Distance to invasive heart centre, performance of acute coronary angiography, and angioplasty and associated outcome in out-of-hospital cardiac arrest: a nationwide study

Tinne Tranberg[1]*, Freddy K. Lippert[2], Erika F. Christensen[3,4], Carsten Stengaard[1], Jakob Hjort[1], Jens Flensted Lassen[1], Frants Petersen[5], Jan Skov Jensen[6], Caroline Bäck[7], Lisette Okkels Jensen[8], Jan Ravkilde[9], Hans Erik Bøtker[1], and Christian Juhl Terkelsen[1]

[1]Department of Cardiology, Aarhus University Hospital, Palle Juul-Jensens Boulevard 99, 8280 Aarhus N, Denmark; [2]Prehospital Emergency Medical Services, The Capital Region of Denmark; [3]Prehospital Emergency Medical Services, The North Denmark Region, Aalborg; [4]Department of Anaesthesiology, Aalborg University Hospital, Aalborg, Denmark; [5]The Heart Centre, Copenhagen University Hospital (Rigshospitalet), Copenhagen, Denmark; [6]Department of Cardiology, Gentofte Hospital, Copenhagen, Denmark; [7]Department of Cardiothoracic Surgery, Copenhagen University Hospital, Copenhagen, Denmark; [8]Department of Cardiology, Odense University Hospital, Odense, Denmark; and [9]Department of Cardiology, Aalborg University Hospital, Aalborg, Denmark

Aims	To evaluate whether the distance from the site of event to an invasive heart centre, acute coronary angiography (CAG)/percutaneous coronary intervention (PCI) and hospital-level of care (invasive heart centre vs. local hospital) is associated with survival in out-of-hospital cardiac arrest (OHCA) patients.
Methods and results	Nationwide historical follow-up study of 41 186 unselected OHCA patients, in whom resuscitation was attempted between 2001 and 2013, identified through the Danish Cardiac Arrest Registry. We observed an increase in the proportion of patients receiving bystander CPR (18% in 2001, 60% in 2013, $P < 0.001$), achieving return of spontaneous circulation (ROSC) (10% in 2001, 29% in 2013, $P < 0.001$) and being admitted directly to an invasive centre (26% in 2001, 45% in 2013, $P < 0.001$). Simultaneously, 30-day survival rose from 5% in 2001 to 12% in 2013, $P < 0.001$. Among patients achieving ROSC, a larger proportion underwent acute CAG/PCI (5% in 2001, 27% in 2013, $P < 0.001$). The proportion of patients undergoing acute CAG/PCI annually in each region was defined as the CAG/PCI index. The following variables were associated with lower mortality in multivariable analyses: direct admission to invasive heart centre (HR 0.91, 95% CI: 0.89–0.93), CAG/PCI index (HR 0.33, 95% CI: 0.25–0.45), population density above 2000 per square kilometre (HR 0.94, 95% CI: 0.89–0.98), bystander CPR (HR 0.97, 95% CI: 0.95–0.99) and witnessed OHCA (HR 0.87, 95% CI: 0.85–0.89), whereas distance to the nearest invasive centre was not associated with survival.
Conclusion	Admission to an invasive heart centre and regional performance of acute CAG/PCI were associated with improved survival in OHCA patients, whereas distance to the invasive centre was not. These results support a centralized strategy for immediate post-resuscitation care in OHCA patients.
Keywords	Out-of-hospital cardiac arrest • Distance from the site of arrest to invasive heart centre • Acute CAG/PCI • Hospital-level-of-care • Population density • 30-day survival

* Corresponding author. Tel: +45 78450000, Fax: +45 78452220, Email: Tinne.Tranberg@rm.dk

Introduction

Surviving out-of-hospital cardiac arrest (OHCA) is highly dependent on time to treatment. Accordingly, early cardiopulmonary resuscitation (CPR) and immediate post-resuscitation care are crucial. Coronary angiography (CAG) is recommended for OHCA patients of presumed cardiac etiology.[1,2] However, it remains elusive whether distance to an invasive heart centre affects survival in OHCA patients and whether longer transportation to distant invasive heart centres is acceptable for providing specialized intervention and critical care. In Denmark, a centralized strategy has been implemented for the treatment of patients with ST-elevation myocardial infarction (STEMI).[3] Prehospital electrocardiographic diagnosis and field-triage of these patients directly to invasive heart centres for primary percutaneous coronary intervention (primary PCI) are routine, whereby local hospitals are bypassed. This strategy has proven successful in reducing treatment delay and mortality in STEMI patients.[4] It is unknown if a STEMI-like approach with field-triage directly to invasive heart centres implying a longer prehospital transportation time is associated with lower mortality in patients with OHCA.

The purpose of the present study was to investigate if survival in OHCA patients is associated with: (i) distance to an invasive heart centre; (ii) performance of acute CAG/PCI within 6 h of the first contact with the health care system, and (iii) hospital-level-of care (field-triage to invasive heart centre vs. admission to local hospital).

Methods

Design

This was a historical follow-up study of an unselected OHCA population based on the Danish Cardiac Arrest Registry. The study period was from 1 January 2001 to 31 December 2013. The Danish Data Protection Agency (file number 2013-41-1758) and The National Board of Health approved the study. In Denmark, ethics approval is not required for register-based studies.

Setting

We conducted a nationwide register-based study in Denmark, which has a population of approximately 5.6 million inhabitants. The emergency telephone number (1–1-2) is used nationwide, with five regional emergency medical dispatch centres (EMDC) providing telephone-guided CPR. The Danish emergency medical service (EMS) system is two-tiered, and operates as a double dispatch service. The first tier involves an ambulance with basic life support (BLS) equipment including a defibrillator. The ambulance is staffed with two emergency medical technicians (EMTs). The second tier consists of an anaesthetist-staffed prehospital critical care team operating a separate vehicle with the capability to provide advanced life support (ALS) and endotracheal intubation. In 2010, a helicopter emergency medical service (HEMS) was launched with one helicopter serving the Eastern part of Denmark and in 2011 one more helicopter was put into action serving the Western part of Denmark. In emergency OHCA calls, the EMDC activates the EMS system and the nearest available ambulance and the prehospital critical care team are dispatched. The EMS treatment protocol adheres to the ESC guidelines for Resuscitation.[1] A national consensus on triage of patients with OHCA was established in 2013 by the Danish Society of Cardiology, recommending acute CAG in patients achieving ROSC and with signs of STEMI, severe ischaemia, cardiogenic shock or hemodynamic instability, need of pacing, and in patients without ROSC when a cardiac cause was suspected. A lack of a consensus before 2013 implies that various referral patterns prevailed in the 5 regions during the study period. Performance of acute CAG/PCI was only possible when patients were field-triaged directly to or transferred to one of the 5 high-volume invasive heart centres with a 24-h CAG/PCI service; Aarhus University Hospital, Aarhus; Rigshospitalet, Copenhagen; Odense University Hospital, Odense; Aalborg University Hospital, Aalborg and Gentofte Hospital, Gentofte (until 2012). In Denmark, therapeutic hypothermia was gradually implemented between 2004 and 2006 in the intensive care units (invasive heart centres and local hospitals). Since 2006, therapeutic hypothermia has been used universally in Denmark as recommended by ESC Guidelines for Resuscitation.[1]

Population

The study population comprised all OHCA patients identified in the Danish Cardiac Arrest Register. Patients were included whenever a clinical condition was followed by a resuscitation attempt either by a layperson or by the EMTs supported by the pre-hospital critical care team. The Danish Cardiac Arrest Register does not register patients with obvious late signs of death in whom resuscitation efforts are not initiated, and such patients were therefore not included in the study. Furthermore, patients were excluded if their civil registration number was invalid or missing and if they were foreign citizens or had emigrated.

Registries

Following every resuscitation effort, the prehospital critical care team and EMTs completes an Utstein template and a medical registration form. These mandatory documents are stored in the Danish Cardiac Arrest Register. The specific time points for the emergency call, arrival on scene, departure from scene and arrival at the local hospital or invasive centre are registered by the EMDC and the EMTs in a separate EMS database. The following data were derived from the Danish Cardiac Arrest Register and the EMS database; date/time of cardiac arrest and EMS call; location (private home or public); address of OHCA; whether the event was witnessed by a layperson, healthcare personnel or EMS; and whether bystander CPR and/or defibrillation was performed, initially recorded rhythm [asystole, pulseless electrical activity (PEA), ventricular fibrillation (VF) or ventricular tachycardia (VT)], time of first rhythm analysis by the EMS and a status of the patient's condition upon arrival to hospital, e.g. ROSC or dead. Hospital level of care (centre with acute CAG/PCI facilities or local hospital) and the patient's home address were obtained from the Danish National Patient Registry. The Western Denmark Heart Registry (VDHD) and the Eastern Denmark Heart Registries (PATS = Patient Analysis & Tracking System) databases provided individual baseline characteristics and procedure-specific information on all CAGs and PCIs. Mortality data were acquired from the Danish Civil Registration System, which contains daily updated vital status on all Danish citizens. Valid individual linkages between all registries were obtained by use of the unique ten-digit civil registration number assigned to all Danish citizens.

Distance to invasive heart centres

The driving distance from the scene of the event to the nearest invasive centre was calculated in kilometres (km) using the Danish geographic grid combined with the Danish Address Web Application Programming Interface Routing Machine.

Statistical analyses

Binary data are presented as percentages and continuous variables as medians with inter-quartile range (IQR). We compared binary variables and

continuous variables using the χ^2 test and the Kruskal–Wallis test, as appropriate. A P-value <0.05 (2-sided) was considered statistically significant. Follow-up was initiated on the date of cardiac arrest and ended on the date of death or April 27 2015 according to precedence. For temporal trends, we compared binary variables and continuous variables using non-parametric test of trend—an extension of the Wilcoxon ranksum test. Univariable and multivariable Cox proportional hazards regression analyses were performed for calculation of hazard ratios (HR), and 95% confidence intervals (CIs) to examine the association between the covariates and mortality and to adjust for potential confounders. The assumptions of linearity were assessed graphically. Variables associated with mortality in the univariable Cox regression analyses were included in the multivariable Cox regression models. Performance of CAG and PCI are a priori associated with improved outcome, i.e. only performed in those achieving ROSC or being admitted with ongoing CPR. Accordingly, in the Cox regression analyses each patient were assigned a CAG/PCI index defined as the proportion of patients undergoing acute CAG/PCI (within 6 h of the first contact with the health care system) annually in each region to reflect the current use of CAG/PCI in the region where the patient lived. Missing values among covariates were replaced by using multiple imputations. Logistic regression modelling was used for binary covariates, ordinal logistic regression modelling was used for categorical variables with more than two values, and linear regression modelling was used for continuous covariates. We imputed 10 data sets. Data management and statistical analyses were performed using STATA SE 14.0 (StataCorp, College Station, TX, USA).

Results

We identified 43 206 OHCA patients in the Danish Cardiac Arrest Register. We excluded 2020 patients because they had an invalid or missing civil registration number, had emigrated or were foreign citizens. The final study population comprised 41 186 OHCA patients. The cumulative 30-day survival was 9% (95% CI: 8–9%) (n = 3550). The median follow-up time for patients with ROSC was 28 (2–1404) days. A total of 8.419 (20%) patients achieved ROSC of which 605 (7%) were conscious/awake at admission to hospital. *Table 1* shows geographical characteristics, patient characteristics and survival stratified according to the five Danish regions. Geographical characteristics differed significantly, e.g. distance to invasive heart centre and population density. Furthermore, the proportion of patients admitted directly to an invasive heart centre, acute CAG/PCI and 30-day survival differed. A total of 1.785 (21%) patients with ROSC had an acute CAG performed and 1.262 (15%) patients had an acute PCI performed after the CAG. More than 90% of the CAG and PCI procedures were performed within 6 h after EMS call. The highest 30-day survival rates were seen in the Capital Region (10%) and in the Central Denmark Region (9%).

Temporal changes in 30-day survival, bystander CPR and ROSC

Throughout the study period, we observed a large increase in the overall 30-day survival (5% in 2001, 12% in 2013, P < 0.001) (*Figure 1A*). Thirty-day survival rose significantly over time in patients with and without bystander CPR (P < 0.001) with the largest increase being observed in those without bystander CPR (3% in 2001, 10% in 2013, P < 0.001) (*Figure 1B*).

A major temporal increase was also observed in the proportion of patients receiving bystander CPR (18% in 2001, 60% in 2013, P < 0.001) (*Figure 2A*) and in the proportion of patients achieving ROSC (10% in 2001, 29% in 2013) (*Figure 2B*). Bystander CPR was associated with lower mortality in the multivariable analyses, (HR of 0.97 (95% CI: 0.95–0.99, P = 0.005)) (*Table 2*).

Admission to invasive centre and performance of acute CAG and PCI

A total of 38% (n = 15 822) of patients with OHCA were not admitted to hospital but declared dead at the site of event. Subgroup analyses revealed considerable heterogeneity between the regions with regard to the proportions of patients declared dead at the site of event. Among the remaining patients (n = 25 364), the majority was admitted to a local hospital (n = 17 991). An increase in survival over time was observed in those admitted directly to an invasive heart centre (*Figure 1C*). However, the proportion of patients admitted directly to invasive heart centres differed significantly between regions (*Figure 2C*). Admission directly to an invasive centre was independently associated with lower mortality (adjusted HR = 0.91 (95% CI: 0.89–0.93, P < 0.001)) (*Table 2*). Among patients achieving ROSC, the use of acute CAG/PCI increased significantly during the study period, with significant differences between the regions (*Figure 2D*). Regional performance of acute CAG/PCI following OHCA (CAG/PCI index) was associated with a lower mortality, revealing an adjusted HR of 0.33 (95% CI: 0.25–0.45, P < 0.001) (*Table 2*).

Return of spontaneous circulation, hospital level-of-care, acute CAG/PCI and 30-day survival according to distance from the site of event to the invasive heart centre

The proportion of patients achieving ROSC declined significantly at distances above 5 kilometres from the nearest invasive centre (P < 0.001) (*Figure 3A*). Increasing distance from the scene of the event to the invasive heart centre was associated with a lower proportion of patients admitted directly to an invasive heart centre (P < 0.001) (*Figure 3B*) and a lower use of acute CAG/PCI (P = 0.005) (*Figure 3C*). A distance below 5 km from the site of the event to the invasive heart centre was associated with lower mortality in the univariable analysis (unadjusted HR of 0.93 (95% CI: 0.89–0.96, P < 0.01), but not in the multivariable analysis (adjusted HR 1.01 (95% CI: 0.96–1.07, P = 0.70) (*Table 2*).

Population density and 30-day survival

The population density determined from the zip code of the site of the event was incorporated in the analyses for each patient. The Capital Region of Denmark had the highest population density and the shortest distance to an invasive centre (*Table 1*). In the univariable analyses, a population density above 2000 per zip code per m^2 was associated with lower mortality (unadjusted HR of 0.95 (95% CI: 0.92–0.97, P < 0.001) (*Table 2*). Population density remained independently associated with lower mortality, corresponding to an adjusted HR of 0.94 (95% CI: 0.89–0.98, P < 0.001) (*Table 2*).

Table 1 Geographical characteristics, patient characteristics and outcome for OHCA patients stratified according to region

	A Capital Region of Denmark	B Central Denmark Region	C South Denmark Region	D Zealand Region	E Northern Denmark Region	*P*-value
Population size	1 749 000	1 271 000	1 202 000	816 270	580 273	—
Area, km^2	2568	13 053	12 191	7273	7933	—
Population density per km^2, official	681	97	99	112	73	<0.001
Population density per km^2 observed in the study population (median)	2366	136	237	126	78	<0.001
Population density per km^2 observed in the study population among 30-day survivors (median)	3070	136	271	139	81	<0.001
Study population, no.	15 745	7751	8119	5726	3845	—
Age, median (IQR), years	71 (60–81)	70 (58–79)	70 (59–80)	70 (60–79)	70 (58–79)	<0.001
Male gender, %	63	66	66	66	68	
(*n*/valid cases)	(9864/15 745)	(5138/7751)	(5344/8119)	(3770/5726)	(2608/3845)	<0.001
Bystander CPR, %	35	39	34	35	36	
(*n*/valid cases)	(4236/12 136)	(2885/7426)	(2762/8040)	(1952/5635)	(1366/3802)	<0.001
Distance to invasive centre, median (IQR), km	9 (5–17)	51 (30–82)	71 (34–122)	82 (61–99)	51 (30–68)	<0.001
Initial shockable rhythm, %	21	22	21	21	21	
(*n*/valid cases)	(2851/13 624)	(1629/7227)	(1634/7691)	(1110/5349)	(773/3626)	0.07
Witnessed arrest, %	55	56	54	52	54	
(*n*/valid cases)	(6786/12 276)	(4242/7570)	(4331/8037)	(2953/5640)	(2056/3799)	<0.001
Charlson comorbidity index score, %						
(*n*/valid cases)						
0	49 (7668/15 745)	54 (4200/7751)	53 (4325/8119)	53 (3017/5726)	55 (2101/3845)	
+1	51 (8077/15 745)	46 (3551/7751)	47 (3794/8119)	47 (2709/5726)	45 (1744/3845)	<0.001
Previous myocardial infarction, %	11	13	12	13	12	
(*n*/valid cases)	(1761/15 688)	(980/7745)	(973/8117)	(746/5726)	(458/3845)	0.001
History of congestive heart failure, %	14	12	12	13	11	
(*n*/valid cases)	(2274/15 688)	(933/7745)	(1008/8117)	(752/5726)	(422/3845)	<0.001
Previous stroke, %	10	7	8	9	7	
(*n*/valid cases)	(1577/15 688)	(584/7745)	(627/8117)	(491/5726)	(281/3845)	<0.001
Hypertension, %	16	15	15	16	16	
(*n*/valid cases)	(2571/15 688)	(1181/7745)	(1270/8117)	(928/5726)	(619/3845)	0.20
Admission to invasive centre, %	33	30	38	3	24	
(*n*/valid cases)	(2958/8823)	(1828/6059)	(1981/5237)	(102/3182)	(504/2062)	<0.001
Acute CAG/PCI in patients with ROSC, %	11	38	32	11	26	
(*n*/valid cases)	(373/3475)	(600/1594)	(490/1541)	(103/982)	(219/827)	<0.001
Acute PCI in patients with ROSC, %	10	23	20	10	16	
(*n*/valid cases)	(348/3475)	(362/1594)	(314/1541)	(103/982)	(135/827)	<0.001
30-day survival, %	10	9	8	6	8	
(*n*/valid cases)	(1515/15 745)	(720/7751)	(658/8119)	(367/5726)	(290/3845)	<0.001

CPR, cardiopulmonary resuscitation; CAG/PCI, coronary angiography/percutaneous intervention; ROSC, return of spontaneous circulation.

Discussion

This nationwide study is currently the largest to investigate the association between OHCA patients' survival and distance to invasive heart centre, performance of acute CAG/PCI and hospital-level of care. The three main results of the study were, first, that admission to an invasive heart centre and regional use of acute CAG/PCI were associated with improved 30-day survival; second, distance from the site of the event to the invasive heart centre was not associated with survival; third, survival was associated with population density, bystander CPR, witnessed arrest and shockable rhythm. These results support a strategy that prioritizes the establishment of an efficient
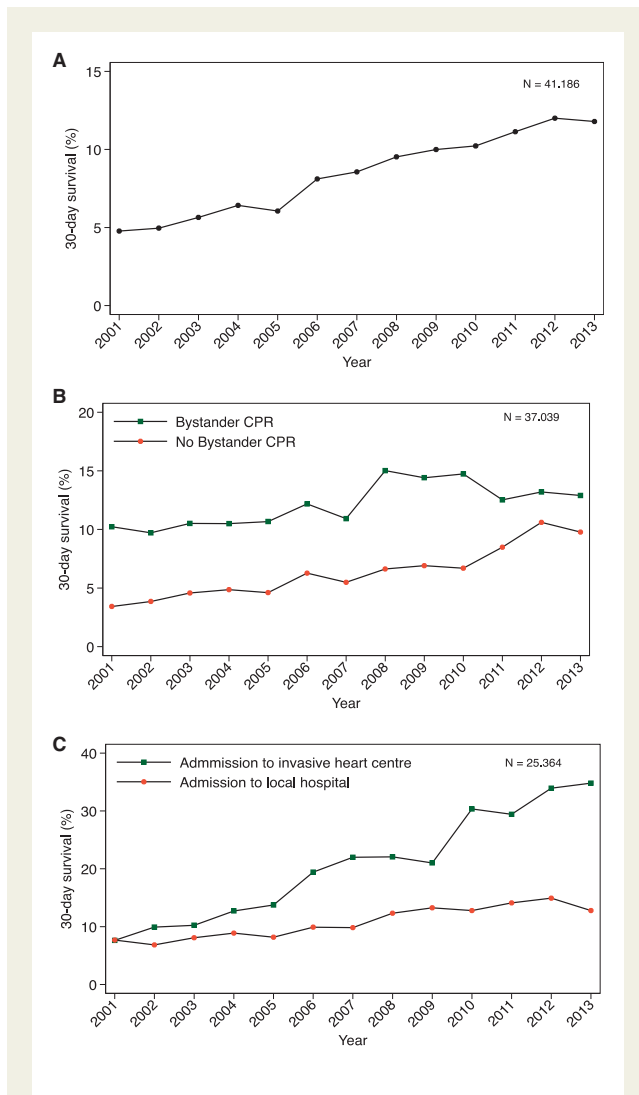
Figure 1 Temporal changes in thirty-day survival stratified according to (*A*) bystander CPR, (*B*) overall 30-day survival, and (*C*) admission to invasive heart centre.

Figure 2 Temporal changes in (*A*) bystander CPR (*B*) achievement of ROSC (*C*) admission to invasive heart centre and (*D*) acute CAG/PCI in patients with OHCA. Stratified according to region. CPR, cardiopulmonary resuscitation; ROSC, return of spontaneous circulation; CAG, coronary angiography; PCI, percutaneous coronary intervention; OHCA, out-of-hospital cardiac arrest.

prehospital organization over the establishment of multiple geographically distributed invasive heart centres.[5,6]

Few studies have assessed the association between distance to hospital and survival in OHCA patients,[7,8] and all of these studies were based on selected study populations small in number. The present study therefore extends previous data. We expected that a longer distance from the site of event to an invasive heart centre would be associated with a lower survival in OHCA patients. Nevertheless, a higher survival rate was seen among OHCA patients only within 5 kilometres of the invasive heart centre. More importantly, in multivariable analyses the distance from the site of event to the nearest invasive heart centre was not associated with survival. Our results reflect that successful prehospital CPR is the key to survival, regardless of whether it is provided by a bystander or EMS, which should ideally be independent of the distance to the invasive centre. However, one would still expect an association between distance and outcome in those treated with PCI,
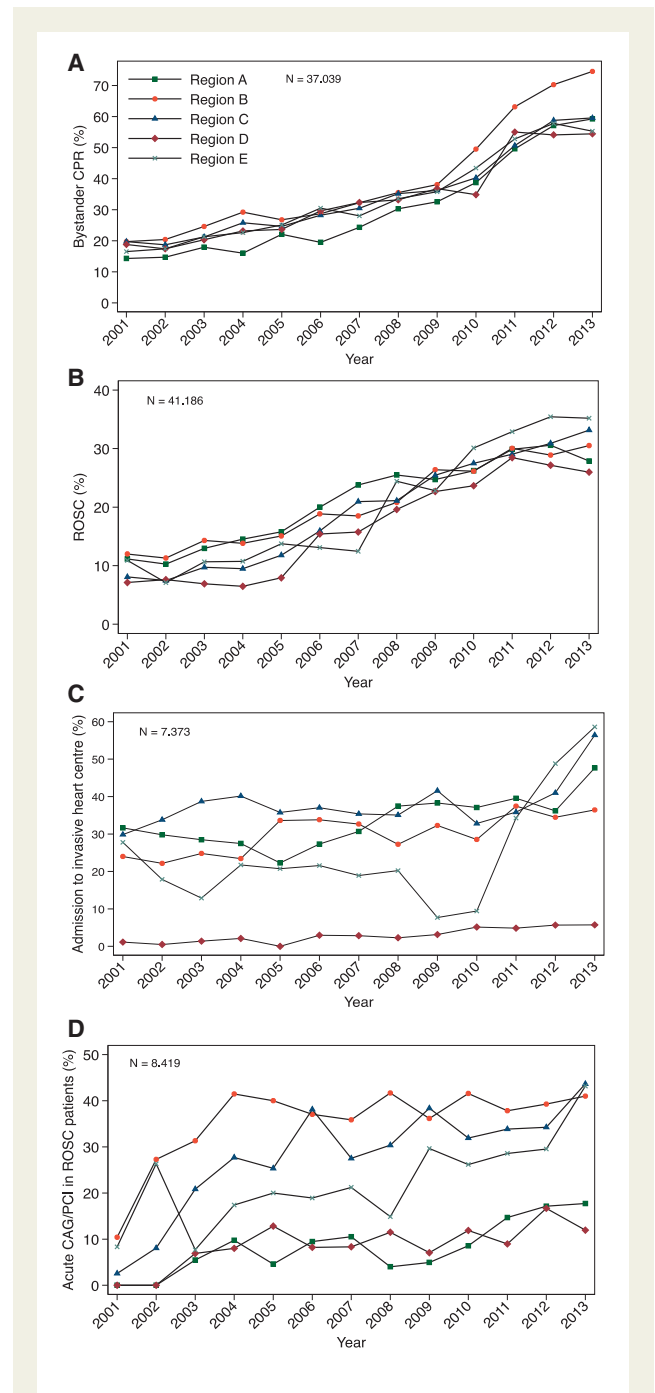
consistent with the findings in STEMI patients.[3] Most likely, a larger sample size is needed to prove this association in OHCA patients.

No randomized studies exist on acute CAG/PCI following OHCA. However, several small observational studies have assessed this issue

Table 2 Hazard ratios of covariates associated with mortality in univariable Cox regression analyses and multivariable analysis (based on imputed datasets)

Covariates included in the analyses	No.	Univariable analysis HR (95% CI)	P-value	Multivariable analysis HR (95% CI)	P-value
Male gender	41 186	0.92 (0.91–0.94)	<0.001	0.99 (0.97–1.01)	0.46
Age, per 10 year increase	41 186	1.06 (1.05–1.06)	<0.001	1.04 (1.03–1.05)	<0.001
Bystander CPR	37 039	0.87 (0.85–0.89)	<0.001	0.97 (0.95–0.99)	0.005
Non-shockable heart rhythm	37 517	1.68 (1.63–1.72)	<0.001	1.48 (1.43–1.52)	<0.001
Witnessed OHCA	37 322	0.79 (0.78–0.81)	<0.001	0.87 (0.85–0.89)	<0.001
Comorbidity index ≥1 (0 reference)	41 186	1.14 (1.12–1.16)	<0.001	1.08 (1.06–1.11)	<0.001
Admission to invasive centre (reference: local hospital)	25 364	0.78 (0.76–0.81)	<0.001	0.91 (0.89–0.93)	<0.001
Acute CAG/PCI per region and year (index)	41 186	0.33 (0.25–0.42)	<0.001	0.33 (0.25–0.45)	<0.001
Population density per zip code per km^2	41 186				
0–100		Reference		Reference	
100–300		0.98 (0.95–1.01)	0.17	0.97 (0.95–1.01)	0.15
300–2000		0.98 (0.95–1.00)	0.10	0.97 (0.94–1.01)	0.17
2000–20 000		0.95 (0.92–0.97)	<0.001	0.94 (0.89–0.98)	0.007
Distance to invasive centre, kilometres	41 186				
0–5 (n = 5414)		0.93 (0.89–0.96)	<0.001	1.01 (0.96–1.07)	0.70
5–10 (n = 5749)		0.97 (0.94–1.01)	0.14	1.02 (0.97–1.08)	0.37
10–20 (n = 4779)		0.98 (0.94–1.02)	0.23	1.00 (0.96–1.05)	0.90
20–50 (n = 8513)		0.99 (0.96–1.03)	0.86	1.03 (0.99–1.07)	0.14
50–100 (n = 10 315)		1.01 (0.98–1.05)	0.40	1.02 (0.99–1.05)	0.23
100–210 (n = 6416)		Reference		Reference	

CPR, cardiopulmonary resuscitation; OHCA, out-of-hospital cardiac arrest; CAG/PCI, coronary angiography/percutaneous intervention; ROSC, return of spontaneous circulation.

using the actual performance of CAG/PCI at patient level.[9–11] It is unsurprising that a strong association then appears simply because CAG/PCI is performed mainly in patients achieving ROSC, with the few exceptions of selected patients transferred to acute CAG/PCI during ongoing CPR. In the present study, we used an index for CAG/PCI activity defined by the proportion of patients having acute CAG/PCI performed annually in each region. This index accordingly reflects the regional level of care with regard to the performance of acute CAG/PCI, and it was significantly associated with improved survival. Whether admission to an invasive heart centre is a surrogate for a higher level of care, performance of acute CAG/PCI or both, our results underline the importance of a centralized post-resuscitation care strategy in OHCA patients. This is in consensus with the statement from the European association for percutaneous cardiovascular interventions (EAPCI)/stent for life (SFL) groups as well as recent ESC Guidelines for Resuscitation.[1,12]

It is hardly surprising that population density is associated with survival; though, the present study is the first to implement population density in a 12-year survival analysis among OHCA patients. Our results are consistent with those of previous studies documenting that survival is higher among OHCA patients in crowded areas, e.g. airports, than in rural areas.[13,14] The association between population density and survival remained significant in the multivariable analyses. However, population density clearly differed from region to region. We cannot rule out that population density is, in part, a proxy for the region and a proxy for distance to the invasive heart centre. Accordingly, one would assume that the region with the highest

population density and the shortest distance to an invasive heart centre, i.e. the Capital Region of Denmark (A), would perform significantly better than the other regions. Nonetheless, the survival rates were comparable in three other regions (B, C, E) with significantly lower population densities and longer distances to the nearest invasive heart centre. One explanation may be that the longer distance and lower population density were counter-balanced by a significantly higher rate of acute CAG/PCI in those regions (B, C, E). Hence, if the association between rate of acute CAG/PCI and survival is causal, a more frequent use of acute CAG/PCI in the Capital Region of Denmark should produce an even higher survival rate in the future. This is, of course, entirely speculative, and it remains to be evaluated in a randomized study whether or not the association between acute CAG/PCI and survival is causal.

Consistent with previous studies, bystander CPR was associated with survival. However, the increase in bystander CPR has partially been used to explain the overall increase in survival.[15–17] The novelty of our study is that the relative increase in survival was even higher among those not receiving bystander CPR and that the overall number of patients achieving ROSC rose. The explanation for this may be improved EMS skills. More importantly, our results indicate that the improved bystander CPR rate is not the only reason for improved survival following OHCA, which is in accordance with a previous study by Chan *et al.*[18]

Whether improved survival observed in patients admitted directly to invasive heart centres is caused by increased use of acute CAG/PCI, therapeutic hypothermia, overall advanced care or selection bias
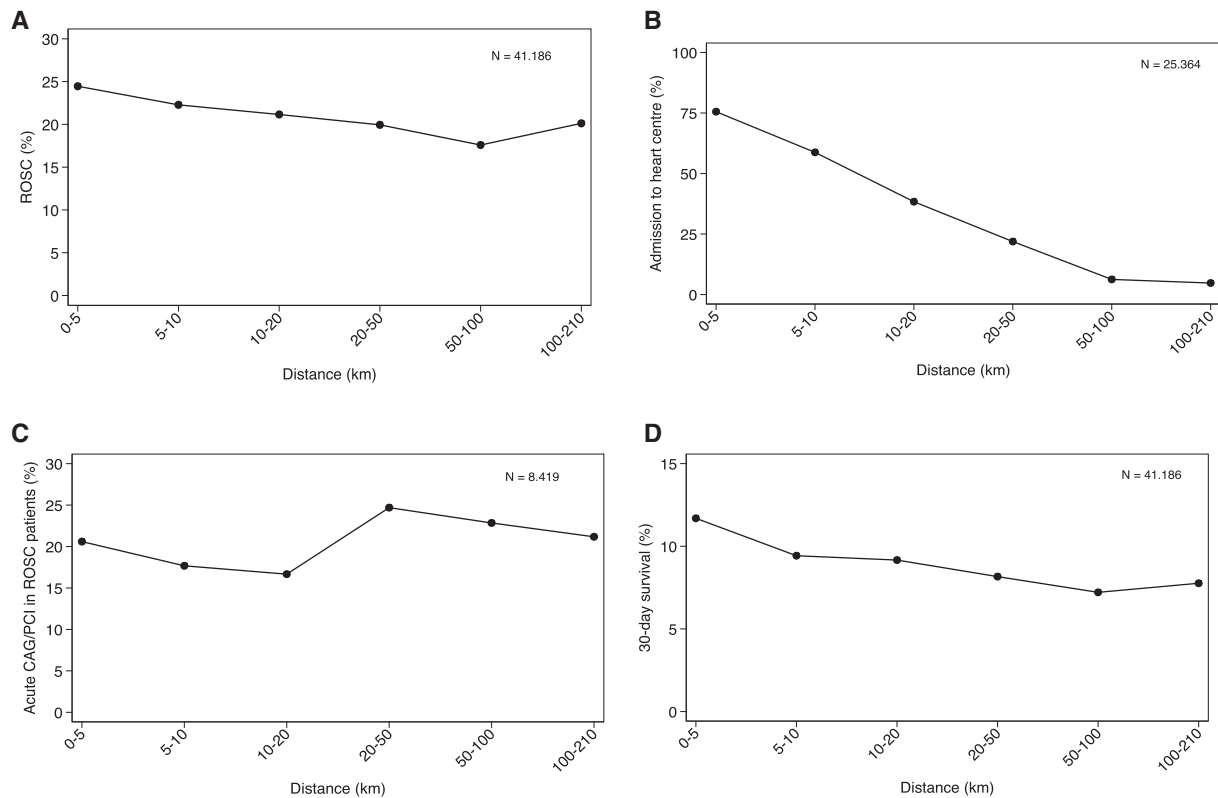
Figure 3 Association between distance to invasive heart centre and (*A*) achievement of ROSC, (*B*) direct admission to invasive heart centre, (*C*) acute CAG/PCI, and (*D*) 30-day survival. CPR, cardiopulmonary resuscitation; ROSC, return of spontaneous circulation; CAG, coronary angiography; PCI, percutaneous coronary intervention.

cannot be determined by the present study. Nevertheless, the totality of components available for optimization by high-volume invasive heart centres represents an argument in favour of centralized post-resuscitation care in OHCA patients.

Strengths and limitations

The strength of this study is the combination of large registries and databases, by far the largest study conducted to date in Denmark in OHCA patients, providing a detailed description of the association between the distance from the site of the event to an invasive heart centre, acute CAG/PCI, hospital level-of-care and survival in patients with OHCA. Our study has limitations. First, it is observational in nature and therefore we cannot rule out some element of selection bias. In this context, the decision to discontinue a resuscitation attempt as well as the decision to transport the patient to an invasive heart centre or a local hospital was left at the discretion of the anaesthetist. However, due to the fact that this was an unselected OHCA population, it is important to emphasize that the potential benefits of centralization may be even better in a population of OHCA patients of presumed cardiac origin. Further, the non-randomized study design does not allow the demonstration of any causal relationship between survival and hospital-level-of care as well as acute CAG/PCI. We do acknowledge that our findings are hypothesis generating only.

Second, it would have been interesting if ECG data were available, which would enable stratified analyses in patients with and without ST-elevations. However, several studies are questioning the value of the ECG in the early post-arrest course as regard to the STEMI diagnosis and patients triage for acute CAG/PCI.[19] Furthermore, important factors about CPR quality, no-flow time (interval between the arrest and the onset of basic life support) and low-flow time (interval between the arrest and ROSC) were not taken into account, due to lack of data. Additionally, data on advanced outcome measurements as target temperature hypothermia and the Cerebral Performance Category score were not available. Thus, it was not possible to take these factors into account and this must be considered as an important limitation, even though the evidence to support hypothermia treatment is sparse. Mild hypothermia is standard care in comatose survivors after cardiac arrest with shockable rhythm and has been extrapolated to survivors with non-shockable rhythm. However, few randomised trials have reported improved outcomes with mild hypothermia compared with normothermia in OHCA patients.[20] Recently, the TTM-trial found no difference in overall mortality or CPC score at a targeted temperature of 33 °C vs. 36 °C.[21] Thus, one could question if normothermia is just as good as hypothermia.

Third, the site of OHCA was unavailable in 23% of the cases and therefore substituted by the home address when calculating the

distance from scene of event to the invasive centre. However, approximately 80% of OHCA occur at home, indicating that the distance calculation was correct in 95% of cases $(0.77 + 0.23*0.8)$.[13] Finally, a number of patients had missing data, but comparing estimates from the observed dataset with estimates from the imputed datasets did not significantly change our results.

Conclusion

Immediate admission to an invasive heart centre and acute CAG/PCI are associated with improved survival in patients with OHCA, whereas distance from site of the event to the invasive heart centre was not. Our results support the establishment of few high-volume invasive heart centres and suggest that OHCA patients should field-triage directly to these centres for optimal post-resuscitation care, regardless of the distance. Clinical randomized studies are needed to clarify the causality between acute CAG/PCI and survival.

Funding

Conflict of interest: none declared.

References

1. Soar J, Nolan JP, Bottiger BW, Perkins GD, Lott C, Carli P, Pellis T, Sandroni C, Skrifvars MB, Smith BG, Sunde K, Deakin CD. European Resuscitation Council Guidelines for Resuscitation 2015: Section 3. Adult advanced life support. *Resuscitation* 2015;**95**:100–147.

2. Larsen JM, Ravkilde J. Acute coronary angiography in patients resuscitated from out-of-hospital cardiac arrest—a systematic review and meta-analysis. *Resuscitation* 2012;**83**:1427–1433.

3. Terkelsen CJ, Sorensen JT, Maeng M, Jensen LO, Tilsted HH, Trautner S, Vach W, Johnsen SP, Thuesen L, Lassen JF. System delay and mortality among patients with STEMI treated with primary percutaneous coronary intervention. *Jama* 2010;**304**:763–771.

4. Rasmussen MB, Frost L, Stengaard C, Brorholt-Petersen JU, Dodt KK, Sondergaard HM, Terkelsen CJ. Diagnostic performance and system delay using telemedicine for prehospital diagnosis in triaging and treatment of STEMI. *Heart* 2014;**100**:711–715.

5. Søholm H, Kjaergaard J, Bro-Jeppesen J, Hartvig-Thomsen J, Lippert F, Køber L, Nielsen N, Engsig M, Steensen M, Wanscher M, Karlsen FM, Hassager C. Prognostic implications of level-of-care at tertiary heart centers compared with other hospitals after resuscitation from out-of-hospital cardiac arrest. *Circulation* 2015;**8**:268–276 http://circoutcomes.ahajournals.org/content/8/3/268.abstract.

6. Nichol G, Aufderheide TP, Eigel B, Neumar RW, Lurie KG, Bufalino VJ, Callaway CW, Menon V, Bass RR, Abella BS, Sayre M, Dougherty CM, Racht EM, Kleinman ME, O'connor RE, Reilly JP, Ossmann EW, Peterson E. American Heart Association Emergency Cardiovascular Care Committee, Council on Arteriosclerosis, Thrombosis, and Vascular Biology, Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation, Council on Cardiovascular Nursing, Council on Clinical Cardiology, Advocacy Committee, Council on Quality of Care and Outcomes Research. Regional systems of care for out-of-hospital cardiac arrest: a policy statement from the American Heart Association. *Circulation* 2010;**121**:709–729.

7. Cudnik MT, Schmicker RH, Vaillancourt C, Newgard CD, Christenson JM, Davis DP, Lowe RA, Investigators ROC. A geospatial assessment of transport distance and survival to discharge in out of hospital cardiac arrest patients: implications for resuscitation centers. *Resuscitation* 2010;**81**:518–523.

8. Lyon RM, Cobbe SM, Bradley JM, Grubb NR. Surviving out of hospital cardiac arrest at home: a postcode lottery? *Emerg Med J* 2004;**21**:619–624.

9. Vyas A, Chan PS, Cram P, Nallamothu BK, McNally B, Girotra S. Early coronary angiography and survival after out-of-hospital cardiac arrest. *Circulation* 2015;**8**:e002321.

10. Spaulding CM, Joly LM, Rosenberg A, Monchi M, Weber SN, Dhainaut JF, Carli P. Immediate coronary angiography in survivors of out-of-hospital cardiac arrest. *N Engl J Med* 1997;**336**:1629–1633.

11. Dumas F, Cariou A, Manzo-Silberman S, Grimaldi D, Vivien B, Rosencher J, Empana J, Carli P, Mira J, Jouven X, Spaulding C. Immediate percutaneous coronary intervention is associated with better survival after out-of-hospital cardiac arrest: insights from the PROCAT (Parisian Region Out of Hospital Cardiac Arrest) Registry. *Circulation* 2010;**3**:200–207.

12. Noc M, Fajadet J, Lassen JF, Kala P, MacCarthy P, Olivecrona GK, Windecker S, Spaulding C. European Association for Percutaneous Cardiovascular Interventions (EAPCI); Stent for Life (SFL) Group. Invasive coronary treatment strategies for out-of-hospital cardiac arrest: a consensus statement from the European association for percutaneous cardiovascular interventions (EAPCI)/stent for life (SFL) groups. *EuroIntervention* 2014;**10**:31–37.

13. McNally B, Robb R, Mehta M, Vellano K, Valderrama AL, Yoon PW, Sasson C, Crouch A, Perez AB, Merritt R, Kellermann A. Centers for Disease Control and Prevention. Out-of-hospital cardiac arrest surveillance—Cardiac Arrest Registry to Enhance Survival (CARES), United States, October 1, 2005–December 31, 2010. *MMWR Surveill Summ* 2011;**60**:1–19.

14. Masterson S, Wright P, O'donnell C, Vellinga A, Murphy AW, Hennelly D, Sinnott B, Egan J, O'reilly M, Keaney J, Bury G, Deasy C. Urban and rural differences in out-of-hospital cardiac arrest in Ireland. *Resuscitation* 2015;**91**:42–47.

15. Wissenberg M, Lippert FK, Folke F, Weeke P, Hansen CM, Christensen EF, Jans H, Hansen PA, Lang-Jensen T, Olesen JB, Lindhardsen J, Fosbol EL, Nielsen SL, Gislason GH, Kober L, Torp-Pedersen C. Association of national initiatives to improve cardiac arrest management with rates of bystander intervention and patient survival after out-of-hospital cardiac arrest. *Jama* 2013;**310**:1377–1384.

16. Malta Hansen C, Kragholm K, Pearson DA, Tyson C, Monk L, Myers B, Nelson D, Dupre ME, Fosbol EL, Jollis JG, Strauss B, Anderson ML, McNally B, Granger CB. Association of bystander and first-responder intervention with survival after out-of-hospital cardiac arrest in North Carolina, 2010-2013. *Jama* 2015;**314**:255–264.

17. Hansen CM, Kragholm K, Granger CB, Pearson DA, Tyson C, Monk L, Corbett C, Nelson RD, Dupre ME, Fosbol EL, Strauss B, Fordyce CB, McNally B, Jollis JG. The role of bystanders, first responders, and emergency medical service providers in timely defibrillation and related outcomes after out-of-hospital cardiac arrest: Results from a statewide registry. *Resuscitation* 2015;**96**:303–309.

18. Chan PS, McNally B, Tang F, Kellermann A. Recent trends in survival from out-of-hospital cardiac arrest in the United States. *Circulation* 2014;**130**:1876–1882.

19. Zanuttini D, Armellini I, Nucifora G, Grillo MT, Morocutti G, Carchietti E, Trillo G, Spedicato L, Bernardi G, Proclemer A. Predictive value of electrocardiogram in diagnosing acute coronary artery lesions among patients with out-of-hospital-cardiac-arrest. *Resuscitation* 2013;**84**:1250–1254.

20. Bernard SA, Gray TW, Buist MD, Jones BM, Silvester W, Gutteridge G, Smith K. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. *N Engl J Med* 2002;**346**:557–563.

21. Nielsen N, Wetterslev J, Cronberg T, Erlinge D, Gasche Y, Hassager C, Horn J, Hovdenes J, Kjaergaard J, Kuiper M, Pellis T, Stammet P, Wanscher M, Wise MP, Aneman A, Al-Subaie N, Boesgaard S, Bro-Jeppesen J, Brunetti I, Bugge JF, Hingston CD, Juffermans NP, Koopmans M, Kober L, Langorgen J, Lilja G, Moller JE, Rundgren M, Rylander C, Smid O, Werer C, Winkel P, Friberg H. TTM Trial Investigators. Targeted temperature management at 33 degrees C versus 36 degrees C after cardiac arrest. *N Engl J Med* 2013;**369**:2197–2206.