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a nationwide study

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Published in:
European Heart Journal

DOI:
10.1093/eurheartj/ehx104

Publication date:
2017

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

Document license
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Citation for published version (APA):
Distance to invasive heart centre, performance of acute coronary angiography, and angioplasty and associated outcome in out-of-hospital cardiac arrest: a nationwide study

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Received 28 June 2016; revised 4 September 2016; editorial decision 13 February 2017; accepted 19 February 2017; online publish-ahead-of-print 29 March 2017

See page 1653 for the editorial comment on this article (doi: 10.1093/eurheartj/ehx160)

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

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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. 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). Prehospital electrocardiographic diagnosis and field-triege 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. It is unknown if a STEMI-like approach with field-triege 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-triege 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. 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-trieged 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.

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 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
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%).

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).

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 m² 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).
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
prehospital organization over the establishment of multiple geographically distributed invasive heart centres.\textsuperscript{5,6}

Few studies have assessed the association between distance to hospital and survival in OHCA patients,\textsuperscript{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.\textsuperscript{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.

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.
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.\textsuperscript{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.\textsuperscript{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 using the actual performance of CAG/PCI at patient level.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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

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

<table>
<thead>
<tr>
<th>Covariates included in the analyses</th>
<th>No.</th>
<th>Univariable analysis</th>
<th>P-value</th>
<th>HR (95% CI)</th>
<th>P-value</th>
<th>Multivariable analysis</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td>41 186</td>
<td>0.92 (0.91–0.94)</td>
<td>&lt;0.001</td>
<td>0.99 (0.97–1.01)</td>
<td>0.46</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, per 10 year increase</td>
<td>41 186</td>
<td>1.06 (1.05–1.06)</td>
<td>&lt;0.001</td>
<td>1.04 (1.03–1.05)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bystander CPR</td>
<td>37 039</td>
<td>0.87 (0.85–0.89)</td>
<td>&lt;0.001</td>
<td>0.97 (0.95–0.99)</td>
<td>0.005</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-shockable heart rhythm</td>
<td>37 517</td>
<td>1.68 (1.63–1.72)</td>
<td>&lt;0.001</td>
<td>1.48 (1.43–1.52)</td>
<td>&lt;0.001</td>
<td></td>
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</tr>
<tr>
<td>Witnessed OHCA</td>
<td>37 322</td>
<td>0.79 (0.78–0.81)</td>
<td>&lt;0.001</td>
<td>0.87 (0.85–0.89)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comorbidity index &gt; 1 (reference)</td>
<td>41 186</td>
<td>1.14 (1.12–1.16)</td>
<td>&lt;0.001</td>
<td>1.08 (1.06–1.11)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Admission to invasive centre (reference: local hospital)</td>
<td>25 364</td>
<td>0.78 (0.76–0.81)</td>
<td>&lt;0.001</td>
<td>0.91 (0.89–0.93)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute CAG/PCI per region and year (index)</td>
<td>41 186</td>
<td>0.33 (0.25–0.42)</td>
<td>&lt;0.001</td>
<td>0.33 (0.25–0.45)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Population density per zip code per km²</td>
<td>41 186</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
<td></td>
<td></td>
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<tr>
<td>0–100</td>
<td></td>
<td>0.98 (0.95–1.01)</td>
<td>0.17</td>
<td>0.97 (0.95–1.01)</td>
<td>0.15</td>
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<tr>
<td>100–300</td>
<td></td>
<td>0.98 (0.95–1.00)</td>
<td>0.10</td>
<td>0.97 (0.94–1.01)</td>
<td>0.17</td>
<td></td>
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<tr>
<td>300–2000</td>
<td></td>
<td>0.95 (0.92–0.97)</td>
<td>&lt;0.001</td>
<td>0.94 (0.89–0.98)</td>
<td>0.007</td>
<td></td>
<td></td>
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<tr>
<td>Distance to invasive centre, kilometres</td>
<td>41 186</td>
<td>0.93 (0.89–0.96)</td>
<td>&lt;0.001</td>
<td>1.01 (0.96–1.07)</td>
<td>0.70</td>
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<tr>
<td>0–5 (n = 5414)</td>
<td></td>
<td>0.97 (0.94–1.01)</td>
<td>0.14</td>
<td>1.02 (0.97–1.08)</td>
<td>0.37</td>
<td></td>
<td></td>
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<tr>
<td>5–10 (n = 5749)</td>
<td></td>
<td>0.98 (0.94–1.02)</td>
<td>0.23</td>
<td>1.00 (0.96–1.05)</td>
<td>0.90</td>
<td></td>
<td></td>
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<tr>
<td>10–20 (n = 4779)</td>
<td></td>
<td>0.99 (0.96–1.03)</td>
<td>0.86</td>
<td>1.03 (0.99–1.07)</td>
<td>0.14</td>
<td></td>
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<tr>
<td>20–50 (n = 8513)</td>
<td></td>
<td>1.01 (0.98–1.05)</td>
<td>0.40</td>
<td>1.02 (0.99–1.05)</td>
<td>0.23</td>
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<tr>
<td>50–100 (n = 10 315)</td>
<td></td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
<td></td>
<td></td>
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<tr>
<td>100–210 (n = 6416)</td>
<td></td>
<td>Reference</td>
<td>Reference</td>
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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 anaesthesit. 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. 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.

Recently, the TTM-trial found no difference in overall mortality or CPC score at a targeted temperature of 33 °C vs. 36 °C. 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

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.
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 m). 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 be triaged 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**

The Danish Heart Foundation, The Savvaerkejsef Foundation and The Danish Cardiac Arrest Registry supported this study. The Danish Cardiac Arrest Registry is supported by TrygFonden and has no commercial interests in the field of OHCA. The study founders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript, or the decision to submit the manuscript for publication.

**Conflict of interest:** none declared.

**References**