Variation in outcome of hospitalised patients with out-of-hospital cardiac arrest from acute coronary syndrome: a cohort study

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Scientific summary

Patient survival factors in out-of-hospital cardiac arrest

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Scientific summary

Background

There are approximately 30,000 treated out-of-hospital cardiac arrests (OHCAs) in the UK each year. Among these patients, 27.5% experience return of spontaneous circulation and 8.4% survive to hospital discharge. Acute coronary syndrome (ACS) describes a spectrum of cardiac conditions, including unstable angina pectoris and myocardial infarction (MI), that affect the coronary blood supply, thereby reducing oxygen delivery to cardiac muscle. Coronary heart disease is a leading cause of death across Europe and is a common cause of OHCA.

Previous studies have shown marked variability in survival, both between ambulance services and between hospitals. Data from UK ambulance services show marked variability between ambulance services in the percentage of patients who survive to hospital discharge (ranging from 2.5% to 12%), which cannot be fully explained by case mix. At present, there are no UK data reporting OHCA survival variation between hospitals, but international data show that, among OHCA patients admitted alive to hospital, survival by hospital ranges from 14% to 59%. This may be partly attributable to variability in patient care.

One strategy to reduce variability in survival and clinical practice may be the establishment of regional cardiac arrest centres. According to this strategy, the ambulance will, provided certain criteria are met, bypass the local emergency department and transfer the patient directly to a regional centre. The rationale behind this strategy is that the disadvantage of longer ambulance transport time is offset by expert care at the regional centre through treatment by clinicians with greater exposure to the condition, improved access to complementary clinical specialties and improved access to imaging and specialist interventions. Such systems have been established in other disease areas [e.g. stroke, major trauma and ST elevation myocardial infarction (STEMI)].

In 2010, the American Heart Association released a policy statement that described a need to establish regionalised cardiac arrest care in the USA to improve patient outcome following OHCA. Subsequently, the 2015 International Liaison Committee on Resuscitation recommended the establishment of regionalised cardiac arrest care systems, but acknowledged that the supporting evidence was typically of low quality. Importantly, none of the studies conducted to date has been undertaken in the UK setting.

Reducing variability in survival provides the opportunity to save more lives if outcomes can be improved to reflect the best-performing systems.

Objectives

The aim of this research was to identify pre-hospital and in-hospital factors that affect survival in adult patients who initially survive an OHCA attributable to ACS.

Methods

We conducted a retrospective cohort study to describe the epidemiology and outcomes among patients admitted to hospital following successful resuscitation from OHCA caused by an ACS, and to identify modifiable pre-hospital and in-hospital factors that affect outcomes in these patients.

The data source was the Myocardial Ischaemia National Audit Project (MINAP) data set. MINAP is a national audit commissioned by the Healthcare Quality Improvement Partnership, which collects data on patients with myocardial ischaemia who are treated at a hospital in England, Wales or Northern Ireland. Data are collected at the hospital level. The data set, as of 2014, contained > 1.25 million records. For each patient record, a series of approximately 130 data points are collected, which cover the patient journey from the onset of symptoms to hospital discharge. The data set includes data on patient demographics, past medical history, pre-hospital interventions, in-hospital laboratory results, in-hospital drug therapy, in-hospital interventions, discharge drugs and interventions, and the patient's status at discharge.

Patients in the MINAP data set were eligible for inclusion in this study if they were an adult (aged ≥ 18 years) who had an OHCA due to an ACS, and where initial resuscitation attempts were successful, leading to admission to hospital. The exclusion criteria were second or subsequent cardiac arrest events and in-hospital cardiac arrest.

The primary study outcome was all-cause in-hospital mortality. The secondary outcomes were neurological outcome at hospital discharge and time to all-cause mortality. The time to all-cause mortality included only patients who were discharged alive from hospital.

Modifiable and non-modifiable variables were categorised in four groups (demographic variables, medical history variables, presenting characteristics of the OHCA variables and discharge care variables) to facilitate data management and analysis.

For hospital-level data [distance to hospital, volume, primary percutaneous coronary intervention (pPCI) centre] we categorised patients by the hospital to which they were first admitted. For hospital volume, we calculated the number of OHCA cases per year at each hospital and categorised volume as low (1–10 cases), medium (11–24 cases) or high (25–82 cases). Patients were then allocated a category based on the first hospital that they attended. A pPCI centre was defined as a hospital that performed at least 100 pPCI procedures per year, as per the British Cardiovascular Intervention Society recommendations for interventional centres (Banning AP, Baumbach A, Blackman D, Curzen N, Devadathan S, Fraser D, *et al.* Percutaneous coronary intervention in the UK: recommendations for good practice 2015. *Heart* 2015;**101**:1–13).

For reperfusion treatment, pPCI and thrombolysis were categorised by the time (early, late, unknown) at which treatment was delivered. Early pPCI was defined as being within 90 minutes of hospital arrival. Early thrombolysis was defined as being within 60 minutes of the call for help. Timings outside these windows were considered late.

As a result of data missingness in the MINAP data set, we used imputation strategies to reduce the risk of bias that may result from incomplete data. Data imputation was undertaken following case identification. No outcomes were imputed. Our imputation strategy was informed by previous work on the MINAP data set and included assigning appropriate imputation modelling strategies (binary logistic regression, polytomous regression, predictive mean matching, default imputation) to specific variables. Convergence was assessed by checking whether or not the imputation chains mixed well for all variables.

We report patient characteristic data for both the pre-imputation data set and the imputed data sets. Continuous data are summarised as mean and standard deviation (SD), median and interquartile range (IQR), and range. Categorical data are presented as number and percentage in each category. For each outcome, we present unadjusted and adjusted analyses that include, for each variable, a point estimate, 95% confidence interval (CI) and *p*-value. Presented odds ratios (ORs) describe the odds of in-hospital death or death/poor neurological outcome. Hazard ratios are used for the time to all-cause mortality analysis. As such, for each analysis, a point estimate greater than one describes a worse outcome.

For the unadjusted analyses for the outcomes of in-hospital mortality and neurological outcome, we used univariate random effects (RE) logistic regression models for each predictor variable, with a RE term for the

hospital. For the adjusted analyses for the outcomes of in-hospital mortality and neurological outcome, we included as many clinically relevant predictor variables in the model as possible, while avoiding including two predictor variables that led to biased OR estimates due to multi-collinearity as a result of the two predictors being highly correlated. We used a similar approach for the analysis of time to all-cause mortality, except that a proportional hazards Cox regression RE model was used. We performed sensitivity analyses to assess the robustness of the results due to the missing data methods used and assumptions made.

This study was secondary research that utilised an anonymised data set. Ethics approval was granted by the University of Warwick Biomedical Research Ethics Committee. MINAP forms part of the National Institute for Cardiovascular Outcomes Research, which is registered as a data controller under the Data Protection Act 1998 and has permission to collect and store patient identifiable information without consent in accordance with section 251 of the National Health Service Act 2006 (Great Britain. *National Health Service Act 2006. Chapter 41.* London: The Stationery Office; 2006).

Results

The data set provided by MINAP comprised 1,127,140 cases that were included in the audit between 2003 and 2015. Of these, 17,604 cases were identified as eligible for the study and included in the analysis of our primary outcome. Analyses for neurological outcome and time to all-cause mortality comprised 15,286 and 12,483 patients, respectively.

In our patient cohort, most patients survived to hospital discharge ($n = 12,557$, 71.3%), but there was variability in survival by hospital. Across the 94 hospitals that contributed at least 60 patient cases, the survival rate ranged from 34% to 89% (median 71.4%, IQR 60.7–76.9%). For discharge with good neurological outcome, 9041 (59.1%) of the 15,286 analysed patients survived to hospital discharge with good neurological outcome. In the cohort of 12,483 patients who survived to hospital discharge, who were included in the time to all-cause mortality analysis, 1926 (15.4%) died during the follow-up period. The mean survival time was 84.3 months (95% CI 83.5 to 85.1 months).

Pre-imputation characteristics of patients included in the in-hospital mortality analysis show that most patients were male ($n = 13,188$, 75.1%) and of white ethnicity ($n = 14,343$, 93.7%), with a mean age of 65.3 years (SD 13.2 years). Most patients were current or former smokers ($n = 8883$, 63.5%) and had at least one comorbidity ($n = 10,729$, 60.9%). The commonest comorbidities were hypertension ($n = 6389$, 41.0%), hypercholesterolaemia ($n = 3906$, 25.9%) and previous acute myocardial infarction (AMI) ($n = 3092$, 19.7%). Cardiac arrest events usually occurred before ambulance arrival ($n = 10,533$, 60.1%), with a presenting rhythm of ventricular fibrillation (VF) or ventricular tachycardia (VT) ($n = 14,778$, 89.6%). Most patients were admitted to the hospital during daytime hours (08.00–19.59 hours) ($n = 11,741$, 66.7%). The most common admission diagnosis was definite MI (anterior infarction: $n = 3897$, 27.0%; other infarction site: $n = 3639$, 25.2%). ST-segment elevation/left bundle branch block were the most common electrocardiographic findings ($n = 12,220$, 71.9%).

The median emergency medical service response time was 8 minutes (IQR 5–14 minutes). The median distance between the patient's home address and the admitting hospital was 8.1 km (IQR 3.9–15.8 km). The patient distribution between low-volume (≤ 10 OHCA cases per year), medium-volume (11–24 OHCA cases per year) and high-volume (25–82 OHCA cases per year) hospitals was 45.4% ($n = 7984$), 37.0% ($n = 6516$) and 17.6% ($n = 3104$), respectively. The first hospital in which most patients ($n = 9804$, 55.7%) were treated was classified as a pPCI centre.

Just over half of patients were admitted to the cardiac care unit (also referred to as the coronary care unit) ($n = 8872$, 51.0%) and approximately one-third of patients were admitted to the intensive care unit ($n = 6154$, 35.4%). Patients typically received aspirin or were already on aspirin ($n = 14,126$, 87.7%) and underwent, a pre-hospital electrocardiogram (ECG) ($n = 11,053$, 75.7%). Reperfusion treatment (pPCI or

thrombolysis) was delivered to 62.8% ($n = 9540$). Of these 9540 patients, the majority received pPCI (pPCI: $n = 6160$, 64.6%; thrombolysis: $n = 3380$, 35.4%). Over the course of the study, there was an increase in the use of reperfusion therapy. Across all groups, there was a move away from the use of thrombolysis to pPCI over the study period. The time point at which the use of pPCI overtakes thrombolysis use is around 2008–9 and, thus, by the end of the study period, very few patients received thrombolysis.

The adjusted model for in-hospital mortality had an R^2-value of 0.361, such that we could explain only 36.1% of the variability in the data. Factors associated with increased mortality included female sex, increased age and increased deprivation. Ethnicity was not associated with hospital mortality.

Some comorbidities [heart failure, cerebrovascular disease, asthma or chronic obstructive pulmonary disease (COPD) and peripheral vascular disease] were associated with an increased mortality, while hypercholesterolaemia and hypertension were associated with reduced mortality. Cardiac arrest following ambulance arrival and an initial cardiac arrest of VF/VT were associated with reduced mortality. Although admission to a percutaneous coronary intervention (PCI) centre seemed to be associated with increased mortality, early PCI and PCI where time was missing were associated with reduced mortality. Similarly, early thrombolysis was associated with reduced mortality. Neither late PCI nor late thrombolysis influenced survival. Each additional kilometre travelled to hospital appeared to be associated with a small decrease in mortality. Hospital volume was not associated with mortality.

In sensitivity analyses, we found that in patients who did not present with a STEMI, night-time hospital admission (between 20.00 and 07.59 hours) was associated with increased mortality and there was no evidence of reduced mortality with the use of a reperfusion treatment.

The results of the adjusted analysis for neurological outcome were broadly similar to those reported for the primary outcome (in-hospital mortality). However, there was an association between in-hospital ECG, compared with pre-hospital ECG, and poorer outcome. In contrast to the primary outcome analysis, neither transfer distance nor admission to a pPCI centre was associated with neurological outcome.

In the analysis of time to all-cause mortality, increased age and deprivation were predictive of increased mortality, but ethnicity and sex were not associated with mortality. Only four medical history variables (previous AMI, heart failure, diabetes mellitus, asthma or COPD) were associated with worse outcome. None of the care pathway variables, such as reperfusion treatment, was associated with time to all-cause mortality. The provision of coronary angiography, cardiology follow-up and cardiac rehabilitation was associated with reduced risk of mortality. Similarly, discharge on beta-blockers or angiotensin-converting enzyme inhibitor was associated with improved outcome. However, antiplatelet therapy on discharge did not influence outcome.

Conclusions

Our study showed evidence of variability in survival between hospitals, such that survival in hospitals with at least 60 cases ranged from 34% to 89% (median 71.4%, IQR 60.7–76.9%). The overall rate of patients who survived was 71.3%. We could explain only 36.1% of this outcome variability through modelling of variables in the MINAP data set. Similarly, there was variability between hospitals in relation to survival with good neurological outcome, which ranged from 13% to 84% (median 58.9%, IQR 44.2–66.8%) across hospitals with at least 60 cases.

The evaluation of modifiable factors in the patient journey produced conflicting results. There was no evidence to suggest that increased transfer distances had a harmful effect, but hospital volume and admission to a specialist services (pPCI centre) either had no effect or were associated with worse outcomes. Early reperfusion, whether by thrombolysis or pPCI, was associated with improved outcome, primarily in STEMI patients.

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