td>57 (50-62)</td>
<td>73 (69-77)</td>
<td>85 (82-88)</td>
<td>-</td>
<td>70 (60-79)</td>
<td>0‡</td>
</tr>
<tr>
<td>Female age</td>
<td>57 (50-62)</td>
<td>74 (70-77)</td>
<td>86 (83-90)</td>
<td>-</td>
<td>75 (65-84)</td>
<td>0‡</td>
</tr>
<tr>
<td>Living alone, n (%)</td>
<td>2,556 (35.4)</td>
<td>2,936 (32.9)</td>
<td>3,007 (56.4)</td>
<td>&lt;0.001</td>
<td>8,499 (39.6)</td>
<td>14 (0.07)</td>
</tr>
<tr>
<td>Arrest in private home, n (%)</td>
<td>4,000 (65.6)</td>
<td>5,715 (75.9)</td>
<td>3,598 (79.0)</td>
<td>&lt;0.001</td>
<td>13,313 (73.2)</td>
<td>3,293 (15.3)</td>
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<tr>
<td>Bystander-witnessed arrest, n (%)</td>
<td>3,679 (53.8)</td>
<td>4,338 (51.1)</td>
<td>2,530 (52.1)</td>
<td>0.004</td>
<td>10,547 (52.3)</td>
<td>1,299 (6.1)</td>
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<td>Bystander CPR, n (%)</td>
<td>3,070 (44.7)</td>
<td>2,575 (30.3)</td>
<td>1,142 (23.4)</td>
<td>&lt;0.001</td>
<td>6,787 (33.5)</td>
<td>1,226 (5.7)</td>
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<td>AED use by bystander, n (%)</td>
<td>167 (2.5)</td>
<td>111 (1.4)</td>
<td>29 (0.6)</td>
<td>&lt;0.001</td>
<td>307 (1.6)</td>
<td>1,921 (8.9)</td>
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<tr>
<td>Median time interval, min§ (25th–75th percentile)</td>
<td>11 (7-18)</td>
<td>11 (7-19)</td>
<td>12 (7-19)</td>
<td>0.01</td>
<td>11 (7-18)</td>
<td>3,702 (17.2)</td>
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<td>Shockable heart rhythm, n (%)</td>
<td>2,477 (36.7)</td>
<td>2,196 (26.5)</td>
<td>859 (17.9)</td>
<td>&lt;0.001</td>
<td>5,532 (27.9)</td>
<td>1,647 (7.7)</td>
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<tr>
<td>AED use by EMS personnel, n (%)</td>
<td>3,480 (53.6)</td>
<td>3,569 (44.3)</td>
<td>1,527 (33.6)</td>
<td>&lt;0.001</td>
<td>8,576 (44.9)</td>
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<td>ROSC on arrival at the hospital, n (%)</td>
<td>1,283 (19.6)</td>
<td>1,079 (13.3)</td>
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<td>2,762 (14.4)</td>
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<td>30-day survival, n (%)</td>
<td>952 (13.2)</td>
<td>497 (5.6)</td>
<td>105 (2.0)</td>
<td>&lt;0.001</td>
<td>1,554 (7.2)</td>
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<td>1-year survival, n (%)</td>
<td>898 (12.4)</td>
<td>446 (5.0)</td>
<td>71 (1.3)</td>
<td>&lt;0.001</td>
<td>1,415 (6.6)</td>
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</tbody>
</table>

*For the entire study period, 2001 consists of 7 months from June to December.
†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.
§Patients with missing or invalid civil registration number used to link information on patient’s age, sex, and survival status were excluded from this study.
¶Estimated time interval from recognition of OHCA to rhythm analysis by EMS.
Abbreviations: AED, automated external defibrillators; CPR, cardiopulmonary resuscitation; EMS, emergency medical service; OHCA, out-of-hospital cardiac arrest; ROSC, return of spontaneous circulation.
Figure Legends:

**Figure 1.** Patient Selection. Flowchart of the patient selection process for the study population 2001–2011. Abbreviations: EMS, emergency medical services

**Figure 2.** Thirty-day Survival in Relation to Age. The distribution of observed 30-day survival rates at each age level. A smoothing transformation was applied to display the overall pattern in 30-day survival rates according to patient age.

**Figure 3.** Bystander CPR and ROSC on Arrival at the Hospital Following Out-of-Hospital Cardiac Arrest, 2001-2011. Temporal trends in proportions of patients who received bystander CPR, and had achieved ROSC on arrival at the hospital, respectively, according to age group. Changes over time were tested a two-sided p-value <0.05 was considered to be statistically significant. Abbreviations: CPR, cardiopulmonary resuscitation; ROSC, return of spontaneous circulation; *, p<0.001.

**Figure 4.** Thirty-day Survival and 1-year Survival Following Out-of-Hospital Cardiac Arrest, 2001-2011. Temporal trends in proportions of patients achieving 30-day survival, and 1-year survival, 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=0.001.

**Figure 5.** 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.

**Figure 6.** Numbers of Thirty-day Survivors Following Out-of-Hospital Cardiac Arrest, 2001-2011. Temporal trends in numbers of 30-day survivors, according to age group. During the study period, the size of the background population was on average: 3,461,617 residents aged 18–65 years; 587,959 residents aged 66–80 years; and 194,921 residents aged >80 years. But when calculating the specific incidences for each calendar year we used the size of the background population for the corresponding calendar year. Changes over time were tested; a two-sided p-value <0.05 was considered to be statistically significant. Abbreviations: * indicates p<0.001; and †, p<0.01.

**Figure 7.** Thirty-day and 1-year Survival in ROSC Patients, 2001–2011. Thirty-day survival and 1-year survival in those patients who had achieved ROSC on arrival at the hospital, 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; ROSC, return of spontaneous circulation; *, p<0.05.

**Figure 8.** New Onset of Anoxic Brain Damage in 1-year Survivors, 2001–2011. Temporal trends in new onset of anoxic brain damage in 1-year survivors aged 18–65 years. New onset was defined as: (1) patients diagnosed with anoxic brain damage during the period from hospital discharge to thirty days post-discharge; and (2) no history of anoxic brain damage up to ten years before the cardiac arrest. Changes over time were tested a two-sided p-value <0.05 was considered to be statistically significant. Abbreviations: *, p<0.01.
36,987 patients with Out-of-Hospital Cardiac Arrest in whom resuscitation was attempted

- 3,953 (10.7%) were excluded because of invalid or missing civil registration number
- 89 (0.2%) were excluded due to patients with second and third time arrest
- 62 (0.2%) were excluded due to missing data concerning hospital admission
- 126 (0.3%) were excluded due to missing data concerning cardiac cause

32,757 patients

- 8,607 (26.3%) were non-cardiogenic arrest and excluded
- 2,536 (10.6%) were EMS-witnessed arrest and excluded

24,016 patients

- 348 (1.1%) were below 18 years of age and excluded

21,480 patients were included for further analyses
Figure 2

![Graph showing thirty-day survival, observed percentages vs. age at cardiac arrest. The graph displays two lines representing 30-day survival: one for observed percentages and another for predicted percentages. The x-axis represents age at cardiac arrest, ranging from 20 to 100, and the y-axis represents thirty-day survival percentage, ranging from 0 to 50.](image-url)
Figure 3

Bystander CPR, %

ROSC in "working-age" patients
Bystander CPR in "early-senior" patients
Bystander CPR in "late-senior" patients

Year

ROSC on Arrival at the Hospital, %

ROSC in "working-age" patients
ROSC in "early-senior" patients
ROSC in "late-senior" patients

Year
Survival in "working-age" patients
Survival in "early-senior" patients
Survival in "late-senior" patients

(1) Patients with a shockable rhythm
(2) Patients with a non-shockable rhythm
Figure 6

"Working-age" survivors

"Early-senior" survivors

"Late-senior" survivors
Survival After Out-of-Hospital Cardiac Arrest in Relation to Age and Early Identification of
Patients with Minimal Chance of Long-Term Survival

Mads Wissenberg, Fredrik Folke, Carolina Malta Hansen, Freddy K. Lippert, Kristian Kragholm,
Bjarke Risgaard, Shahzleen Rajan, Lena Karlsson, Kathrine Bach Søndergaard, Steen M. Hansen,
Rikke Normark Mortensen, Peter Weeke, Erika Frischknecht Christensen, Søren L. Nielsen, Gunnar
H. Gislason, Lars Køber and Christian Torp-Pedersen

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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/2015/03/06/CIRCULATIONAHA.114.013122

Data Supplement (unedited) at:
http://circ.ahajournals.org/content/suppl/2015/03/06/CIRCULATIONAHA.114.013122.DC1
**SUPPLEMENTAL MATERIAL**

**Supplemental Tables**

**Supplemental Table 1. Discharge Diagnoses from Hospital up to 10 Years before Cardiac Arrest and Patient’s Use of Medicine up to 180 Days before Cardiac Arrest**

<table>
<thead>
<tr>
<th>Comorbidity, n (%)</th>
<th>Working-Age*</th>
<th>Early-Senior*</th>
<th>Late-Senior*</th>
<th>p-value†</th>
<th>All patients</th>
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<tbody>
<tr>
<td>Peripheral vascular disease</td>
<td>501 (6.9)</td>
<td>1,205 (13.5)</td>
<td>610 (11.4)</td>
<td>&lt;0.001</td>
<td>2,316 (10.8)</td>
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<tr>
<td>Cerebral vascular disease</td>
<td>516 (7.1)</td>
<td>1,280 (14.4)</td>
<td>913 (17.1)</td>
<td>&lt;0.001</td>
<td>2,709 (12.6)</td>
</tr>
<tr>
<td>Ischemic heart disease (MI excluded)</td>
<td>1,312 (18.2)</td>
<td>2,641 (29.6)</td>
<td>1,603 (30.1)</td>
<td>&lt;0.001</td>
<td>5,556 (25.9)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>631 (8.7)</td>
<td>1,232 (13.8)</td>
<td>904 (17.0)</td>
<td>&lt;0.001</td>
<td>2,767 (12.9)</td>
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<td>Cardiac dysrhythmia</td>
<td>732 (10.1)</td>
<td>1,902 (21.3)</td>
<td>1,543 (28.9)</td>
<td>&lt;0.001</td>
<td>4,177 (19.5)</td>
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<td>Heart failure</td>
<td>949 (13.1)</td>
<td>2,075 (23.3)</td>
<td>1,507 (28.3)</td>
<td>&lt;0.001</td>
<td>4,531 (21.1)</td>
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<td>Diabetes</td>
<td>1,041 (14.4)</td>
<td>1,540 (17.3)</td>
<td>708 (13.3)</td>
<td>&lt;0.001</td>
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<td>Condition</td>
<td>n</td>
<td>(%)</td>
<td>n</td>
<td>(%)</td>
<td>n</td>
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<td>COPD</td>
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<td>1,665</td>
<td>(18.7)</td>
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<td>Malignancy</td>
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<td>1,127</td>
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<td>Renal disease</td>
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<td>Liver disease</td>
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<td>154</td>
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<td>Peptic ulcer</td>
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<td>Psychiatric illness</td>
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<td>Dementia</td>
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**Pharmacotherapy, n (%)**

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<th>n</th>
<th>(%)</th>
<th>n</th>
<th>(%)</th>
<th>n</th>
<th>(%)</th>
<th>p-value</th>
<th>(trend)</th>
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<td>Antithrombotic agents</td>
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<td>(57.3)</td>
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<td>Cholesterol lowering drugs</td>
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<td>2,669</td>
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<td>920</td>
<td>(17.3)</td>
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<td>Drug Class</td>
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<td>Calcium inhibitors</td>
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<td>(13.9)</td>
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<td>Glucose lowering medication</td>
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<td>(13.7)</td>
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<td>Bronchial dilators</td>
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<td>(18.1)</td>
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<td>(5.8)</td>
<td>(12.7)</td>
<td>(11.4)</td>
<td></td>
<td>(10.1)</td>
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<td>Antidepressants</td>
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<td>3,721</td>
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<td>(14.5)</td>
<td>(17.3)</td>
<td>(21.2)</td>
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<td>(17.3)</td>
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<td>Medical Class</td>
<td>Working-Age</td>
<td>Early-Senior</td>
<td>Late-Senior</td>
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<td>Sedatives/anxiolytics</td>
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<td>(20.5)</td>
<td>(26.4)</td>
<td>(29.2)</td>
<td></td>
<td>(25.1)</td>
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<tr>
<td>Anti-psychotic medication</td>
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<td>(6.8)</td>
<td>(6.9)</td>
<td></td>
<td>(7.6)</td>
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</tr>
<tr>
<td>Analgesics‡</td>
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<td>(31.6)</td>
<td>(40.7)</td>
<td>(48.6)</td>
<td></td>
<td>(39.6)</td>
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</tbody>
</table>

*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
Supplemental Table 2. Associations between Pre-Selected Age Groups and (1) Bystander CPR and (2) ROSC upon Arrival at the Hospital according to Observed Dataset and Imputed Datasets

<table>
<thead>
<tr>
<th>Reference group: working-age-patients</th>
<th>Observed dataset</th>
<th>Imputed datasets</th>
<th>Number with Missing Data n (%)</th>
</tr>
</thead>
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<tr>
<td></td>
<td>Odds ratio</td>
<td>Odds ratio</td>
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</tr>
<tr>
<td></td>
<td>(95% CI)</td>
<td>(95% CI)</td>
<td></td>
</tr>
<tr>
<td>Bystander CPR vs. without bystander CPR</td>
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<td>-</td>
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</tr>
<tr>
<td>Early-senior-patients</td>
<td>0.538</td>
<td>0.541</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>(0.503-0.575)</td>
<td>(0.506-0.578)</td>
<td></td>
</tr>
<tr>
<td>Late-senior-patients</td>
<td>0.379</td>
<td>0.369</td>
<td>-</td>
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<td></td>
<td>(0.349-0.411)</td>
<td>(0.341-0.400)</td>
<td></td>
</tr>
<tr>
<td>ROSC vs. no ROSC upon arrival at the hospital</td>
<td>-</td>
<td>-</td>
<td>2,274</td>
</tr>
<tr>
<td>Early-senior-patients</td>
<td>0.632</td>
<td>0.629</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>(0.579-0.691)</td>
<td>(0.577-0.685)</td>
<td></td>
</tr>
<tr>
<td>Reference group:</td>
<td>Observed dataset</td>
<td>Imputed datasets</td>
<td>Number with Missing Data</td>
</tr>
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<td>------------------</td>
<td>-------------------------</td>
</tr>
<tr>
<td>calendar year as a continuous variable</td>
<td>Odds ratio (95% CI)</td>
<td>Odds ratio (95% CI)</td>
<td>n (%)</td>
</tr>
<tr>
<td>1-year increase in calendar year</td>
<td>Late-senior-patients</td>
<td>0.398 (0.353-0.448)</td>
<td>0.389 (0.346-0.439)</td>
</tr>
<tr>
<td></td>
<td>Bystander CPR vs. without bystander CPR</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>working-age-patients</td>
<td>1.163 (1.145-1.182)</td>
<td>1.165 (1.147-1.184)</td>
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<tr>
<td></td>
<td>Early-senior-patients</td>
<td>1.212 (1.193-1.232)</td>
<td>1.215 (1.196-1.234)</td>
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<td></td>
<td>Late-senior-patients</td>
<td>1.208 (1.179-1.237)</td>
<td>1.219 (1.190-1.247)</td>
</tr>
<tr>
<td>ROSC vs. no ROSC upon Arrival at the Hospital</td>
<td>-</td>
<td>-</td>
<td>2,274</td>
</tr>
<tr>
<td>Age Group</td>
<td>CI</td>
<td>Abbreviations: CI=confidence interval; CPR, cardiopulmonary resuscitation; ROSC, return of spontaneous circulation.</td>
<td></td>
</tr>
<tr>
<td>---------------------------</td>
<td>----------------</td>
<td>-------------------------------------------------</td>
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</tr>
<tr>
<td>working-age-patients</td>
<td>1.174 (1.150-1.198)</td>
<td>1.180 (1.156-1.204)</td>
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<tr>
<td>Early senior-patients</td>
<td>1.175 (1.151-1.199)</td>
<td>1.175 (1.151-1.199)</td>
<td></td>
</tr>
<tr>
<td>Late senior-patients</td>
<td>1.158 (1.118-1.200)</td>
<td>1.166 (1.125-1.209)</td>
<td></td>
</tr>
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Supplemental Figures and Figure Legends

Supplemental Figure 1

**Absolute Incidence of Out-of-Hospital Cardiac Arrest, 2001-2011**

Temporal trends in absolute incidence of out-of-hospital cardiac arrest, according to age group.

During the study period, the size of the background population was on average: 3,461,617 residents aged 18–65 years; 587,959 residents aged 66–80 years; and 194,921 residents aged >80 years. But when calculating the specific incidences for each calendar year we used the size of the background population for the corresponding calendar year. Changes over time were tested; a two-sided p-value <0.05 was considered to be statistically significant.

Abbreviations: NS, not significant; OHCA, out-of-hospital cardiac arrest; * p<0.01
Supplemental Figure 2

Supplemental Figure 2. Bystander CPR in Witnessed Arrest Following Out-of-Hospital Cardiac Arrest, 2001–2011

Temporal trends in proportions of witnessed cardiac arrest patients who received bystander CPR, according to age group. Changes over time were tested; a two-sided p-value <0.05 was considered to be statistically significant.

Abbreviations: CPR, cardiopulmonary resuscitation;
*, p<0.001
Supplemental Figure 3

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.
Supplemental Figure 4. Initial Shockable Heart Rhythm in ROSC Patients, 2001–2011

Shockable rhythm, as first recorded heart rhythm, in those patients who achieved ROSC upon arrival at the hospital, 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; ROSC, return of spontaneous circulation; *, p=0.01; †, p<0.05
Supplemental Figure 5

Proportion of patients with invalid or missing Civil Registration Number

Temporal trend in proportion of patients with invalid or missing Civil Registration Number. Changes over time were tested a two-sided p-value <0.05 was considered to be statistically significant. There was no significant change over time, p=0.096.

The number of cardiac arrest patients with: (1) invalid or missing Civil Registration Number; and (2) known date of cardiac arrest was n = 3675 which corresponds to 9.9% of the patients before any selection. This is a little lower compared to the 10.7% represented in Figure 1, and is due to patients with unknown date of cardiac arrest, as these patients could not be included in the temporal trend analysis. Abbreviations: NS, not significant.
Supplemental Figure 6

Supplemental Figure 6. Proportion of patients achieving ROSC in relation to missing Civil Registration Number

Temporal trends in proportion of cardiac arrest patients (all cause) who had achieved ROSC upon hospital arrival according to whether Civil Registration Number was invalid or missing. Changes over time were tested a two-sided p-value <0.05 was considered to be statistically significant. The number of cardiac arrest patients with: (1) invalid or missing Civil Registration Number; (2) known date of cardiac arrest; and (3) known status of ROSC was n = 3404 which corresponds to 9.2% of the patients before any selection. This is a little lower compared to the 10.7% represented in Figure 1, and is due to a combination of patients with unknown date of cardiac arrest and unknown status of ROSC, as these patients could not be included in the temporal trend analysis. Abbreviations: * indicates p<0.001