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

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

Methods and Results—Using data from the nationwide Danish Cardiac Arrest Registry (2001–2011), we identified 21,480 patients ≥18 years old with a presumed cardiac-caused out-of-hospital cardiac arrest for which resuscitation was attempted. Patients were divided into 3 preselected age-groups: working-age patients 18 to 65 years of age (33.7%), early senior patients 66 to 80 years of age (41.5%), and late senior patients >80 years of age (24.8%). Characteristics in working-age patients, early senior patients, and late senior patients were as follows: witnessed arrest in 53.8%, 51.1%, and 52.1%; bystander cardiopulmonary resuscitation in 44.7%, 30.3%, and 23.4%; and prehospital shock from a defibrillator in 54.7%, 45.0%, and 33.8% (all \(P<0.05\)). Between 2001 and 2011, return of spontaneous circulation on hospital arrival increased: working-age patients, from 12.1% to 34.6%; early senior patients, from 6.4% to 21.5%; and late senior patients, from 4.0% to 15.0% (all \(P<0.001\)). Furthermore, 30-day survival increased: working-age patients, 5.8% to 22.0% (\(P<0.001\)); and early senior patients, 2.7% to 8.4% (\(P<0.001\)), whereas late senior patients experienced only a minor increase (1.5% to 2.0%; \(P=0.01\)). Overall, 3 of 94,99 patients achieved 30-day survival if they met 2 criteria: had not achieved return of spontaneous circulation on hospital arrival and had not received a prehospital shock from a defibrillator.

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

Key Words: age ■ heart arrest ■ resuscitation ■ survival

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

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In parallel with national initiatives to improve cardiac arrest management in Denmark, survival approximately tripled between 2001 and 2010. However, the impact of patient 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 prehospital criteria to identify patients with a very low chance of 30-day survival, regardless of age, because 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 ≈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 to rendezvous with basic life support ambulances. Throughout the study period, treatment was given according to the latest guidelines on resuscitation and emergency cardiovascular care.

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 in whom resuscitation attempts were not initiated. The capture of OHCA cases is close to complete because EMS is activated for all severe clinical conditions in Denmark (including cardiac arrests) and EMS is required to fill out a case report form for every OHCA, thereby forming the Danish Cardiac Arrest Registry. For the present study, we included information on date; time; location of arrest (outside private home versus inside private home); whether the collapse was not witnessed or witnessed by a bystander or EMS; whether a bystander initiated cardiopulmonary resuscitation (CPR) or defibrillated the patient using an automatic external defibrillator located outside the hospital; first observed heart rhythm (shockable rhythm [ventricular fibrillation or pulseless ventricular tachycardia] or nonshockable rhythm [asystole or pulseless electric 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 and from 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) on arrival at the hospital.

To study and compare a more homogeneous group of patients, we categorized cardiac arrests into presumed noncardiac cause and presumed cardiac cause of arrest, as recommended by the Utstein template and as done previously. 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 noncardiac cause. Trauma, including various accidents, violent attacks, and attempted suicides, was, together with drug overdose, defined as a noncardiac cause regardless of other diagnoses.

Patients with age <18 years, a presumed noncardiac cause of arrest, and an EMS-witnessed arrest were excluded from the final study population (Figure 1). The patients were then divided into preselected age groups in different ways, with the primary age groups being working-age patients 18 to 65 years of age, early senior patients 66 to 80 years of age, and late senior patients >80 years of age. To acknowledge that aging represents a continuum with a gradual decrease in physiological reserve and functioning throughout life, 30-day survival was also tested in smaller age intervals. In addition, a smoothing spline transformation was conducted to display the overall pattern in 30-day survival rates at each age level, which illustrated a nonlinear relationship (Figure 2).

To identify patients with a minimal chance of long-term survival, regardless of age, we tested the 30-day survival rate among patients with a nonshockable rhythm. This was inspired by our earlier study in which the first recorded heart rhythm appeared to be one of the strongest prehospital factors associated with 30-day survival. Furthermore, inspired by the termination of resuscitation rule by Verbeek et al, we tested 30-day survival rate in patients who met 2 criteria: had not received a shock from a defibrillator in the prehospital 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 from nationwide registries. This number is used in all interactions with the Danish government agencies, including all contacts with the...
single-payer tax-funded public healthcare system, and ensures that
the administrative registries are close to complete.

Information on age, sex, vital status, and civil status was obtained
from the Civil Registry. Discharge diagnosis codes, provided by phy-
sicians, and admission and discharge dates from all Danish hospitals
were obtained from the Danish National Patient Registry. To investi-
gate patients’ comorbidity, discharge diagnoses were examined up
to 10 years before OHCA. In addition, new onset of anoxic brain
damage in 1-year survivors was examined. New onset was defined as
a diagnosis of anoxic brain damage during the period from hospital
discharge to 30 days after discharge and no history of anoxic brain
damage up to 10 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 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 clas-
sified according to the Anatomical Therapeutic Chemical system. All
administrative registries have been described in detail elsewhere.15

End Points

The main outcome measures were ROSC on hospital arrival and
30-day survival according to preselected age groups.

Statistics

To test for differences between the preselected age groups, we used a
χ² test for binary variables and the Kruskal-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 regres-
sion models were used to test for temporal changes in binary vari-
able, and Poisson regression analyses were used to test for temporal
changes in OHCA incidence and number of 30-day survivors. When
percentages and medians were calculated, 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). To test whether missing data could introduce bias into the
study, we applied the multivariate imputation by chained equations
method. With the use of the multivariate imputation by chained equa-
tions method, missing values were imputed using information from all
variables in the Table and Table I in the online-only Data Supplement,
and 10 imputed data sets were constructed (complete data sets with
observed and imputed values). We then compared estimates from the
original data set (incomplete data set containing missing data) with
estimates from the imputed data sets. A 2-sided value of P<0.05 was
considered statistically significant. Data management and analyses
were carried out with SAS version 9.4 (SAS Institute Inc, Cary, NC)
and R version 2.15.2 (R Development Core Team).

Ethics

This study was approved by the Danish Data Protection Agency
02735). In Denmark, ethics approval is not required for retrospec-
tive 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=7227 (33.7%), n=8919 (41.5%), and n=5334 (24.8%), respectively
(Table). The average incidence rates were 19.7, 143.4, and 258.6
OHCAs per 100,000 persons per year (with the background
population being, on average, 3,461,617 residents 18–65 years of
age, 587,959 residents 66–80 years of age, and 194,921 residents
>80 years of age),15 respectively (Figure I in the online-only Data
Supplement). The median age was 57 years (25th–75th percent-
ile [Q1-Q3], 50–62 years), 73 years (Q1-Q3, 69–76 years), and
85 years (Q1-Q3, 82–88 years), respectively, and male sex con-
stituted 75.0%, 69.2%, and 54.3%, respectively.

The distribution of comorbidities and use of medicine dif-
fered between the age groups (Table I in the online-only Data
Supplement). Roughly, all disease frequencies, including cardio-
vascular disease and cancer, were higher with increasing age.
A few exceptions were observed. Liver disease and psychiatric
illness were more frequent in working-age patients, and chronic
obstructive pulmonary disease, diabetes mellitus, and peripheral
vascular disease were more frequent in early senior patients.

Cardiac Arrest–Related Characteristics

With increasing age, patients were less likely to have an arrest
outside of the home (34.4% versus 24.1% versus 21.0%), to
receive bystander CPR (44.7% versus 30.3% versus 23.4%),
to have a shockable rhythm as a first recorded heart rhythm
(36.7% versus 26.5% versus 17.9%), and to receive a prehos-
pital shock from a defibrillator by either a bystander or EMS
personnel (54.7% versus 45.0% versus 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% versus 51.1% versus 52.1%; and 11 versus
11 versus 12 minutes, respectively). All cardiac arrest–related
characteristics stratified by age group are shown in the Table.

Temporal Changes in Resuscitative Efforts by
Bystanders

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 with working-age patients. This pattern
was consistent when only bystander-witnessed arrests were
analyzed (Figure II in the online-only Data Supplement).
Overall, bystander defibrillation remained limited and
decreased with increasing age group (2.5% versus 1.4% ver-
sus 0.6%; P<0.001). Only working-age patients and early
Male sex, n (%) 5417
(75.0) 4170 (69.2) 2894 (64.3) 14481 (67.4)

Median age (25th–75th percentile), y 57
(50–62) 73 (69–77) 85 (83–89) ... 72 (62–80)

Male age, y 57
(50–62) 73 (69–77) 85 (82–88) ... 70 (60–79)

Female age, y 57
(50–62) 74 (67–77) 86 (68–90) ... 75 (65–84)

Living alone, n (%) 2556
(35.4) 2936 (32.9) 3007 (64.4) 8499 (39.6)

Arrest in private home, n (%) 4000
(65.6) 5715 (75.9) 3598 (79.0) 13313 (73.2)

Bystander-witnessed arrest, n (%) 3679
(53.8) 4338 (51.1) 2530 (52.1) 10547 (50.3)

Bystander CPR, n (%) 3070
(44.7) 2575 (30.3) 1142 (23.4) 6787 (33.5)

AED use by bystander, n (%) 167
(2.5) 111 (1.4) 29 (0.6) 307 (1.6)

Median time interval (25th–75th percentile), min 11
(7–18) 11 (7–19) 12 (7–19) 11 (7–18)

Shockable heart rhythm, n (%) 2477
(36.7) 2196 (26.5) 859 (17.9) 5532 (27.9)

AED use by EMS personnel, n (%) 3480
(53.6) 3569 (44.3) 1527 (33.6) 8576 (44.9)

ROSC on arrival at the hospital, n (%) 1283
(19.6) 1079 (13.3) 400 (8.8) 2762 (14.4)

30-d survival, n (%) 952
(13.2) 497 (5.6) 105 (2.0) 1554 (7.2)

1-y survival, n (%) 898
(12.4) 446 (6.0) 71 (1.3) 1415 (6.6)

AED indicates automated external defibrillator; CPR, cardiopulmonary resuscitation; EMS, emergency medical service; OHCA, out-of-hospital cardiac arrest; and ROSC, return of spontaneous circulation.

*For the entire study period, 2001 consists of 7 months from June to December.
†Patients were divided into 3 preselected age groups: working-age patients 18 to 65 years of age; early senior patients 66 to 80 years of age; and late senior patients >80 years of age.
‡The χ² test was used to test for differences between 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 the χ² test. A value of P<0.05 was considered 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.

Long-Term Survival in ROSC Patients
Thirty-day survival and 1-year survival in those patients who had achieved ROSC on hospital arrival are depicted in Figure III in the online-only Data Supplement and when patients were stratified according to the first recorded heart rhythm (Figure 5). In addition, 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 versus 2010–2011) was 3.04 (95% confidence interval, 2.51–3.68) in working-age patients, 2.88 (95% confidence interval, 2.20–3.76) in early senior patients, and 1.81 (95% confidence interval, 0.96–3.42) in late senior patients.

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 on 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), whereas the increase was numerically smaller in late senior patients. A similar tendency was observed when patients were stratified into smaller age intervals (Figure III in the online-only Data Supplement) and when patients were stratified according to the first recorded heart rhythm (Figure 5). In addition, 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 versus 2010–2011) was 3.04 (95% confidence interval, 2.51–3.68) in working-age patients, 2.88 (95% confidence interval, 2.20–3.76) in early senior patients, and 1.81 (95% confidence interval, 0.96–3.42) in late senior patients.
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, whereas 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 (Figure IV in the online-only Data Supplement) 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 after 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), whereas 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

Of 14301 patients with a nonshockable rhythm as the first recorded heart rhythm, 238 patients (1.7%) achieved 30-day survival. Nonshockable rhythm appeared to be a fairly strong predictor for not achieving 30-day survival in late senior patients (30-day survival, 0.6%, 22 patients) but was less strong in early senior patients (30-day survival, 1.3%, 80 patients) and in working-age patients (30-day survival, 3.2%, 136 patients).

In addition, we tested 30-day survival in patients who met 2 criteria: had not achieved ROSC on hospital arrival and had not received a prehospital shock from a defibrillator. With the use of only the first criterion, 53 of 16444 patients (0.3%) achieved 30-day survival. With the use of only the second criterion, 103 of 10385 patients (0.99%) achieved 30-day survival. With the use of both criteria, 3 of 9499 patients (0.03%) achieved 30-day survival during the entire study period of 10.6 years. The three 30-day survivors were equally distributed, with 1 survivor in each of the preselected age groups: working-age patients, 1 of 2683 (0.04%); early senior patients, 1 of 4047 (0.02%); and late senior patients, 1 of 2769 (0.04%).
Other Analyses

If the 2 above-mentioned criteria were fulfilled, a similar pattern was observed when patients with a presumed non-cardiac cause were included (a total of 28,861 patients); 5 of 13,799 patients (0.04%) who fulfilled the 2 criteria achieved 30-day survival. The distribution of the five 30-day survivors according to age group was as follows: working-age patients, 3 of 4,885 (0.06%); early senior patients, 1 of 5,396 (0.02%); and late senior patients, 1 of 3,518 (0.03%).

In terms of missing data, the associations between preselected age groups and receiving bystander CPR and achieving ROSC on arrival at the hospital were similar between 2000-2002, 2004, 2006, 2008, 2010, and 2012.

Figure 5. Thirty-day survival in relation to first recorded heart rhythm, 2001 to 2011. Temporal trends in proportions of patients achieving 30-day survival for patients with a shockable rhythm and a nonshockable rhythm according to age group. Changes over time were tested; a 2-sided value of \( P<0.05 \) was considered statistically significant. \( \dagger P<0.001; \dagger P<0.01. \)

Figure 6. Numbers of 30-day survivors after out-of-hospital cardiac arrest, 2001 to 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 18 to 65 years of age, 587,959 residents 66 to 80 years of age, and 194,921 residents >80 years of age. However, 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 2-sided value of \( P<0.05 \) was considered statistically significant. \( * P<0.001; \dagger P<0.01. \)
the original data set with missing data and the imputed data sets (Table II in the online-only Data Supplement). In addition, the associations between 1-year increase in calendar year and receiving bystander CPR and achieving ROSC on arrival at the hospital were similar between the original data set and the imputed data sets (Table II in the online-only Data Supplement).

In terms of patients who were excluded from the study because of missing Civil Registration Number, the excluded proportion (10.7% in Figure 1) was fairly stable over time (Figure V in the online-only Data Supplement), and the ROSC rates in these patients were fairly similar to ROSC rates in patients with valid Civil Registration Numbers (Figure VI in the online-only Data Supplement).

**Discussion**

Our study had 3 major findings. First, a large increase in patients who had achieved ROSC on hospital arrival was observed in each of the 3 age groups. Second, working-age patients and early senior patients experienced a large increase in 30-day survival, whereas late senior patients experienced only a minor increase in 30-day survival; a similar tendency was observed when patients were stratified into smaller age intervals. Finally, 2 criteria could be used to identify patients with close to no chance of 30-day survival, regardless of age: no ROSC on hospital arrival and no prehospital shock from a defibrillator.

**Age-Related Differences**

Several national initiatives have been undertaken 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 on hospital arrival roughly tripled in each age group, along with a 3-fold increase in bystander CPR rates, which generally indicates that the national initiatives undertaken to improve cardiac arrest management have had a positive impact on all age groups in the prehospital 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 >80 years of age. The patients’ prearrest condition (physiological reserve and comorbidity) could be an explanation of why long-term survival remained low in late senior patients. With a >3-fold increase in the numbers of patients who had achieved ROSC on hospital arrival over time, it is very likely that the long-term survival potential in these additional ROSC patients has been lower, leading toward 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 before 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 because this probably reflects how senior patients were more susceptible to critical illness with a higher risk of dying during hospitalization, therefore only leaving a few, but well-conditioned, long-term survivors. Notably, other studies support the notion that most older OHCA survivors are in acceptable health.\textsuperscript{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 overcome these challenges and to standardize the decision-making process, it has been widely debated whether it is possible to define a priori a specific patient group in whom a resuscitation attempt is considered futile.\textsuperscript{17,22-25} Several proposals have emerged, with one suggestion being the termination of resuscitation rule by Verbeek et al.\textsuperscript{17} The termination of resuscitation rule is based on 3 prehospital criteria: there has been no ROSC, no shock has been given, and the arrest has not been witnessed by EMS personnel.\textsuperscript{17} Inspired by this rule, we retrospectively selected patients and tested 30-day survival if 2 criteria were fulfilled: no ROSC on hospital arrival and no prehospital shock from a defibrillator. Overall, these 2 criteria identified patients with no chance of 30-day survival fairly well, regardless of patient age. The third criterion by Verbeek et al was already fulfilled because the EMS-witnessed arrests were excluded in this study; this is an important aspect that overall ensures a reasonable amount of time to use a defibrillator or to achieve ROSC in the prehospital setting. The 3 patients who survived the criteria illustrate how it is always possible to construct or observe a scenario where following a guideline can be questionable and demonstrate the obvious limitations related to extrapolation from group findings to individual cases. Even though termination of resuscitation guidelines should never overrule clinical judgment or replace efforts to improve handling and treatment in the most vulnerable cases, they could be useful in the decision-making process regarding when to terminate a resuscitation attempt.

In terms of the use of first recorded heart rhythm versus status of defibrillation as a selection criterion, overall, 28\% of the patients had a shockable rhythm as the first recorded heart rhythm, whereas 46\% received a prehospital shock from a defibrillator. This illustrates how having a nonshockable rhythm can be a dynamic condition with a chance of conversion to a shockable rhythm during treatment. The criterion of not receiving a prehospital shock from a defibrillator acknowledges this aspect, whereas not having 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. The relationships between variables represent associations and offer no direct causal link between factors. In addition, although 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. Similarly, 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. Naturally, setting-related characteristics are important for the external validation of this study, and differences in systems of care, including ambulance response time and advanced postresuscitation 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 had no qualitative data on more advanced outcome measures and no data on neurological outcome scores such as the Cerebral Performance Category score; however, we used discharge diagnosis codes to assess neurological 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-year survivors are a favorable group of patients or that 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; 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 (Figure I in the online-only Data Supplement). 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. However, to adjust for the possibility that the increased survival percentages over time could be driven by increasingly underreporting 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 because of invalid or missing Civil Registration Number (Individual-level linkage of information between the nationwide registries was impossible without the Civil Registration Number). The 10.7\% includes tourists and other foreigners without permanent residence in Denmark. Because data are missing, we cannot be completely certain that this has not affected the absolute number of 30-day survivors who survived with the 2 criteria of not achieving ROSC on hospital arrival and not receiving a prehospital 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 in which only 3 of 9499 patients achieved 30-day survival. Moreover, missing data on Civil Registration Number should not affect the temporal changes in survival systematically or the age-related
differences in survival because 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, regardless of age. In addition, patients with invalid or missing Civil Registration Number were not associated with lower ROSC rates compared with 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 data set (incomplete data set containing missing data) with estimates from the imputed data sets (complete data sets 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 age on changes in survival during an 11-year study period. The increase in ROSC on hospital arrival was observed regardless of patient age, whereas the increase in 30-day and 1-year survival was most prominent in patients 18 to 80 years of age, and little to no change was observed in patients >80 years of age. These findings indicate that the national initiatives undertaken 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 >80 years of age. Finally, with the use of only 2 criteria on 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 when to terminate a resuscitation attempt.

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Disclosures
Dr Lippert serves as a board member for TrygFonden. Dr Köber 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 serves as a consultant for Cardiome, Merck, Sanofi, and Daiichi and has received funding from the Novo Nordisk Foundation. Dr Torp-Pedersen serves as a consultant for Cardiome, Merck, Sanofi, and Daiichi and has received payment for speaking at a symposium arranged by Servier. Drs Lippert and Fosbol report no conflicts.

References


**CLINICAL PERSPECTIVE**

Between 2001 and 2011 in Denmark, national initiatives were undertaken to improve cardiac arrest management, including widespread cardiopulmonary resuscitation training of the population, strengthening of the emergency medical service system, and improvements in advanced care. In parallel, bystander cardiopulmonary resuscitation and survival rates have more than doubled, indicating that, although out-of-hospital cardiac arrest is a devastating medical condition associated with a poor prognosis, systematic efforts can result in improvement in overall survival. On the basis of these findings, we assessed how these changes over time were reflected in different adult age groups. The main findings indicate that the national initiatives undertaken to improve cardiac arrest management have had a positive impact in the prehospital setting, regardless of patient age, with a large increase in return of spontaneous circulation on arrival at the hospital. Long-term survival also increased but was numerically negligible in patients >80 years of age. Importantly, rates of anoxic brain damage were low in senior long-term survivors; overall, emphasizing that patient age alone should not be used as a criterion for whether a resuscitation attempt should be terminated. In contrast, with the use of only 2 criteria (no return of spontaneous circulation on hospital arrival and no prehospital shock from a defibrillator), it was possible to identify patients with minimal chance of 30-day survival, regardless of age. Hence, only 3 of 9499 patients achieved 30-day survival if they met these 2 criteria on arrival at the hospital. This information could be helpful in the decision-making process regarding when to terminate a resuscitation attempt.
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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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

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<th>Comorbidity</th>
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<th>Late-Senior*</th>
<th>p-value†</th>
<th>All patients</th>
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<td>Ischemic heart disease (MI excluded)</td>
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<td>n (%)</td>
<td>n (%)</td>
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**Pharmacotherapy, n (%)**

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<th>n (%)</th>
<th>p-value</th>
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<td>(23.0)</td>
<td>(18.1)</td>
<td>(18.5)</td>
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<td>Corticosteroids(systemic)</td>
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<td>(11.4)</td>
<td>(10.1)</td>
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<td>Antidepressants</td>
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<td>(17.3)</td>
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<td>Medical Class</td>
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<td>Early Senior</td>
<td>Late Senior</td>
<td>P-value</td>
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<td>Sedatives/anxiolytics</td>
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<td>(25.1)</td>
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<td>Anti-psychotic medication</td>
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<td>369</td>
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<td>(9.0)</td>
<td>(6.8)</td>
<td>(6.9)</td>
<td>(7.6)</td>
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<tr>
<td>Analgesics‡</td>
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<td>(40.7)</td>
<td>(48.6)</td>
<td>(39.6)</td>
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</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

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<thead>
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<th>Observed dataset</th>
<th>Imputed datasets</th>
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<td>Observed</td>
<td>Imputed</td>
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</tr>
<tr>
<td></td>
<td>Odds ratio</td>
<td>Odds ratio</td>
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<tr>
<td></td>
<td>(95% CI)</td>
<td>(95% CI)</td>
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<tr>
<td>Early-senior-patients</td>
<td>0.538</td>
<td>0.541</td>
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<tr>
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<td>(0.503-0.575)</td>
<td>(0.506-0.578)</td>
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<tr>
<td>Late-senior-patients</td>
<td>0.379</td>
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<td>(0.349-0.411)</td>
<td>(0.341-0.400)</td>
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<td><strong>ROSC vs. no ROSC upon arrival at the hospital</strong></td>
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</tr>
<tr>
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<td>Observed</td>
<td>Imputed</td>
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<tr>
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<td>Odds ratio</td>
<td>Odds ratio</td>
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</tr>
<tr>
<td></td>
<td>(95% CI)</td>
<td>(95% CI)</td>
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<tr>
<td>Early-senior-patients</td>
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<td>(0.577-0.685)</td>
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<td>Imputed</td>
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<td>calendar year as a continuous variable</td>
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<td>1-year increase in calendar year</td>
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<td>Bystander CPR vs. without bystander CPR</td>
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<td>ROSC vs. no ROSC upon Arrival at the Hospital</td>
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<td>-</td>
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<td>CI</td>
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<td>(1.150-1.200)</td>
<td>(1.151-1.199)</td>
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<td>Late-senior-patients</td>
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<td>(1.118-1.200)</td>
<td>(1.125-1.209)</td>
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Abbreviations: CI=confidence interval; CPR, cardiopulmonary resuscitation; ROSC, return of spontaneous circulation.
Supplemental Figures and Figure Legends

Supplemental Figure 1

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

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. 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.

Changes over time, all P-value < 0.001.

Except:
Patients aged 80-89, P-value = 0.037.
Patients aged ≥ 90, P-value = 0.006.

Supplemental Figure 3. Thirty-day Survival Following Out-of-Hospital Cardiac Arrest, 2001-2011
Supplemental Figure 4

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

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