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

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

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Abstract

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

Keith Couper,[1,2] Peter K Kimani,[1] Chris P Gale,[3,4] Tom Quinn,[5] Iain B Squire,[6] Andrea Marshall,[1] John JM Black,[7] Matthew W Cooke,[1] Bob Ewings,[8] John Long[8] and Gavin D Perkins[1,2]*

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Background: Each year, approximately 30,000 people have an out-of-hospital cardiac arrest (OHCA) that is treated by UK ambulance services. Across all cases of OHCA, survival to hospital discharge is less than 10%. Acute coronary syndrome (ACS) is a common cause of OHCA.

Objectives: To explore factors that influence survival in patients who initially survive an OHCA attributable to ACS.

Data source: Data collected by the Myocardial Ischaemia National Audit Project (MINAP) between 2003 and 2015.

Participants: Adult patients who had a first OHCA attributable to ACS and who were successfully resuscitated and admitted to hospital.

Main outcome measures: Hospital mortality, neurological outcome at hospital discharge, and time to all-cause mortality.

Methods: We undertook a cohort study using data from the MINAP registry. MINAP is a national audit that collects data on patients admitted to English, Welsh and Northern Irish hospitals with myocardial ischaemia. From the data set, we identified patients who had an OHCA. We used imputation to address data missingness across the data set. We analysed data using multilevel logistic regression to identify modifiable and non-modifiable factors that affect outcome.

Results: Between 2003 and 2015, 1,127,140 patient cases were included in the MINAP data set. Of these, 17,604 OHCA cases met the study inclusion criteria. Overall hospital survival was 71.3%. Across hospitals with at least 60 cases, hospital survival ranged from 34% to 89% (median 71.4%, interquartile range 60.7–76.9%). Modelling, which adjusted for patient and treatment characteristics, could account for

only 36.1% of this variability. For the primary outcome, the key modifiable factors associated with reduced mortality were reperfusion treatment [primary percutaneous coronary intervention (pPCI) or thrombolysis] and admission under a cardiologist. Admission to a high-volume cardiac arrest hospital did not influence survival. Sensitivity analyses showed that reperfusion was associated with reduced mortality among patients with a ST elevation myocardial infarction (STEMI), but there was no evidence of a reduction in mortality in patients who did not present with a STEMI.

Limitations: This was an observational study, such that unmeasured confounders may have influenced study findings. Differences in case identification processes at hospitals may contribute to an ascertainment bias.

Conclusions: In OHCA patients who have had a cardiac arrest attributable to ACS, there is evidence of variability in survival between hospitals, which cannot be fully explained by variables captured in the MINAP data set. Our findings provide some support for the current practice of transferring resuscitated patients with a STEMI to a hospital that can deliver pPCI. In contrast, it may be reasonable to transfer patients without a STEMI to the nearest appropriate hospital.

Future work: There is a need for clinical trials to examine the clinical effectiveness and cost-effectiveness of invasive reperfusion strategies in resuscitated OHCA patients of cardiac cause who have not had a STEMI.

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List of abbreviations

ACE	angiotensin-converting enzyme
ACS	acute coronary syndrome
AIC	Akaike information criterion
AMI	acute myocardial infarction
CABG	coronary artery bypass graft
CCU	cardiac care unit
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CPR	cardiopulmonary resuscitation
ECG	electrocardiogram
ED	emergency department
EMS	emergency medical service
GRACE	Global Registry of Acute Coronary Events
HR	hazard ratio
ICC	intraclass correlation
ILCOR	International Liaison Committee on Resuscitation
IMD	Index of Multiple Deprivation
IQR	interquartile range
LBBB	left bundle branch block
LVEF	left ventricular ejection fraction
MI	myocardial infarction
MICE	multiple imputation by chained equations
MINAP	Myocardial Ischaemia National Audit Project
NICE	National Institute for Health and Care Excellence
NICOR	National Institute for Cardiovascular Outcomes Research
NSTEMI	non-ST elevation myocardial infarction
OHCA	out-of-hospital cardiac arrest
ONS	Office for National Statistics
OR	odds ratio
PCI	percutaneous coronary intervention
PEA	pulseless electrical activity
PMM	predictive mean matching
pPCI	primary percutaneous coronary intervention
PPI	patient and public involvement
RE	random effects
ROSC	return of spontaneous circulation
SD	standard deviation
SE	standard error
STEMI	ST elevation myocardial infarction
VF	ventricular fibrillation
VT	ventricular tachycardia

Plain English summary

Each year, approximately 30,000 people have an out-of-hospital cardiac arrest (OHCA) that is treated by UK ambulance services. Cardiac arrest is often caused by a condition that affects blood supply to the heart (e.g. a heart attack). At present, less than 1 in 10 OHCA patients survive to leave hospital following OHCA, but this varies significantly across the country.

In this research study, we used data about OHCA patients from the Myocardial Ischaemia National Audit Project (MINAP) registry to identify reasons why survival may vary. The MINAP registry collects data about patients admitted to hospital who have had a heart attack or other condition that affects blood supply to the heart. We used statistical techniques to try to identify which factors were associated with hospital survival following OHCA.

We analysed information from 17,604 patients who had an OHCA between 2003 and 2015, and who were included in the MINAP registry. The overall rate of patients who survived to leave hospital was 71%. We found that survival rates by hospital did vary, but we could explain only some of this variation. Treatment with a drug or procedure to reopen blocked blood vessels in the heart reduced the likelihood of dying in hospital. However, these treatments require admission to a specialist hospital and seem to benefit only patients who have a specific type of heart attack. Patients who did not have that type of heart attack did not seem to benefit from admission to a specialist hospital, and could possibly be safely treated at the nearest hospital.

This research study has helped us to better understand which patients, following OHCA, may benefit from care in specialist hospitals, but the best treatment for some patients remains uncertain. It will be necessary to conduct research in the future to help understand the best treatment for these patients.

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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Chapter 1 Introduction

Cardiac arrest and its epidemiology

Cardiac arrest describes the sudden cessation of heart function. Cardiac arrests may occur in the hospital setting (in-hospital cardiac arrest) or outside the hospital [out-of-hospital cardiac arrest (OHCA)]. Cardiac arrest is a time-critical condition, such that each minute of delay in initiating key treatments, such as chest compressions and defibrillation, is associated with a significant decrease in survival.[1,2] Survival following cardiac arrest can be categorised as either return of spontaneous circulation (ROSC), which describes the resumption of effective cardiac activity, or longer-term survival, often measured at discharge or 30 days following the cardiac arrest event.

There are approximately 60,000 OHCAs in the UK each year, and treatment is delivered in approximately half of cases.[3,4] In 2014, there were 28,729 treated cardiac arrests in England that were reported to the Out of Hospital Cardiac Arrest Outcomes project, based at the University of Warwick.[5] This corresponds to an incidence of 53.2 per 100,000 people. In this cohort, where data were available, 27.5% had a ROSC at hospital transfer and 8.4% survived to hospital discharge. Neurological outcome and long-term survival is not recorded in the data set, but other data demonstrate that hospital survivors often have a reasonable long-term prognosis and quality of life.[6–8]

Acute coronary syndrome (ACS) describes a spectrum of cardiac conditions that affect the coronary blood supply, thereby affecting oxygen delivery to cardiac muscle. ACS includes conditions such as unstable angina pectoris, non-ST elevation myocardial infarction (NSTEMI), and ST elevation myocardial infarction (STEMI). Coronary heart disease is a leading cause of death across Europe, causing 1.8 million deaths per year, which equates to approximately 20% of all European deaths.[9] In the UK, coronary heart disease causes 73,500 deaths each year and is responsible for 15% of male and 8% of female premature deaths, which is defined as death in people aged < 75 years.[10]

Cardiac arrest represents the end point of all critical illnesses, including cardiovascular disease, trauma, sepsis and stroke. Clinically, it can be difficult to accurately identify the cause of a cardiac arrest during the resuscitation attempt. However, OHCAs are often sudden events that are likely to have been caused by ACS. Until recently, international OHCA reporting guidelines recommended that the cause of OHCA be categorised as one of cardiac disease, trauma, submersion, drug overdose, asphyxia, exsanguination or any other non-cardiac cause.[11,12] Based on this categorisation, 81.2% of English cardiac arrests to which a cause is attributed are classified as due to a cardiac cause.[5] This proportion is similar to that reported in other studies.[2,13–15] A systematic review of patients who underwent angiography following resuscitation from OHCA without an obvious non-cardiac cause reported that 59–71% patients had evidence of significant coronary artery disease.[16]

The cardiac arrest chain of survival

The cardiac arrest chain of survival describes the four key processes that are necessary for optimum recovery from OHCA (*Figure 1*).[18,19] Developed originally in 1991 by the American Heart Association, the chain was updated in 2005 to reflect the importance of both cardiac arrest prevention and post-resuscitation care.[17,19,20] The process is conceptualised as a chain because any link that is missed, delayed or delivered ineffectively reduces the likelihood of survival.

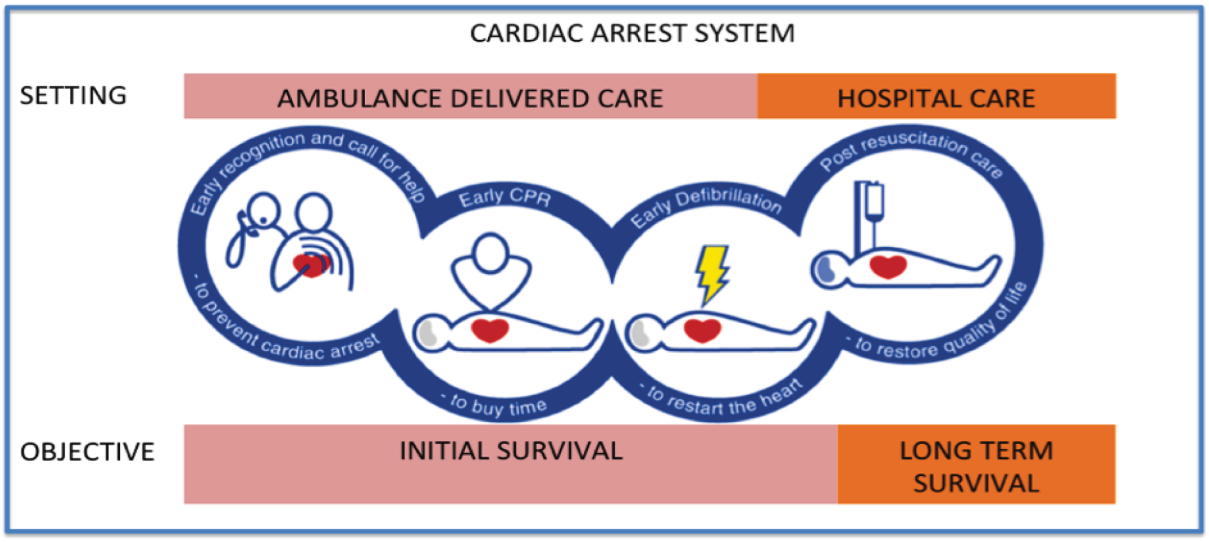

FIGURE 1 The chain of survival and relationship with different settings and objectives in the patient journey. Adapted from European Resuscitation Council Guidelines for Resuscitation 2005 Section 1: Introduction, JP Nolan, *Resuscitation*, 67, Supplement 1, S3–S6, 2005, with permission from Elsevier.[17] CPR, cardiopulmonary resuscitation.

For OHCA, the first three links [early access, early cardiopulmonary resuscitation (CPR) and early defibrillation] are delivered in the pre-hospital setting and focus on the initial ROSC. This fourth link (post-resuscitation care) describes care that is predominantly delivered in the hospital setting, which focuses on the restoration of quality of life.

Hospital care plays a key role in patient outcome following cardiac arrest. After successful resuscitation from cardiac arrest, patients develop post-cardiac-arrest syndrome, in which four separate, but inter-related, physiological processes assault the cardiac arrest survivor.[21] These process are post-cardiac-arrest brain injury, post-cardiac-arrest myocardial dysfunction, a systemic ischaemia–reperfusion response and the underlying cause of the original cardiac arrest event.

In a before-and-after study conducted in Norway, the implementation of a cardiac arrest care bundle in patients with OHCA of cardiac aetiology admitted to the intensive care unit was associated with a significant improvement in survival with good neurological outcome.[22] The care bundle included the use of therapeutic hypothermia, cardiac reperfusion therapy and physiological targets for blood glucose, blood pressure and ventilation. In a multivariate analysis, the delivery of a standardised treatment bundle was the strongest predictor of good outcome.

Variability in survival

The incidence of treated OHCA in the UK (53.2 per 100,000 person-years) is similar to that in North America (54.6 per 100,000 person-years), although it is slightly higher than that in the rest of Europe (35 per 100,000 person-years).[5,23] However, the reported rates of ROSC (27.5%) and overall survival to hospital discharge (8.4%) lag significantly behind those of other nations.

In Europe, the EuReCa One project captured OHCA data from 7146 patients who had an OHCA across 27 European countries in October 2014.[24] The overall reported rate of ROSC was 28.6%, which is similar to UK data, but there was marked variability even among countries contributing a large number of cases, with reported ROSC rates ranging from < 10% to > 40%. Across the data set, the overall reported hospital/30-day survival rate was 10.3%, with reported rates varying from 1.1% to 30.8%.

High-performing health systems report OHCA hospital survival rates across all patients as exceeding 15%, with survival in some subgroups exceeding 50%.[25,26] Thus, it is likely that many UK OHCA deaths are avoidable. However, these headline figures mask variability in survival that may result from both ambulance service and hospital factors.

Ambulance-level variability

In the UK, there is evidence, as shown in *Figure 2*, of wide variability in ROSC and survival-to-discharge rates across ambulance services.[3] In 2011, the survival-to-discharge rate following OHCA by ambulance service ranged from 2.5% to 12%.[3] Although the number of cases was small, the variation was not reduced through standardisation using the Utstein patient subgroup (witnessed arrest in a shockable rhythm with bystander CPR), and neither was the variation in outcome associated with ambulance response times.[11,12] Such variation in outcome following OHCA across emergency medical service (EMS) systems has also been observed in other countries.[26–28]

Hospital-level variability

In the UK, ambulance service data show variability in outcome in survival to discharge among ambulance services with similar rates of ROSC (e.g. compare Great Western with Yorkshire and East of England Ambulance Services in *Figure 2*).[3] In the UK, conventional management for OHCA is that the patient will be transferred to the nearest appropriate emergency department (ED) according to locally agreed protocols.

At present, there are no UK data reporting OHCA survival variation between hospitals. International data from Sweden, Australia and North America show survival rates by hospital in OHCA patients admitted alive to hospital, and these range from 14% to 59%.[29–32] However, in the UK, there is evidence of variability in practice. A recent survey of 208 UK intensive care units that treat cardiac arrest patients found that only 28 units could provide all of the interventions [24/7 primary percutaneous coronary intervention (pPCI), ventilator care bundle, targeted temperature management and access to neurophysiology tests] recognised as essential for the effective intensive care management of cardiac arrest patients.[33] This availability is important as the availability and delivery of key interventions is associated with improved hospital outcome.[30,34]

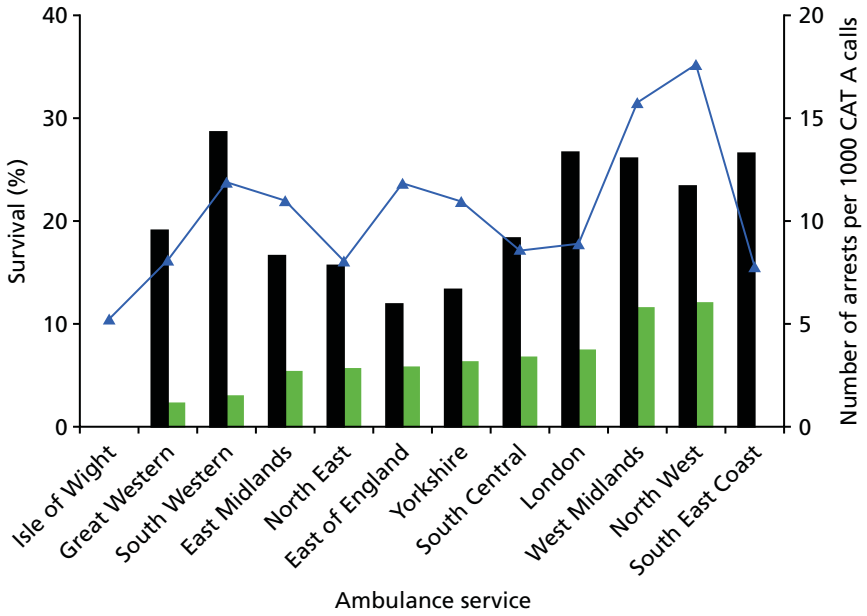

FIGURE 2 Variability in OHCA survival rates across English ambulance services. The navy line corresponds to the right vertical axis to describe the number of cardiac arrest calls per 1000 category A emergency calls. The black and green bars correspond to the left vertical axis to describe ROSC (black bar) and survival to hospital discharge (green bar) for services where data were available. Reproduced from Variability in cardiac arrest survival: the NHS Ambulance Service Quality Indicators, GD Perkins and MW Cooke, *Emergency Medicine Journal*, vol. 29, pp. 3–5, 2011, with permission from BMJ Publishing Group Ltd.[3]

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 that certain criteria are met, bypass the local ED and transfer the patient directly to a regional centre. The rational is that the disadvantage of a longer ambulance transport time is offset by expert care at the regional setting through treatment by clinicians with greater exposure to the condition, improved access to complementary clinical specialities and improved access to imaging and specialist interventions.

Regionalised systems of care are already in place for conditions, such as stroke, STEMI and trauma. However, recent systematic reviews in the clinical areas of stroke and trauma do not show improved outcome when patients are taken directly to a specialist centre, rather to a non-specialist centre.[35,36] In contrast, there is evidence that treatment of STEMI patients with pPCI in a high-volume hospital is clinically effective and cost-effective.[37–39]

In the context of cardiac arrest, the American Heart Association released a policy statement in 2010 describing a need to establish regionalised cardiac arrest care in the USA to improve patient outcome following OHCA.[40] In 2015, the International Liaison Committee on Resuscitation (ILCOR) review of evidence led to a treatment recommendation that supported the establishment of regionalised cardiac arrest care systems.[41] However, in making this recommendation, ILCOR acknowledged that the supporting evidence was of a low quality, that much of the evidence was retrospective and that there was inconsistency between studies as to which hospital factors were associated with improved outcome.

Importantly, none of the studies conducted to date has been undertaken in the UK setting. A recently published trial did demonstrate that it was feasible to undertake a randomised controlled trial comparing transfer to a specialist centre and consideration of percutaneous coronary intervention centre (PCI) with standard care in resuscitated OHCA patients without ST elevation on the electrocardiogram (ECG), and an effectiveness trial is now being planned.[42] As such, it is not currently possible to estimate the effects of such a system of care in the UK, where environmental factors (e.g. disease prevalence, response times, distances travelled), EMS systems (e.g. initial response time, ambulance staff skill mix, transfer time to hospital) and hospital configurations vary.

Out-of-hospital cardiac arrest as a health and research priority

Out-of-hospital cardiac arrest is recognised as an important UK health priority.[43] Reducing variability in survival provides the opportunity to save more lives if outcomes can be improved to reflect the best performing systems. The importance of OHCA as a health priority has been recognised in a series of government publications.

In 2011, the National Audit Office report on transforming NHS ambulance services highlighted wide variation in cost, methods of data collection and outcomes across ambulance services.[44] In the same year, OHCA survival was identified by the Department of Health as a key ambulance service quality indicator.[45,46] More recently, the 2013 Department of Health Cardiovascular Disease Outcome Strategy described a commitment to saving 1000 lives per year through improved health-care delivery to OHCA patients.[47] It is, therefore, timely to evaluate the potential for regionalised cardiac arrest care to improve survival from cardiac arrest.

Chapter 2 Research questions/objectives

This research aimed to answer the following question:

- In adult patients who initially survive an OHCA attributable to ACS, which pre-hospital and in-hospital factors affect survival?

The specific objectives of this research were to:

1. describe the epidemiology and outcomes among patients admitted to hospital following successful resuscitation from a cardiac arrest caused by ACS
2. identify the effect of modifiable factors that affect the outcomes of patients hospitalised following resuscitation from an OHCA
3. develop recommendations for optimising pre-hospital and hospital organisation of services
4. develop a prioritised list of recommendations for further research in this area.

Chapter 3 Methods

We conducted a retrospective cohort study using data from the Myocardial Ischaemia National Audit Project (MINAP) data set to describe the epidemiology and outcomes among patients admitted to hospital following successful resuscitation from a cardiac arrest caused by an ACS, and to identify modifiable pre-hospital and in-hospital factors that affect outcome in these patients.

The Myocardial Ischaemia National Audit Project

The MINAP is a national audit commissioned by the Healthcare Quality Improvement Partnership. MINAP collects data on patients with myocardial ischaemia who are treated at a hospital in England, Wales or Northern Ireland. Established in 1999, the project is managed by the National Institute for Cardiovascular Outcomes Research (NICOR), based at University College London. Data are primarily collected for audit. The full details of MINAP can be found on the project website and in its annual report.[48,49]

The Myocardial Ischaemia National Audit Project data set

As of 2014, the MINAP data set contained > 1.25 million records, with an additional 90,000 records being uploaded each year. For each patient record, a series of data points are collected. These data points cover the patient journey from the onset of symptoms to hospital discharge. The current data set includes approximately 130 fields. This 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. A full list of the MINAP fields is included in *Appendix 1*.

Four fields in the data set relate directly to cardiac arrest, namely the date/time of cardiac arrest (field 3.13), cardiac arrest location (field 3.14), arrest presenting rhythm (field 3.15) and outcome of arrest (field 3.16). One other field (field 3.10 – delay before treatment) has cardiac arrest as a listed response.

The MINAP data set can be linked to Office for National Statistics (ONS) data to provide additional information on long-term mortality and deprivation.

Collection of the Myocardial Ischaemia National Audit data set

The MINAP data set is collected at the hospital level. In 2014, it was reported that all English, Welsh and Northern Irish hospitals that admitted patients with myocardial ischaemia collected and uploaded data, with the exception of Scarborough Hospital.[48] MINAP is part of the national clinical audit programme, such that hospital participation is mandated under section 26.1.2 of the service conditions of the NHS standard contract.[50]

The precise process for collecting data, such as methods for identifying eligible cases and the personnel involved in collecting and uploading data, varies between hospitals. This creates the potential for ascertainment bias and is a recognised limitation of the MINAP data set.[48] Data are uploaded using a secure online system. Each patient record must contain, as a minimum, the date and time of hospital admission, the hospital code, the patient's hospital number and the admission diagnosis. MINAP has developed a handbook that includes definitions of data points to standardise data collection, which is available on the MINAP website.[49]

For some data points, there is a real-time data validation check. For example, the system will query the serum cholesterol entry (field 2.15) if it is outside the range 2.5–25 mmol/l. In addition, MINAP performs an annual data validation assessment in which hospitals re-enter data for 20 randomly selected patients with a diagnosis of NSTEMI. The agreement between the original and re-entered data is recorded and reported to the hospital.

Process of obtaining data from the Myocardial Ischaemia National Audit Project

The primary purpose of MINAP is that of a national audit, but research is recognised as an important ancillary purpose. MINAP has developed an approval purpose for researchers who wish to obtain data for this purpose. Previously, researchers have used the data set to describe the epidemiology of myocardial ischaemia patients and to answer important research questions in this patient group, including the impact of pre-hospital ECGs on outcome and treatment in ACS, the association between hospital volume and PCI performance, and an international hospital comparison of treatment and outcome in patients that have an acute myocardial infarction (AMI).[51–53] However, this study is one of the first times that MINAP data have been used for a research question that specifically focuses on OHCA.

In order to demonstrate the feasibility of this project and to secure funding, MINAP provided our team with a random sample of 84,194 cases, of which 1431 (1.7%) were identified as cardiac arrest. Following on from the funding award and project commencement, we were informed by MINAP that we would need to submit only a revision to our original data application, rather than a new application for data. Despite this preparatory work, we experienced significant delays in receiving data and unfortunately we had to return to MINAP on several occasions as the data items that we had requested were not provided. This process is summarised in *Table 1*. The key challenge that we experienced was the release of incomplete data sets, as well as a lack of clarity regarding timelines, processes and the combination of data items that could be released.

These delays meant that the team were required to request two no-cost extensions from the funder.

Inclusion/exclusion criteria and case identification process

Patient events in the MINAP data set were eligible for inclusion in this study if:

1. they were an adult (aged $\geq$ 18 years)
2. they had sustained an OHCA attributable to ACS and
3. initial resuscitation attempts were successful, leading to admission to hospital.

TABLE 1 Summary timeline of project MINAP data releases

Date	Process
1 March 2014	Project start date
19 June 2014	Application amendment submitted to MINAP
12 September 2014	MINAP advised research team that application would need to be reviewed by the HQIP before it could be released
10 October 2014	Research team advised that HQIP would review application at meeting on 14 October 2014
27 November 2014	MINAP advised research team that HQIP had approved data release
12 December 2014	Data extract released (number of key data items not included)
17 December 2014	Further data extract released (some key data items still missing)
23 April 2015	Further data extract released
10 June 2015	MINAP promised full case review to explore reasons for delays and incomplete data releases
23 June 2015	Further data extract released (uncleaned extract with cleaning instructions provided two days later)
27 November 2015	Final data extract released

HQIP, Healthcare Quality Improvement Partnership.

Patient events were excluded if they were:

1. second or subsequent cardiac arrests, or
2. in-hospital cardiac arrest only.

We identified eligible cases using a seven-stage process, which first identified eligible cases and then excluded cases in accordance with the predefined eligibility criteria. Details of the process are included in *Table 2*. As ACS can be difficult to diagnose immediately post OHCA, we made the assumption that all patients included in the MINAP data set had been assumed to have ACS at the point of admission.

Data were not imputed before case identification, and, thus, we did not include cases if data required for determining eligibility were missing.

Outcome measures

The primary study outcome was all-cause in-hospital mortality. This was mainly identified through data field 4.04, 'death in hospital.' If field 4.04 was missing, alternative fields were used, such as field 3.16, 'outcome of arrest,' field 4.16, 'discharge destination', and ONS data.

The secondary outcomes were neurological outcome at hospital discharge and time to all-cause mortality.

TABLE 2 Case identification process

Stage	Process	Process to identify cases
1	Identify all cases of cardiac arrest	Any one of: • field 3.10 (delay before treatment) – response of cardiac arrest • field 3.13 (cardiac arrest date/time) – any response • field 3.14 (cardiac arrest location) – response of before ambulance arrival, after ambulance arrival, A&E, CCU, medical ward, elsewhere in hospital, catheter lab • field 3.15 (arrest presenting rhythm) – any response • field 3.16 (outcome of arrest) – any response
2	Identify all cases of OHCA	Case eligible if field 3.14 (cardiac arrest location) contained response of 'before ambulance arrival' or 'after ambulance arrival' If field 3.14 is not completed, then case eligible if date/time in field 3.13 (cardiac arrest date/time) preceded date/time in field 3.06 (date/time arrival at hospital)
3	Identify adult cases of OHCA	Age derived from field 1.06 (date of birth) Case eligible if age was ≥ 18 years
4	Identify first case of OHCA	Cases were excluded if 3.13 (cardiac arrest date/time – first arrest only) was missing
5	Exclude all cases with no ROSC or where resuscitation was not attempted	Cases were excluded if 3.16 (outcome of arrest) was recorded as no return of circulation or resuscitation not attempted
6	Exclude duplicate records	Cases were excluded if they were duplicated in the data set (e.g. same case entered twice, transfer to another hospital leading to record duplication). This process used anonymised patient identifiers (e.g. anonymised NHS number) and probabilistic matching (e.g. matching cases based on age, sex, admission hospital, admission time)
7	Exclude records where primary outcome was missing	Cases were excluded if the primary outcome (hospital survival) was missing

A&E, accident and emergency; CCU, cardiac care unit.

For neurological outcome at hospital discharge, we dichotomised patients as either survival to hospital discharge with good neurological outcome or death/poor neurological outcome at hospital discharge. Neurological outcome was based on field 3.16 (outcome of arrest). Where field 3.16 was missing, we used the primary outcome data to determine if the patient was dead at hospital discharge. Field 3.16 categorises patient status at discharge as being either with or without neurological deficit, but there are no clear and objective criteria on which to make this assessment detailed in the MINAP data set. Thus, this measure of neurological recovery may not be as useful as either the cerebral performance category or modified Rankin score, which are usually used in cardiac arrest studies.[54]

For time to all-cause mortality, we limited the analysis to patients who were discharged alive from hospital. MINAP linked the data set to ONS data to provide survival days from the date of the cardiac arrest event and mortality status at this time point (alive or dead). Where these data were unavailable and the patient survived to hospital discharge, we used the days to discharge as the survival time and identified these patients as censored (alive) at that point. This applied mainly to patients in later years, when data had not yet been linked with ONS data.

Modifiable and non-modifiable variables

We categorised variables into five groups to facilitate data management and analysis. These groups were demographic variables, medical history variables, presenting characteristics of the OHCA variables, care pathway variables and discharge care variables. Full details of MINAP variables and categories, and how they were used in the analysis, are included in *Appendix 1*. Within each group, we recategorised variables where it was clinically meaningful to do so, particularly where the number of patients in a particular group was small.

In order to prevent the release of data that may enable identification of individual patients, MINAP provided only the month and year of patient admission. For time fields, the time of hospital admission was categorised as time point zero and other time fields were then described as a number of minutes, hours or days prior to or following time point zero.

Demographic variables

This group included age, sex, ethnicity and the deprivation score. Ethnicity was recategorised, as detailed in *Table 3*.

The Index of Multiple Deprivation (IMD) is a score of deprivation supplied by the ONS based on postcode data.[55] Geographical areas with an approximate population of 1500 are scored based on seven domains (income, employment, education, health, crime, barriers to housing and services, and living environment). In our analysis, we used the absolute score (rather than rank), so a higher score indicates increased deprivation.

Medical history variables

This group included smoking status, diabetes mellitus status, hypercholesterolaemia, heart failure, cerebrovascular disease, previous AMI, asthma or chronic obstructive pulmonary disease (COPD), chronic renal failure, peripheral vascular disease, previous angina pectoris, previous PCI, previous coronary artery bypass graft (CABG) and hypertension. Diabetes status and smoking status were recategorised as shown in *Table 3*. Most definitions are based on documented history of the disease. For all variables, a response of unknown was categorised as missing.

Presenting characteristics of out-of-hospital cardiac arrest variables

This group included time point of cardiac arrest (before or after ambulance arrival), cardiac arrest rhythm, serum glucose (mmol/l), creatinine (μmol/l), left ventricular ejection fraction (LVEF), haemoglobin (g/dl), serum cholesterol (mmol/l), admission diagnosis, systolic blood pressure at admission, ECG that determined treatment, time of day of admission (day/night), Killip class, mini-GRACE (Global Registry of Acute Coronary Events) score and year of admission. The variable ECG that determined treatment was recategorised, as shown in *Table 3*.

TABLE 3 Recategorisation of categorical data points

Field	Original responses	Recategorised responses
Baseline demographics		
Ethnicity (field 1.13)	White	White
	Black	Black
	Asian	Asian
	Mixed	Other
	Other	Other
Medical history		
Smoking status (field 2.16)	Current smoker	Ever smoked
	Ex-smoker	Ever smoked
	Never smoked	Never smoked
	Non-smoker – smoking history unknown	Never smoked
Diabetes status (field 2.17)	Not diabetic	Not diabetic
	Diabetes (dietary control)	Diabetic
	Diabetes (oral medicine)	Diabetic
	Diabetes (insulin)	Diabetic
	Insulin plus oral medication	Diabetic
Presenting characteristics of OHCA		
ECG that determined treatment (field 2.03)	ST segment elevation	ST segment elevation or LBBB
	LBBB	ST segment elevation or LBBB
	ST segment depression	ST segment depression or T-wave changes only
	T-wave changes only	ST segment depression or T-wave changes only
	Other acute abnormality	Other acute abnormality or no acute changes
	No acute changes	Other acute abnormality or no acute changes
Care pathway		
Time point of aspirin administration (field 2.04)	Already on aspirin/antiplatelet drug	Already on aspirin/antiplatelet drug
	Aspirin/antiplatelet drug given out of hospital	Aspirin/antiplatelet drug given pre hospital
	Aspirin/antiplatelet drug given after arrival in hospital	Aspirin/antiplatelet drug given in hospital
	Aspirin/antiplatelet contraindicated	Not given
	Not given	Not given
Admitting consultant (field 2.22)	Cardiologist	Cardiologist
	Other general physician	Other consultant
	Other	Other consultant

continued

TABLE 3 Recategorisation of categorical data points (*continued*)

Field	Original responses	Recategorised responses
Place where ECG performed (field 2.23)	Ambulance	Pre hospital
	Other health-care facility	Pre hospital
	In hospital	In hospital
Admission ward (field 3.17)	CCU	CCU
	Intensive therapy unit	Intensive therapy unit
	Died in A&E	Died in emergency department
	Cardiac ward (non-CCU)	Cardiac ward (non-CCU)
	Acute admissions unit	General medical ward or other
	General medical ward	General medical ward or other
	Stepdown ward	General medical ward or other
Discharge care		
Discharge diagnosis (field 4.02)	MI (ST elevation)	ACS
	ACS (troponin positive)/NSTEMI	ACS
	ACS (troponin negative)	ACS
	Threatened MI	ACS
	MI (unconfirmed)	ACS
	Chest pain of uncertain cause	Other
	Other diagnosis	Other
	Takotsubo cardiomyopathy	Other
	PCI-related MI	Other
Echocardiography (field 4.11)	Yes	Yes or planned
	Planned after discharge	Yes or planned
	No	No
	Not indicated	No
Coronary angiography (field 4.13)	Protocol-driven investigation performed in this hospital	Protocol driven
	Protocol-driven investigation performed at another hospital	Protocol driven
	Symptom-driven investigation performed in this hospital	Symptom driven
	Symptom-driven investigation performed at another hospital	Symptom driven
	Not applicable	None
	Patient refused	None
	Not performed	None
Coronary intervention (field 4.14)	PCI	PCI
	PCI planned after discharge	PCI
	CABG	CABG
	CABG planned after discharge	CABG
	Not applicable	None
	Patient refused	None
	Not performed or arranged	None

TABLE 3 Recategorisation of categorical data points (*continued*)

Field	Original responses	Recategorised responses
Discharge drugs[a]	Yes	Yes
	No	No
	Contraindicated	No
	Patient declined treatment	No
	Not applicable	No
	Not indicated	No

A&E, accident and emergency; CABG, coronary artery bypass graft; CCU, cardiac care unit; LBBB, left bundle branch block; MI, myocardial infarction.
a Applies to beta-blocker (field 4.05), angiotensin-converting enzyme inhibitor (field 4.06), statin (field 4.07), aspirin (field 4.08), thienopyridine inhibitor (field 4.27) and ticagelor (field 4.31).

For admission diagnosis, we combined two fields (2.01, initial diagnosis, and 2.36, site of infarct) to create a single field to describe both the initial diagnosis and, where appropriate, the site of the infarct. To create the new field, we recategorised ACS, chest pain cause and other initial diagnosis in field 2.01 as a single category of other diagnosis. For participants who were recorded in field 2.01 as having a definite myocardial infarction (MI), we broke down these participants by infarct site from 2.36. The revised field had three categories: definite MI – anterior infarction; definite MI – other infarction site; and other initial diagnosis.

Time of hospital arrival (field 3.06) was used to classify whether the patient was admitted during the day (admission time 08.00–19.59 hours) or at night (20:00–07:59 hours). There is little consistency as to the cut-offs to be used when categorising night and day in studies of OHCA, MI and temporal variability. Some studies dichotomise as night and day, albeit with variability in time cut-off points, whereas some studies add an additional category for evening admissions, and other studies include an additional category for the weekend.[56–64] On this basis, we took the pragmatic decision to categorise as discussed above, which is consistent with a previous OHCA study and similar to the method used in a previous MI study.[56,62] We were unable to analyse the impact of a weekend effect on survival in this study as, despite recent interest in this issue in the UK, NICOR was unable to release these data on the basis that, in combination with other variables, it might enable the identification of individual patients.[65–67]

Laboratory values (glucose, cholesterol, creatinine, haemoglobin) are the first recorded value following hospital admission, and these are recorded within the first 24 hours of admission. Systolic blood pressure and heart rate are the first values recorded when the patient is in a stable cardiac rhythm (e.g. sinus rhythm).

Before June 2013, haemoglobin levels in the MINAP data set were reported as g/dl. In June 2013, the unit of measurement was changed to g/l. An analysis of data suggested that different hospitals were using both sets of units during 2013. To ensure consistency, we divided all values from 2014 and 2015 by 10 so that we could report them as g/dl. For 2013, values above 30 were considered to have been reported as g/l, so were also divided by 10.

The GRACE score is a validated score to predict outcome following acute coronary score, derived from key patient presenting characteristics.[68,69] As not all data points may be available in the MINAP data set, a mini-GRACE score has been derived, which has been reported and used by the National Institute for Health and Care Excellence (NICE).[70,71] The score has been tested and validated using the MINAP data set.[71] It is derived from eight data points in the MINAP data set, as described in *Table 4*.

TABLE 4 Derivation of the mini-GRACE score

Variable	Derivation	Category	Score
Cardiac arrest	All patients in study data set	Cardiac arrest – yes (required for patients to be eligible for the study)	30
Age (years)	Date of birth (field 1.06) supplied as age	< 30	0
		30–39	1.7 × (age – 30)
		40–49	17 + [1.6 × (age – 40)]
		50–59	33 + [1.7 × (age – 50)]
		60–69	50 + [1.7 × (age – 60)]
		70–79	67 + [1.6 × (age – 70)]
		80–89	83 + [1.7 × (age – 80)]
		≥ 90	100
Loop diuretic	Loop diuretic (field 3.34)	Yes	20
		No	0
ECG – ST-segment deviation	ECG determining treatment (field 2.03)	ST segment elevation	17
		ST segment depression	17
		No acute changes	0
		LBBB	0
		T-wave changes only	0
		Other acute abnormality	0
Cardiac enzymes elevated	Cardiac markers raised (field 2.14)	Yes	13
		No	0
Creatinine level (μmol/l)	Creatinine (field 2.34)	< 200	5
		≥ 200	20
Pulse rate (b.p.m.)	Heart rate (field 2.21)	< 50	0
		50–59	0.3 × (heart rate – 50)
		60–69	3 + [0.3 × (heart rate – 60)]
		70–79	6 + [0.3 × (heart rate – 70)]
		80–89	9 + [0.3 × (heart rate – 80)]
		90–99	12 + [0.3 × (heart rate – 90)]
		100–109	15 + [0.3 × (heart rate – 100)]
		110–149	18 + [0.3 × (heart rate – 110)]
		150–199	30 + [0.3 × (heart rate – 150)]
		≥ 200	46
SBP (mmHg)	SBP (field 2.20)	< 80	58
		80–99	58 – [0.5 × (SBP – 80)]
		100–109	48 – [0.5 × (SBP – 100)]
		110–119	43 – [0.4 × (SBP – 110)]
		120–129	39 – [0.5 × (SBP – 120)]
		130–139	34 – [0.5 × (SBP – 130)]
		140–149	29 – [0.5 × (SBP – 140)]

TABLE 4 Derivation of the mini-GRACE score (*continued*)

Variable	Derivation	Category	Score
		150–159	24 – [0.5 × (SBP – 150)]
		160–179	19 – [0.45 × (SBP – 160)]
		180–199	10 – [0.5 × (SBP – 180)]
		≥ 200	0

b.p.m., beats per minute; LBBB, left bundle branch block; SBP, systolic blood pressure.

Care pathway variables

This variable group included hospital volume (OHCA cases per year), hospital pPCI capability, EMS response time, EMS travel distance, admitting consultant, cardiological care during admission, admission ward, time point of aspirin administration, place where first 12-lead ECG performed, in-hospital administration of angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, in-hospital use of loop diuretic, reperfusion treatment and timing, assessment at non-interventional hospital, assessment at intervention centre, intended reperfusion procedure, procedure performed, reason for no angiography, reason for no intervention and reason treatment not given.

The following variables were recategorised, as shown in *Table 3*: time point of aspirin administration, admitting consultant, place first 12-lead ECG performed and admission ward.

For hospital-level data (distance to hospital, volume and PCI centre), we categorised patients by the hospital to which they were first admitted. We were supplied with both a hospital code and hospital location using northings–eastings data. Initial data review suggested that some hospitals may have been assigned more than one code, so the northings–eastings were used to identify individual hospital locations. Northings–eastings were not available for eight hospitals (91 patients), so the MINAP hospital codes were used to categorise these patients.

Distance to hospital was calculated using the Euclidian distance between the participant's home address (northings–eastings data to the nearest km) and the hospital to which they were first admitted (northings–eastings data to the nearest kilometre). MINAP does not collect data on event location, so we made the assumption that the cardiac arrest event occurred at the patient's home. This assumption is supported by UK and international data that show that most cardiac arrests happen at the patient's home.[5,24] For example, English data show that, where location is recorded, 83.2% of OHCA events occur in the home.[5] However, on the basis that some participants would not have had a cardiac arrest at home (e.g. they had it at work or in a public place), we considered how to identify cases where there was clear evidence that the patient had the cardiac arrest outside the home, so that we could classify these data as missing. Our initial plan to create an upper limit proved to be problematic as the distance was likely to be significantly greater in rural areas than urban areas. Therefore, for each case, we calculated the distance between the home address and nearest hospital. When the distance between the participant's home address and the hospital they were admitted to was large (> 95th centile) compared with the distance between the participant's home address and nearest hospital, we concluded that the cardiac arrest did not happen at the participant's home, so we recorded these data as missing.

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 to a category based on the initial hospital in which they were treated.

Primary percutaneous coronary intervention centres were defined as a hospital that performed at least 100 pPCI procedures per year, based on the British Cardiovascular Intervention Society recommendation

for interventional centres.[72] We calculated the number of pPCIs each hospital did per year using the entire MINAP data set, using MINAP field 3.39 (initial reperfusion therapy). If a patient was treated in a hospital in a year that it was designated as a pPCI centre, then the patient was categorised as being treated in a pPCI centre.

Emergency medical service response time was defined as the time (in minutes) from the call for help (MINAP field 3.02) to arrival of ambulance (field 3.04) or, if this field was missing, to the arrival of a first responder (field 3.03).

In the MINAP data set, reperfusion treatment data are collected in four key fields, namely initial reperfusion therapy (field 3.39), additional reperfusion therapy (field 3.40), thrombolytic drug (field 3.36) and date/time of reperfusion therapy (field 3.09). In our analysis, we considered only the initial reperfusion treatment, which was classified as either pPCI or thrombolysis. If field 3.39 was missing but the participant was recorded as having received a thrombolytic drug (field 3.36) then they were classified as having received thrombolysis. For each reperfusion therapy, we classified the timing as either early, late or not recorded. We classified early pPCI as a pPCI started within 90 minutes of hospital arrival, and early thrombolysis as administration of a thrombolytic with 60 minutes of the call for help. Timings outside these windows were considered late. Current NICE and European Society of Cardiology guidelines do not specifically state a timeframe within which thrombolysis and pPCI should be performed, except that the chosen therapy should be delivered as soon as possible and thrombolysis should be considered if pPCI cannot be commenced within 120 minutes.[73,74] As such, our threshold for early thrombolysis was based on the standard described in the Department of Health's National Service Framework for Coronary Heart Disease.[75] Our threshold for early PCI was based on the European Society Guidelines, which describe a period from first medical contact to PCI of up to 90 minutes as an appropriate target.[73]

Discharge care variables

Discharge care variables included discharge diagnosis, echocardiography, coronary angiography, coronary intervention, provision of cardiology follow-up, cardiac rehabilitation, discharge drugs (beta-blocker, angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, statin, aspirin, thienopyridine inhibitor, ticagrelor), provision of smoking cessation advice and provision of dietary advice.

Discharge diagnosis, echocardiography, coronary angiography, coronary intervention and discharge drugs were recategorised as detailed in *Table 3*.

For echocardiography, coronary angiography and coronary intervention, we acknowledged that these interventions may occur before or following discharge and that when undertaken prior to discharge they may inform in-hospital treatment. However, we considered them to be best categorised in this domain.

In addition, for antiplatelet drugs (aspirin, thienopyridine inhibitor, ticagrelor) we created three categories: no antiplatelet therapy on discharge, monotherapy on discharge or dual antiplatelet therapy on discharge. The category of no antiplatelet therapy was used when a patient received none of the three drugs on discharge. Monotherapy was used when a patient received any one of the three drug groups. Dual antiplatelet therapy was used if the patient was prescribed aspirin plus either a thienopyridine inhibitor or ticagrelor.

Missingness and imputation

The MINAP data are incomplete because, for some patients, there are missing observations for the outcomes and/or variables.[76] There are a number of potential reasons for missingness, including:

- omission during data input
- data field introduced during data collection period, but data may have been available prior to that point [e.g. serum glucose (field 2.28) was introduced as a data field in 2005]

- data field introduced during data collection period and treatment/data would not be available prior to that date (e.g. the drug ticagrelor was first licensed in the UK in 2010)
- the patient died before intervention was appropriate (e.g. discharge drugs are not applicable if patient died during admission)
- data field not relevant given delivery of other care [e.g. why was no angiography performed? (field 3.51) is not relevant if angiography was performed].

In view of this missingness, a complete-case analysis would lead to discarding a high proportion of data and create a high risk of bias. To reduce this risk of bias, we used data imputation strategies to minimise data missingness.

Classifying data as missing

To ensure that data were valid, we classified some available data as missing, and these were then imputed.

For some continuous variables, we applied upper and lower cut-off values to some continuous variables beyond which data were considered implausible, and thus were classed as missing. For each variable, we carefully considered the MINAP data definition, as well as the balance between when a variable became implausible rather than just unlikely. This was based on clinical judgement and review of the data distribution. The cut-off points that were used are detailed in *Table 5*.

For categorical variables, data recorded as unknown or not applicable in individual fields were categorised as missing.

Imputation strategy

Data imputation was undertaken following case identification. No outcomes were imputed.

Our imputation strategy was based on the approach described by Cattle *et al.*,[76] in relation to the MINAP data set. The imputation method for specific data points is described in *Table 6*.

Default imputation was used for some variables. For the remaining variables, multiple imputation by chained equations (MICE) was used.[77] This involves fitting a model for each variable included in the imputation model. For binary variables, a logistic regression was fitted, where the binary variable for which missing values were being imputed was the outcome variable and the other variables in the imputation model are used as predictor variables. For categorical variables with more than two categories, polytomous regression, which generalises binary logistic regression to allow more than two categories in the variable for which missing

TABLE 5 Cut-off points used for baseline continuous variables

Variable	Unit of measurement	Cut-off point	
		Lower	Upper
EMS response time	minutes	< 0	> 180
Cholesterol	mmol/l	≤ 0	> 30
SBP	mmHg	< 50	> 230
Heart rate	b.p.m.	< 25	> 180
Glucose	mmol/l	< 1	> 60
Creatinine	µmol/l	≤ 0	–
Haemoglobin	g/dl	< 5	> 30
Reperfusion treatment time	–	< 0 minutes	> 72 hours
IMD score	–	≤ 0	–

b.p.m., beats per minute; SBP, systolic blood pressure.

TABLE 6 Imputation strategy used

Variable	Modelling strategy
Demographic	
Age	No missingness
Sex	Binary logistic regression
Ethnicity	Polytomous regression
IMD score	PMM
Medical history	
Smoking status	Binary logistic regression
Diabetes status	Binary logistic regression
Hypercholesterolaemia	Default imputation – missing responses categorised as no
Heart failure	Default imputation – missing responses categorised as no
Cerebrovascular disease	Default imputation – missing responses categorised as no
Previous AMI	Default imputation – missing responses categorised as no
Asthma or COPD	Default imputation – missing responses categorised as no
Chronic renal failure	Default imputation – missing responses categorised as no
Peripheral vascular disease	Default imputation – missing responses categorised as no
Previous angina	Default imputation – missing responses categorised as no
Previous PCI	Default imputation – missing responses categorised as no
Previous CABG	Default imputation – missing responses categorised as no
Hypertension	Default imputation – missing responses categorised as no
Presenting characteristics of OHCA	
Time point of cardiac arrest	Binary logistic regression
Cardiac arrest rhythm	Polytomous regression
Serum glucose (mmol/l)	PMM
Creatinine	PMM
LVEF	Polytomous regression
Haemoglobin (g/dl)	PMM
Serum cholesterol (mmol/l)	PMM
Admission diagnosis	Polytomous regression
SBP at admission (mmHg)	PMM
ECG that determined treatment	Polytomous regression
Heart rate at admission	PMM
Time of the day of admission (day/night)	No missingness
Year of admission	No missingness

TABLE 6 Imputation strategy used (*continued*)

Variable	Modelling strategy
Care pathway	
Hospital volume (OHCA cases per year)	No missingness
Hospital pPCI capability	No missingness
EMS response time	PMM
EMS travel distance	PMM
Admitting consultant	Binary logistic regression
Cardiological care during admission	Binary logistic regression
Admission ward	Polytomous regression
Time point of aspirin administration	Polytomous regression
Place where ECG performed	Polytomous regression
Angiotensin-converting enzyme inhibitor (in-hospital use)	Default imputation – missing responses categorised as no
Loop diuretic (in-hospital use)	Default imputation – missing responses categorised as no
Reperfusion treatment and timing	Default imputation – missing responses categorised as no
Discharge care	
Discharge diagnosis	Binary logistic regression
Echocardiography	Binary logistic regression
Coronary angiography	Polytomous regression
Coronary intervention	Polytomous regression
Followed up by cardiologist	Polytomous regression
Cardiac rehabilitation	Polytomous regression
Discharged on beta-blocker	Binary logistic regression
Discharged on angiotensin-converting enzyme inhibitor	Binary logistic regression
Discharged on statin	Binary logistic regression
Discharged on aspirin	Binary logistic regression
Discharged on thienopyridine inhibitor or ticagrelor	Year 2003–8: default imputation – missing responses categorised as no Year 2009–15: polytomous regression

PMM, predictive mean matching; SBP, systolic blood pressure.

values are being imputed was used. For continuous variables, predictive mean matching (PMM) was used to impute missing values. PMM involves fitting a linear model with the imputed value being an observed (non-missing) value sampled from the values closest to the value suggested by the linear model. The models for different variables are fitted in a chain. To achieve true target distributions, several iterations (each iteration consists of one chain of models for all imputed variables) are required.

For the fields that relate to thienopyridine inhibitors at discharge, we were not supplied with data before 2009. We therefore default imputed for the period before 2009, and incorporated two year slopes (2003–8 and 2009–15) in our adjusted analysis.

The MICE package in the R statistical program (The R Foundation for Statistical Computing, Vienna, Austria) (R is a language and environment for statistical computing) was used to perform the multiple imputation.[77]

Default imputation was first performed for the appropriate predictor variables (such as medical history predictor variables). Subsequently, we used the resulting data set as the 'complete-cases' data set to impute 25 data sets with 30 iterations. Convergence was assessed by checking whether or not the imputation chains mixed well for all variables.

Statistical approach

Data were analysed by the study statistician (PK). The initial data processing, as described above, and descriptive analyses for complete cases were performed using SPPS statistics, version 22 (IBM SPSS Statistics, Armonk, NY, USA). The R statistical program was used for multiple imputation, descriptive analysis after multiple imputation, fitting models for in-hospital mortality and neurological outcome [using the gamm4 package (Simon Wood and Fabian Scheipl, 2016. gamm4: Generalised Additive Mixed Models using 'mgcv' and 'lme4'. R package version 0.2–4. https://CRAN.R-project.org/package=gamm4)], and time to all-cause mortality [using coxme package (Terry M Therneau, 2015. coxme: Mixed Effects Cox Models. R package version 2.2–5. https://CRAN.R-project.org/package=coxme)].

Categorical predictor variables are reported as the number of patients in each category and the corresponding percentages. For continuous predictor variables, mean and median are reported to describe typical values and dispersion is described using standard deviation (SD), range and interquartile range (IQR).

In-hospital mortality and neurological outcome analyses

Unadjusted analysis of in-hospital mortality

The primary outcome of in-hospital mortality was analysed using univariate random effects (RE) logistic regression models for each predictor variable. The RE term for the hospital allowed for similarity of in-hospital mortality rates within a hospital and variability between hospitals to be modelled to account for the multilevel nature of the data and to distinguish between hospital- and patient-level factors. For each predictor variable, unadjusted odds ratios (ORs) were obtained from the univariate model using both the pre-imputation and the imputed data sets. For each variable, we report the OR and 95% confidence intervals (CIs), as well as the *p*-values, which test the null hypothesis that the OR is equal to 1. ORs with a value greater than one indicate increased in-hospital mortality rate and a value less than 1 indicates reduced in-hospital mortality.

For analysis after multiple imputation, a RE logistic regression model was fitted to obtain the estimate for the log of the OR [$\log_e$(OR)] and the standard error (SE) for each imputed data set. Estimates from each of the 25 imputed data sets were combined using Rubin's rules[78] to get an estimate for $\log_e$(OR) and SE of all imputed data sets. These were used to calculate the corresponding 95% CI and the *p*-value. Results are presented as OR and 95% CI by taking the exponent of the estimate for $\log_e$(OR) and confidence limits of the CI on $\log_e$(OR) scale.

The model fit for each model was assessed using the adjusted R^2 and the Akaike information criterion (AIC). For the pre-imputation analysis, the different number of complete cases for each different predictor variable means that only adjusted R^2 was used to compare model fit. For the analysis of imputed data sets, the median (from separate analyses of the 25 imputed data sets) adjusted R^2 and AICs are used.

The RE estimate was used to assess if a predictor variable explains the variability of in-hospital mortality across hospitals. A variable that predicts in-hospital mortality and explains substantial variability, and that has a large imbalance across hospitals, would have a large R^2-value and small RE estimate. Using the RE and the latent formulation, the intraclass correlation (ICC) was obtained using the following formula:[79]

$$\text{ICC} = \frac{\text{RE}}{\text{RE} + (\pi^2/3)}. \quad (1)$$

Relationship for continuous predictor variables and in-hospital mortality

Before fitting the models for continuous variables, the form of the relationships between the primary outcome and the continuous predictor variables were explored. For each continuous predictor variable, patients were grouped using deciles and the proportion of in-hospital mortality, and the log of the ratio of proportion of those who died in hospital to the proportion of those who survived to hospital discharge (the logit) was calculated. We then plotted the mid-point values in the deciles against the logits. If this relationship was approximately linear, a linear term was used. If this relationship was approximately convex (or concave), linear and quadratic terms were included in the model. If the linear relationship seemed linear but with different slopes for two different intervals, two linear parameters for the different intervals were included in the model.

Adjusted analysis of in-hospital mortality

A multivariate RE (multilevel) logistic regression model was used to predict in-hospital mortality. 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 multicollinearity as a result of the two predictors being highly correlated. Modifiable variables were added after adding non-modifiable predictor variables to enable us to assess how the prediction improves when modifiable variables are added to a model that includes non-modifiable predictor variables only. The model included an adjustment for year of admission. We used two slopes in the model (2003–8 and 2009–15) to reflect missingness of thienopyridine inhibitor data and the point that pPCI became the most frequently used emergent reperfusion treatment in the MINAP data set.[48] *Appendix 1* shows details of which variables were included in the model.

We added groups of variables to the model in the following order: demographic variables, medical history variables, presenting characteristics of OHCA variables, and care pathway variables. In each group, the first predictor variable added to the model was the one, based on unadjusted results, that explained the most variability in the data. Generally, predictor variables were added into the model by balancing the variability explained by the model (quantified by the adjusted R^2 and the AIC) and the variability across hospitals explained in the model (quantified by RE estimate). Variables were retained in the model even if the OR estimates were not statistically significant. As variables were added in the model, the change in OR estimates, the adjusted R^2, AIC and RE estimates were noted to allow assessment of multicollinearity and model fits. The only reasons that a variable was not included in the model were if there was evidence of multicollinearity or the OR estimate was clearly confounded by an unmeasured confounding variable. It was concluded that there was a multicollinearity problem if combined OR estimates changed markedly and graphical data representations (e.g. bar graphs, box plots) showed a high degree of correlation. R^2-values were used to quantify the amount of variability in in-hospital mortality across patients explained by the predictor variables. RE and ICC estimates for the null and the adjusted model were compared to quantify the amount of variability in in-hospital mortality across hospitals explained by the model.

Adjusted analysis of the neurological outcome

Neurological outcome was analysed as a binary outcome, with the two categories being (1) discharged with good neurological outcome and (2) discharged with poor neurological outcome or died in hospital. We used the same approach as was used for the primary outcome. Therefore, only one adjusted model, corresponding to the final adjusted model fitted for the primary outcome, was fitted for this outcome.

Appendix 1 shows details of which variables were included in the model for this analysis.

Analysis of time to all-cause mortality

Proportional hazards Cox regression RE models were used to analyse time to all-cause mortality for each predictor variable. Unadjusted hazard ratios (HRs) were obtained for a model using both the pre-imputation and the imputed data sets. For each variable, we report the HR and 95% CIs, as well as the *p*-values, which tests the null hypothesis that the HR is equal to 1. A HR greater than one indicates a higher hazard rate of death and a HR less than 1 indicates lower hazard rate of death.

For analysis after multiple imputation, results were combined using Rubin's rules,[78] as for the analysis for in-hospital mortality, except that HR and log(HR) are used in place of OR and log(OR).

Appendix 1 shows details of which variables were included in the model for time to all-cause mortality.

Model fits for different models were assessed using the AIC. For the analysis using imputed data sets, the median (from separate analyses of the 25 imputed data sets) AICs were used. The AIC reported by the 'coxme' package is the difference between the AIC of the fitted model and the AIC of the null model, with a higher AIC value indicating a better fit.

For the adjusted analysis, the final model was developed in a similar way to that described for the in-hospital mortality.

Sensitivity analyses

We performed sensitivity analyses to assess the robustness of the results to the missing data methods used and assumptions made.[80,81] For the in-hospital mortality and neurological outcome analyses, we conducted five analyses, namely patients admitted to hospital between 2003 and 2008; patients admitted to hospital between 2009 and 2015; patients where the ECG determining treatment showed ST elevation or left bundle branch block (LBBB); patients where the ECG determining treatment showed something other than ST elevation or LBBB; and a complete-case analysis. When the defining category was missing in the pre-imputation data set, the case was not included in the sensitivity analysis. The rationale for the cut-off point for the two time periods was that it was between 2008 and 2009 that the use of PCI became more frequent than thrombolysis as a reperfusion treatment.[48] For the time to all-cause mortality analysis, we conducted a complete-case analysis. These complete-case analyses included only patients for whom all relevant data points were available.

Sample size

In preparation for this project, MINAP provided a random sample of 84,194 cases, from which we identified 1431 eligible cardiac arrest events. Of these cases, 345 patients (24%) died in hospital, 847 patients (59%) survived to leave hospital and the outcome was missing in the remaining 239 (17%) patients.

Therefore, taking the most conservative approach (assuming the sample data set is representative of the whole data set), we expected to identify approximately 14,310 eligible OHCA cases, of whom 3434 (24% × 14,310) would die in hospital. For logistic regression and Cox regression models, it is recommended that there are 10 events for each predictor variable, so that 3434 events (in-hospital deaths) will be sufficient to model the MINAP data to answer our research question.[82] Based on these projections, we are able to reliably detect a rate difference of 4% or more with at least 90% power at a 5% significance level. When the prevalence of a predictor variable reaches 50%, it will be possible to detect a rate difference of 2% with a power of approximately 70%.

Patient and public involvement input

The project was supported by two patient and public representatives (BE and JL), who were full members of the research team. They contributed to finalising the objectives of the research, interpretation of analysis and reviewing and approving the final version of this report.

Ethics considerations

This study was secondary research that utilised an anonymised data set. In accordance with the policies of author's institutions, ethics review was sought from and granted by the University of Warwick Biomedical Research Ethics Committee.

The Myocardial Ischaemia National Audit Project forms part of NICOR, which is registered as a data controller under the Data Protection Act 1998[83] and has permission to collect and store patient-identifiable information without consent in accordance with section 251 of the National Health Service Act 2006.[84]

Chapter 4 Results

Case identification

The data set provided by MINAP comprised 1,127,140 cases that were included in the audit between 2003 and 2015. To this data set, we applied the seven-stage case identification process described in *Table 2*. We identified 73,875 cases of cardiac arrest, although the majority of these were in-hospital cardiac arrests or the location/time was not recorded ($n = 50,836$). We excluded five cases in which the participant was aged under 18 years and a further 38 cases in which the age was not recorded. Of the remaining 22,906 cases, 2743 were excluded because it was not described as the participant's index cardiac arrest event and 1240 cases were excluded because resuscitation was not attempted or there was no ROSC. In step 6, a further 1241 records were excluded because of evidence of record duplication. Finally, in step 7, 78 cases were excluded because they were missing primary outcome data. The case identification process is shown in *Figure 3*.

In total, 17,604 cases were included in the analysis of our primary outcome, which represents 1.6% of the entire data set.

The analysis of neurological outcome included 15,286 patients. There were 2542 patients for whom field 3.16 was not recorded or the patient was recorded as transferred to another hospital. We reduced this missingness by cross-referencing against the primary outcome and identifying 222 patients who died before discharge. As such, neurological outcome data were missing for 2318 (13.2%) patients in the cohort.

The time to all-cause mortality analysis included 12,483 patients. After excluding patients who died before discharge ($n = 5047$), there were 810 patients for whom ONS long-term survival data were not available. We reduced this missingness by using the combination of time to discharge and survival status at discharge.

Data missingness and performance of imputation

Data categorised as missing

As described in the methods, we applied cut-off points to some continuous variables, such that markedly outlying values were removed and categorised as missing. In total, these cut-off points affected 4707 values across 10 data fields. Often, this was because data had been incorrectly recorded as zero. Full details are included as *Table 7*.

Summary of missingness across the study cohort

The missingness in individual data points varied markedly. In our data set, missingness varied between 0% (age, admission time) and 98.3% (why no angiography), with the missingness for most variables being in the range 10–20%. *Table 8* shows the missingness for all variables across all patients (cohort used for the hospital mortality/neurological analyses) and the cohort used for the time to all-cause mortality analysis.

For demographic variables, there were only 46 cases with sex missing. The number of cases missing at least one demographic variable was 4182 (23.8%) as missingness for demographic variables was not simultaneous, so, for example, cases missing ethnicity do not necessarily have IMD score missing. After default imputation for medical history variables, the only predictor variables with missing values were diabetes status ($n = 1885$, 10.7%) and smoking status ($n = 3615$, 20.5%). The number of cases missing at least one demographic variable or diabetes status or smoking status value was 7281 (41.4%).

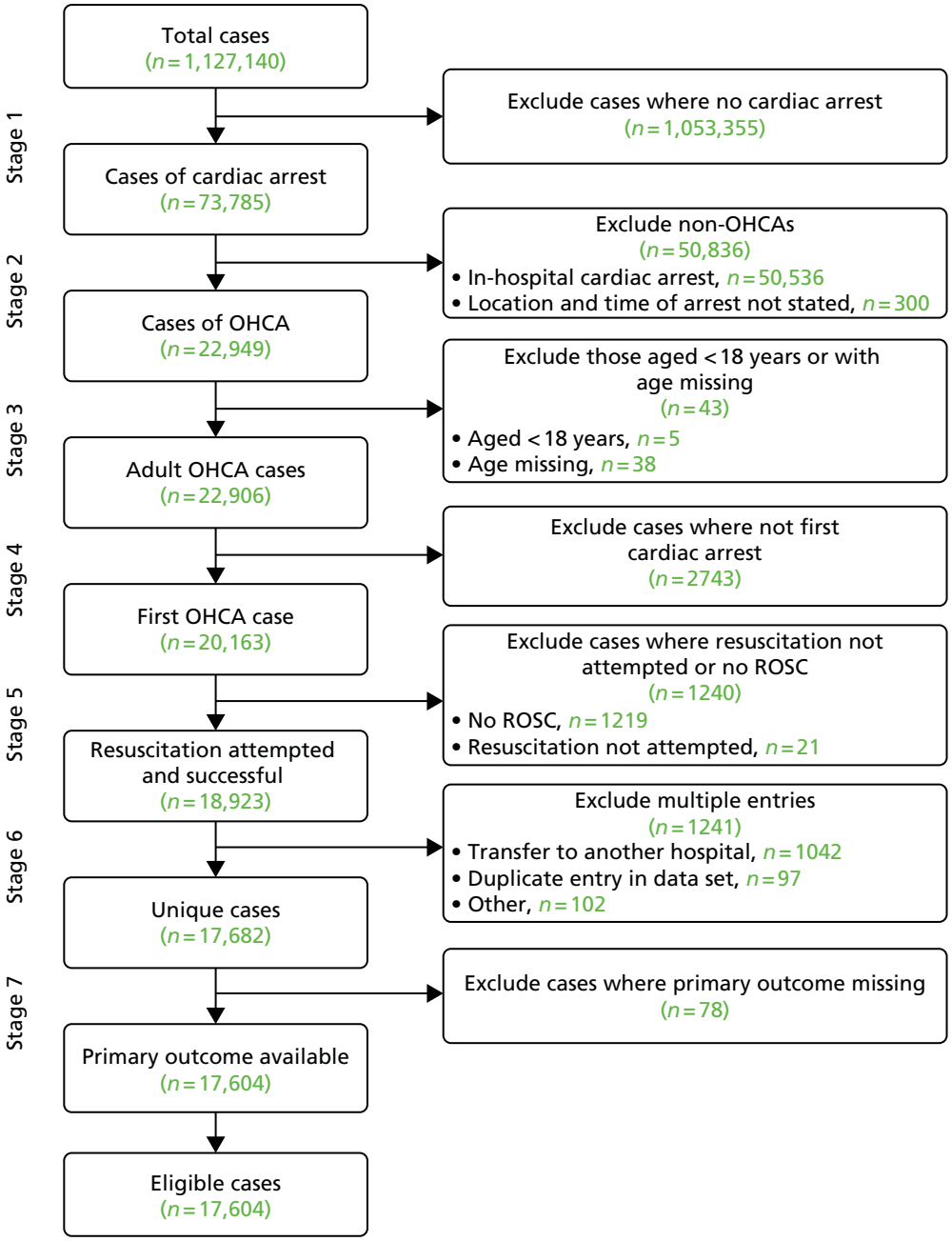

FIGURE 3 Study case identification diagram. Adapted from Couper *et al.*,[85] with permission from Elsevier. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

In the OHCA presenting characteristics group, location of cardiac arrest was missing for only 67 cases. Systolic blood pressure and heart rate tended to be missing simultaneously, so the number of cases missing either of them was 3348 (19.0%), which is close to the individual missing proportions. Similarly, haemoglobin and creatinine levels tended to be missing simultaneously, with the number of cases missing either of them being 6173 (35.1%). There are few cases of missing data values for cardiac arrest rhythm ($n = 1104$, 6.3%) and ECG that determined treatment ($n = 612$, 3.5%), but there are large proportions of missing values for admission diagnosis ($n = 3185$, 18.1%) and LVEF ($n = 9954$, 56.5%). Across the OHCA presenting characteristic variable group, there was at least one missing value in 14,520 (82.5%) cases.

In care pathway variables, EMS response time and EMS distance were not generally missing simultaneously, with the number of cases missing at least one value for these variables being 6269 (35.6%). The proportions of missing values for admitting consultant ($n = 321$, 1.8%) and admission ward ($n = 204$, 1.2%) were low.

TABLE 7 Summary of data categorised as missing

Variable	Number of cases in which data were removed	Details
EMS response time	36	Upper cut-off point: data from 33 patients removed as response time > 180 minutes Lower cut-off point: data from 3 patients removed as response time < 0 minutes
Cholesterol	447	Upper cut-off point: data from 13 patients removed as recorded cholesterol > 30 mmol/l Lower cut-off point: data from 434 patients removed as recorded cholesterol = 0 mmol/l
SBP (mmHg)	268	Upper cut-off point: data from 36 patients removed as recorded SBP > 230 mmHg Lower cut-off point: data from 232 patients removed as recorded SBP < 50 mmHg
Heart rate (b.p.m.)	284	Upper cut-off point: data from 74 patients removed as recorded heart rate > 180 b.p.m. Lower cut-off point: data from 210 patients removed as recorded heart rate < 25 b.p.m.
Glucose (mmol/l)	138	Upper cut-off point: data from 21 patients removed as recorded glucose > 60 mmol/l Lower cut-off point: data from 117 patients removed as recorded glucose < 1 mmol/l
Creatinine (μmol/l)	158	Upper cut-off point: no upper cut-off point Lower cut-off point: data from 158 patients removed as recorded creatinine = 0 μmol/l
Haemoglobin (g/dl)	690	Upper cut-off point: data from 425 patients removed as recorded haemoglobin > 30 g/dl Lower cut-off point: data from 265 patients removed as recorded haemoglobin < 5 g/dl
Reperfusion treatment time	20	Upper cut-off point: data from 16 patients removed as recorded reperfusion treatment time > 72 hours Lower cut-off point: data from four patients removed as recorded reperfusion treatment time < 0 hours
IMD score	1048	Upper cut-off point: no upper cut-off point Lower cut-off point: data from 1048 patients removed as recorded IMD score of ≤ 0
EMS distance (km)	1618	Upper cut-off point: data from 1618 cases where distance from home postcode to treating hospital was over 31 km further than distance from home postcode to closest hospital Lower cut-off point: no lower cut-off

b.p.m., beats per minute; SBP, systolic blood pressure

TABLE 8 Missingness across all data fields

Variable	All patients ($N = 17,604$), n (%)	Time to all-cause mortality analysis ($N = 12,483$), n (%)
Demographic variables		
Age (years)	Only patients with age known included	
Sex	46 (0.3)	40 (0.3)
Ethnicity	2296 (13.0)	1586 (12.7)
IMD score	2276 (12.9)	1620 (13.0)
Medical history variables		
Smoking status	3615 (20.5)	1513 (12.1)
Diabetes status	1885 (10.7)	919 (7.4)
Hypercholesterolaemia	2503 (14.2)	1414 (11.3)
Heart failure	2274 (12.9)	1244 (10.0)
Cerebrovascular disease	2279 (12.9)	1253 (10.0)
Previous AMI	1905 (10.8)	1001 (8.0)
Asthma or COPD	2337 (13.3)	1319 (10.6)
Chronic renal failure	2300 (13.1)	1268 (10.2)
Peripheral vascular disease	2377 (13.5)	1325 (10.6)
Previous angina	2110 (12.0)	1134 (9.1)
Previous PCI	2123 (12.1)	1151 (9.2)
Previous CABG	2058 (11.7)	1120 (9.0)
Hypertension	2019 (11.5)	1063 (8.5)
Presenting characteristics of OHCA variables		
Time point of cardiac arrest	67 (0.4)	45 (0.4)
Cardiac arrest rhythm	1104 (6.3)	743 (6.0)
Serum glucose (mmol/l)	5082 (28.9)	3205 (25.7)
Creatinine (μmol/l)	5432 (30.9)	3588 (28.7)
LVEF	9954 (56.5)	6119 (49.0)
Haemoglobin (g/dl)	6019 (34.2)	4032 (32.3)
Serum cholesterol (mmol/l)	8105 (46.0)	4414 (35.4)
Admission diagnosis	3185 (18.1)	2307 (18.5)
SBP at admission (mmHg)	2955 (16.8)	1887 (15.1)
ECG that determined treatment	612 (3.5)	321 (2.6)
Heart rate at admission (b.p.m.)	3304 (17.2)	1948 (15.6)
Time of the day of admission (day/night)	0 (0)	0 (0)
Killip class	11,712 (66.5)	8320 (66.7)
Mini-GRACE score	9040 (51.4)	NA
Year of admission	0 (0)	0 (0)

TABLE 8 Missingness across all data fields (*continued*)

Variable	All patients ($N = 17,604$), *n* (%)	Time to all-cause mortality analysis ($N = 12,483$), *n* (%)
Care pathway variables		
Hospital volume (OHCA cases per year)	0 (0)	0 (0)
Hospital pPCI capability	0 (0)	0 (0)
EMS response time	4179 (23.7)	2837 (22.7)
EMS travel distance	2922 (16.6)	2169 (17.4)
Admitting consultant	321 (1.8)	183 (1.5)
Cardiological care during admission	4424 (25.1)	2937 (23.5)
Admission ward	204 (1.2)	137 (1.1)
Time point of aspirin administration	1503 (8.5)	860 (6.9)
Place where ECG performed	3000 (17.0)	2000 (16.0)
Angiotensin-converting enzyme inhibitor (in-hospital use)	2843 (16.1)	1876 (15.0)
Loop diuretic (in-hospital use)	2968 (16.9)	2006 (16.1)
Reperfusion treatment and timing	2431 (13.8)	1467 (11.8)
Assessment at non-intervention hospital	6392 (36.3)	4569 (36.6)
Assessment at intervention centre	10,616 (60.3)	7156 (57.3)
Intended reperfusion procedure	10,365 (58.9)	6976 (55.9)
Procedure performed	10,506 (59.7)	7100 (56.9)
Reason for no angiography	17,308 (98.3)	12,343 (98.9)
Reason for no intervention	16,585 (94.2)	11,785 (94.4)
Reason treatment not given	3961 (22.5)	3178 (25.5)
Discharge care variables		
Discharge diagnosis	285 (1.6)	71 (0.6)
Echocardiography	2516 (14.3)	1273 (10.2)
Coronary angiography	2150 (12.2)	1580 (12.7)
Coronary intervention	3130 (17.8)	2329 (18.7)
Followed up by cardiologist	NA	3373 (27.0)
Cardiac rehabilitation	NA	1800 (14.4)
Discharged on beta-blocker	NA	2662 (21.3)
Discharged on angiotensin-converting enzyme inhibitor	NA	2723 (21.8)
Discharged on statin	NA	2661 (21.3)
Discharged on aspirin	NA	2598 (20.8)
Discharged on thienopyridine inhibitor	NA	6558 (52.5)
Discharged on ticagrelor	NA	10,977 (87.9)
Discharged on thienopyridine inhibitor or ticagrelor	NA	6201 (49.7)
Smoking cessation advice	NA	3365 (27.0)
Dietary advice on discharge	NA	5506 (44.1)

b.p.m., beats per minute; NA, not applicable, SBP, systolic blood pressure.

The proportion of missing data for the other care pathway predictor variables included in the modelling were between 10% and 20%. Across all cases, the number of cases with a missing value for a care pathway predictor variable was 10,152 (57.7%).

Across all variable groups, the number of cases with at least one missing value was 16,163 (91.8%).

Performance of the imputation

Multiple imputation chains for all variables mixed well, suggesting that convergence was achieved (see *Figures 11–14* in *Appendix 2*).

Overview of cohort

Our cohort of 17,604 patients who had an OHCA attributable to ACS, and who survived to hospital admission, was collected over a 12-year period between January 2003 and June 2015. Overall, the number of cases recorded per year increased over the course of the study, with a peak of 2129 cases in 2012 (*Figure 4*). This was principally driven by an increase in STEMI cases, but the actual proportion of STEMI cases was relatively consistent over time (68–78% of cases per year were STEMI cases).

Patient cases were collected from 239 hospitals. The median number of cases reported per hospital over the study period was 46 (IQR 21–92; range 1–517).

In our patient cohort, most patients survived to hospital discharge ($n = 12{,}557$, 71.3%), but there was variability in survival by hospital. *Figure 5* shows hospital mortality 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. As shown in *Figure 6*, there was evidence of variability between the 94 hospitals that contributed at least 60 patients (range 13–84%; median 58.9%, IQR 44.2–66.8%).

Of the 12,483 patients who survived to hospital 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).

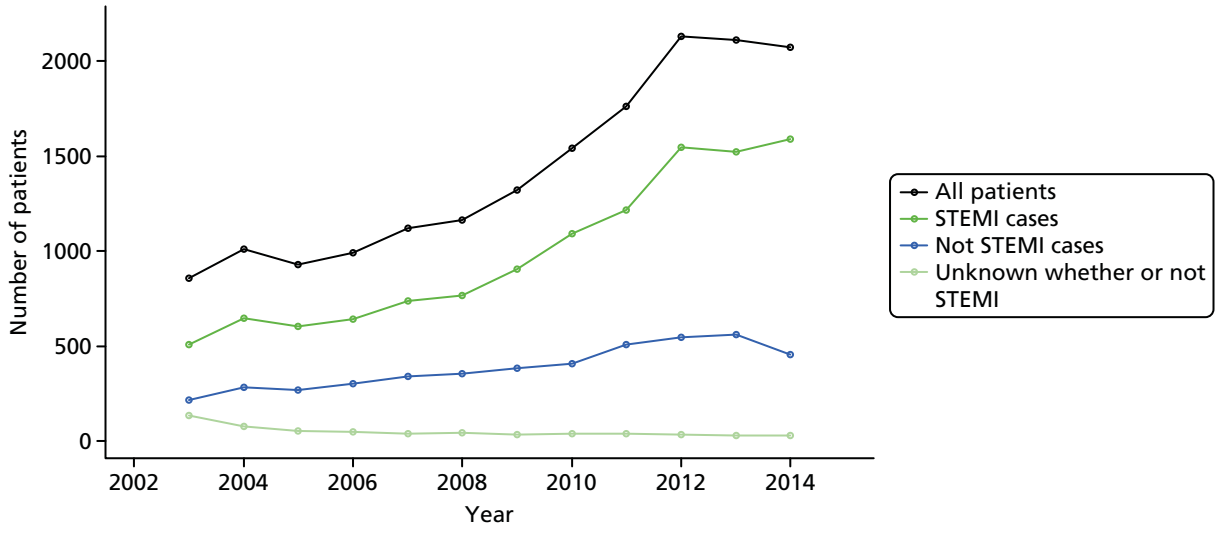

FIGURE 4 Number of cases per year for complete years (2003–14) with breakdown by diagnosis. Adapted from Couper *et al.*,[85] with permission from Elsevier. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

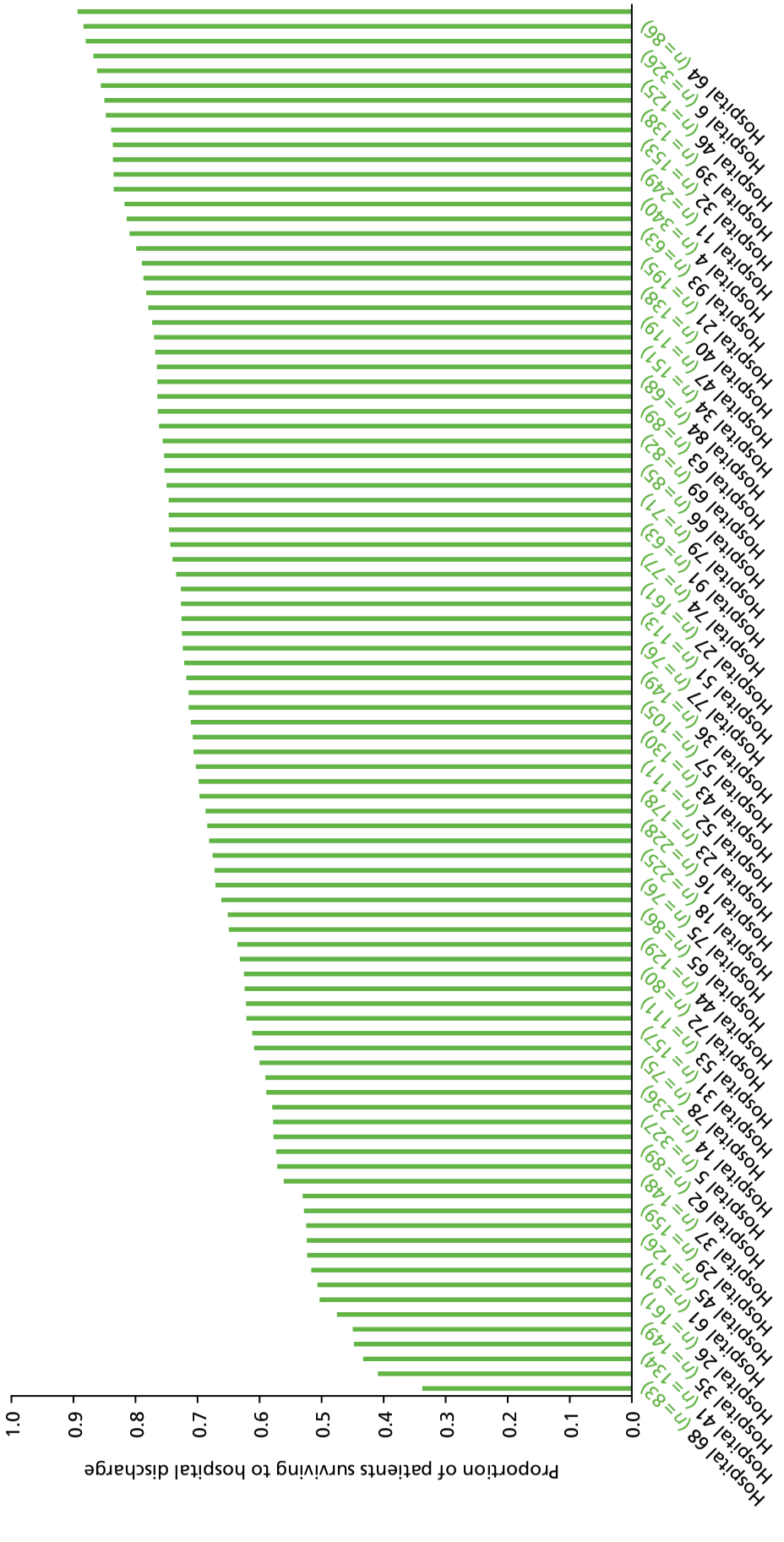

FIGURE 5 Variability in hospital survival across the 94 hospitals with at least 60 cases. Adapted from Couper *et al.*,[85] with permission from Elsevier. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

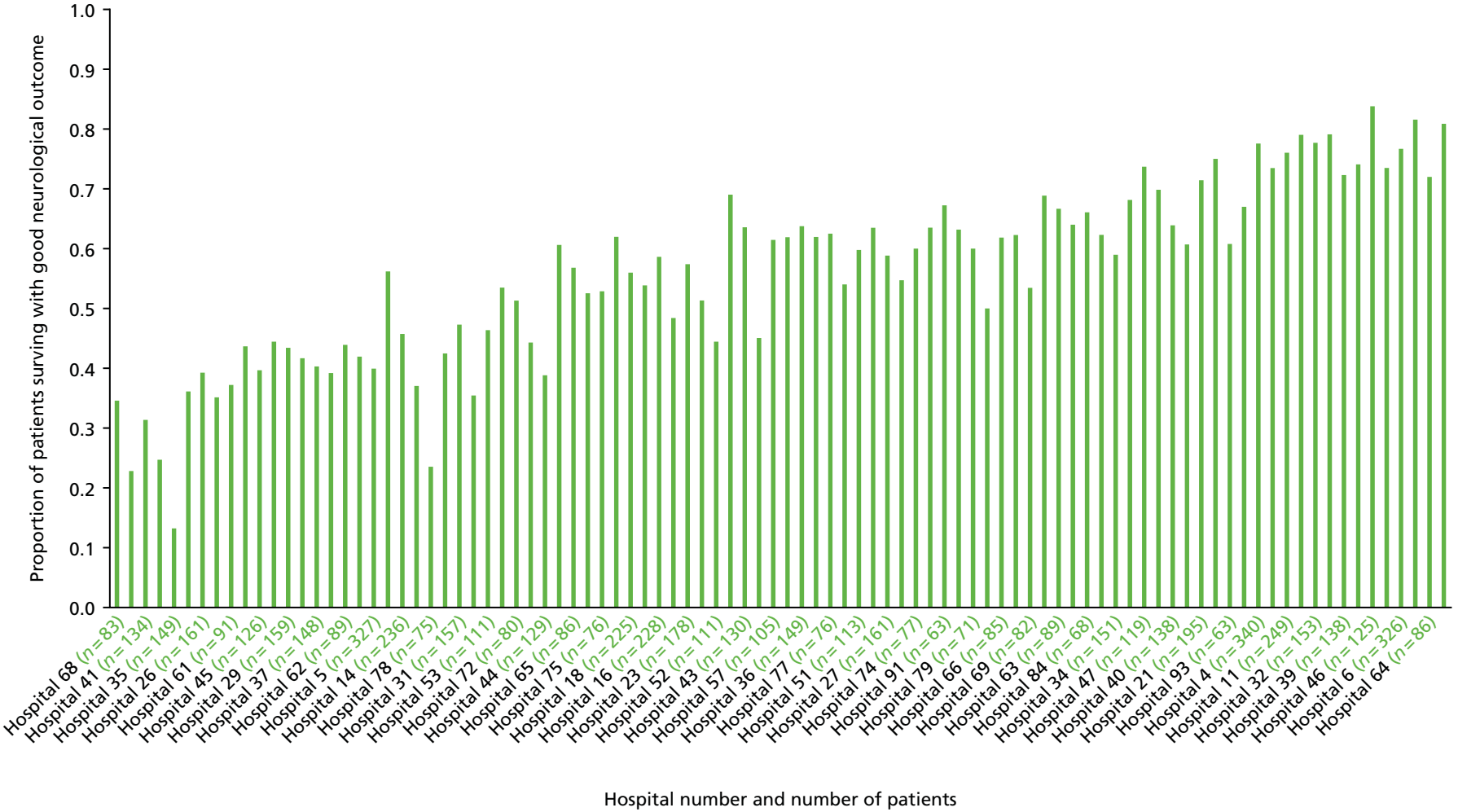

FIGURE 6 Variability in hospital survival with good neurological outcome across the 94 hospitals with at least 60 cases.

Patient characteristics

Table 9 shows the characteristics of patients included in the in-hospital mortality analysis for both the pre-imputation and the imputed data sets.

Comparison of the two data sets shows that reported characteristics across them are similar where logistic regression, polytomous regression or PMM was used to impute missing values. However, as expected, the percentages are different where default imputation was used (e.g. medical history variables).

In this section, we summarise key characteristics based on the pre-imputation data set.

Patient demographics

In our patient cohort, most patients were male ($n = 13{,}188$, 75.1%) and of white ethnicity ($n = 14{,}343$, 93.7%) and the mean age was 65.3 years (SD 13.2 years). The mean IMD score, where a higher score indicates increased deprivation, was 22.3 (SD 15.9; range 0.59–85.6).

Past medical history

Most patients were current or former smokers ($n = 8883$, 63.5%). The most common comorbidities were hypertension ($n = 6389$, 41.0%), hypercholesterolaemia ($n = 3906$, 25.9%), previous AMI ($n = 3092$, 19.7%), angina pectoris ($n = 2758$, 17.8%), diabetes mellitus ($n = 2158$, 13.7%) and asthma/COPD ($n = 1814$, 11.9%). The incidence of other comorbidities (cerebrovascular disease, heart failure, peripheral vascular disease and chronic renal failure) was < 10% for each disease. A minority of patients had previously received a PCI ($n = 1061$, 6.9%) or CABG ($n = 790$, 5.1%). Most patients ($n = 10{,}729$, 60.9%) had at least one comorbidity.

Presenting characteristics of out-of-hospital cardiac arrest

Most cardiac arrest events 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%). For the non-shockable presenting rhythms, the breakdown between asystole ($n = 885$, 5.4%) and pulseless electrical activity (PEA) ($n = 837$, 5.1%) was similar. 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/LBBB was the most common ECG finding ($n = 12{,}220$, 71.9%).

The mean admission systolic blood pressure and heart rate were 125.7 mmHg (SD 29.2 mmHg) and 89.2 beats per minute (SD 24.8 beats per minute), respectively.

Care pathway

The median for EMS response time was 8 minutes (IQR 5–14 minutes). The median distance between the patient's home address and the hospital to which they were first admitted 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 PCI centre if the centre performed at least 100 pPCIs in the year that patient was admitted.

Most patients were admitted under a consultant cardiologist ($n = 10{,}680$, 61.8%) and received cardiological care during admission ($n = 11{,}960$, 90.7%). Just over half of patients were admitted to the cardiac care unit (CCU) (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 received a pre-hospital ECG ($n = 11{,}053$, 75.7%).

TABLE 9 Overview of participant characteristics for in-hospital mortality cohort (pre-imputation and imputed data sets)

Variable	Pre imputation[a]	After imputation ($N = 17,604$)
Demographic variables,* n *(%)		
Age (years)		
Range	20–114	20–114
Mean (SD)	65.3 (13.15)	65.3 (13.15)
Median (IQR)	65.7 (56–75)	65.7 (56–75)
Sex		
Female	4370 (24.9)	4385 (24.9)
Ethnicity		
White	14,343 (93.7)	15,916 (90.4)
Asian	531 (3.5)	797 (4.5)
Black	131 (0.9)	416 (2.4)
Other	303 (2.0)	475 (2.7)
IMD score		
Range	0.59–85.59	0.59–85.59
Mean (SD)	22.31 (15.91)	22.17 (15.87)
Median (IQR)	17.8 (10.3–30.9)	17.6 (10.2–30.7)
Medical history variables,* n *(%)		
Smoking status		
Ever smoked	8883 (63.5)	10,941 (62.1)
Never smoked	5106 (36.5)	6663 (37.8)
Diabetes status		
Diabetic	2158 (13.7)	2428 (13.8)
Not diabetic	13,561 (86.3)	15,176 (86.2)
Hypercholesterolaemia		
Yes	3906 (25.9)	3906 (22.2)
Heart failure		
Yes	760 (5.0)	760 (4.3)
Cerebrovascular disease		
Yes	1071 (7.0)	1071 (6.1)
Previous AMI		
Yes	3092 (19.7)	3092 (17.6)
Asthma or COPD		
Yes	1814 (11.9)	1814 (10.3)
Chronic renal failure		
Yes	555 (3.6)	555 (3.2)
Peripheral vascular disease		
Yes	587 (3.9)	587 (3.3)
Previous angina		
Yes	2758 (17.8)	2758 (15.7)

TABLE 9 Overview of participant characteristics for in-hospital mortality cohort (pre-imputation and imputed data sets) (*continued*)

Variable	Pre imputation[a]	After imputation (*N* = 17,604)
Previous PCI		
Yes	1061 (6.9)	1061 (6.0)
Previous CABG		
Yes	790 (5.1)	790 (4.5)
Hypertension		
Yes	6389 (41.0)	6389 (36.3)
Presenting characteristics of OHCA variables,* n *(%)		
Time point of cardiac arrest		
Before ambulance arrival	10,533 (60.1)	10,571 (60.0)
After ambulance arrival	7004 (39.9)	7033 (40.0)
Cardiac arrest rhythm		
Asystole	885 (5.4)	963 (5.5)
PEA	837 (5.1)	912 (5.2)
VF/VT	14,778 (89.6)	15,729 (89.3)
Serum glucose (mmol/l)		
Range	1–59	1–59
Mean (SD)	10.94 (5.00)	10.97 (5.07)
Median (IQR)	10.0 (7.3–13.2)	10.0 (7.3–13.3)
Creatinine (μmol/l)		
Range	1–1512	1–1512
Mean (SD)	108.12 (55.72)	109.66 (57.01)
Median (IQR)	99 (81–121)	100 (81–123)
LVEF		
Good	2783 (36.4)	5712 (32.4)
Moderate	3131 (40.9)	6260 (35.6)
Poor	1736 (22.7)	5632 (32.0)
Haemoglobin (g/dl)		
Range	5–23.50	5–23.50
Mean (SD)	13.57 (2.03)	13.55 (2.06)
Median (IQR)	13.9 (12.2–15.0)	13.9 (12.2–15.0)
Serum cholesterol (mmol/l)		
Range	1–30	1–30
Mean (SD)	4.80 (1.51)	4.65 (1.53)
Median (IQR)	4.7 (3.8–5.6)	4.5 (3.6–5.5)
Admission diagnosis		
Definite MI – anterior infarction	3897 (27.0)	5045 (28.7)
Definite MI – other infarction site	3639 (25.2)	5652 (32.1)
Other initial diagnosis	6883 (47.7)	6907 (39.2)

continued

TABLE 9 Overview of participant characteristics for in-hospital mortality cohort (pre-imputation and imputed data sets) (*continued*)

Variable	Pre imputation[a]	After imputation ($N = 17,604$)
SBP at admission (mmHg)		
Range	50–230	50–230
Mean (SD)	125.69 (29.17)	125.39 (29.40)
Median (IQR)	124 (107–143)	124 (106–143)
ECG that determined treatment		
ST segment elevation or LBBB	12,220 (71.9)	12,472 (70.8)
ST segment depression or T-wave changes only	2325 (13.7)	2508 (14.2)
Other acute abnormality or no acute changes	2447 (14.4)	2624 (14.9)
Heart rate at admission (b.p.m.)		
Range	25–180	25–180
Mean (SD)	89.22 (24.79)	89.15 (25.00)
Median (IQR)	86 (72–104)	86 (72–104)
Time of the day of admission (day/night)		
08.00 to < 20.00 hours	11,741 (66.7%)	11,741 (66.7%)
Killip class		Not imputed
Basal crepitations and/or elevated venous pressure	796 (13.5)	
Pulmonary oedema	317 (5.4)	
Cardiogenic shock	1029 (17.5)	
No evidence of heart failure	3612 (61.3)	
Not applicable	138 (2.3)	
Mini-GRACE score		Not imputed
Range	69–275	
Mean (SD)	173 (28.37)	
Median (IQR)	172 (153–193)	
Care pathway variables,* n *(%)		
Hospital volume (OHCA cases per year)		
1 to 10 cases	7984 (45.4)	7984 (45.4)
11 to 24 cases	6516 (37.0)	6516 (37.0)
25 to 82 cases	3104 (17.6)	3104 (17.6)
Hospital pPCI capability		
pPCI capable	7800 (44.3)	7800 (44.3)
pPCI incapable	9804 (55.7)	9804 (55.7)
EMS response time (minutes)		
Range	0–180	0–180
Mean (SD)	11.53 (11.82)	11.62 (12.42)
Median (IQR)	8.00 (5–14)	8.00 (5–14)
EMS travel distance (km)		
Range	0–242	0–242
Mean (SD)	11.24 (10.08)	11.46 (10.23)
Median (IQR)	8.07 (3.86–15.82)	8.28 (3.94–16.24)

TABLE 9 Overview of participant characteristics for in-hospital mortality cohort (pre-imputation and imputed data sets) (*continued*)

Variable	Pre imputation[a]	After imputation (*N* = 17,604)
Admitting consultant		
Cardiologist	10,680 (61.8)	10,825 (61.5)
Other consultant	6603 (37.5)	6779 (38.5)
Cardiological care during admission		
Yes	11,960 (90.7)	14,034 (79.7)
Admission ward		
CCU	8872 (51.0)	8966 (50.9)
Cardiac ward – non CCU	500 (2.9)	502 (2.9)
Intensive therapy unit	6154 (35.4)	6225 (35.4)
General medical ward or other	1534 (8.8)	1565 (8.9)
Died in ED	340 (1.9)	346 (2.0)
Time point of aspirin administration, *n* (%)		
Already on aspirin/antiplatelet drug	2636 (16.4)	2865 (16.3)
Aspirin/antiplatelet given pre hospital	5324 (33.1)	5681 (32.3)
Aspirin/antiplatelet given in-hospital	6166 (38.3)	6759 (38.4)
Not given	1975 (12.3)	2299 (13.1)
Place where ECG performed		
Ambulance	11,053 (75.7)	12,206 (69.3)
In hospital	3551 (24.3)	5398 (30.7)
Angiotensin-converting enzyme inhibitor (in-hospital use), *n* (%)		
Yes	5333 (36.1)	5333 (30.3)
Loop diuretic (in-hospital use)		
Yes	4486 (30.7)	4486 (25.5)
Reperfusion treatment and timing		
None	5633 (37.1)	8064 (45.8)
Thrombolysis (performed early)	1080 (7.1)	1080 (6.1)
Thrombolysis (performed late)	1930 (12.7)	1930 (11.0)
Thrombolysis (time missing)	370 (2.4)	370 (2.1)
pPCI (performed early)	4424 (29.2)	4424 (25.1)
pPCI (performed late)	1063 (7.0)	1063 (6.0)
pPCI (time missing)	673 (4.4)	673 (3.8)
Assessment at non-intervention hospital		Not imputed
No contact with non-interventional hospital	8928 (79.6)	
Patient remains in ambulance	34 (0.3)	
ED	1870 (16.7)	
Acute assessment unit	34 (0.3)	

continued

TABLE 9 Overview of participant characteristics for in-hospital mortality cohort (pre-imputation and imputed data sets) (*continued*)

Variable	Pre imputation[a]	After imputation (*N* = 17,604)
CCU/cardiac facility	170 (1.5)	
Self-referral	27 (0.2)	
Already in hospital	93 (0.8)	
Other	56 (0.5)	
Assessment at intervention centre		Not imputed
Assessed in ED	2158 (30.9)	
Acute assessment unit	51 (0.7)	
CCU/cardiac facility	1064 (15.2)	
Catheter laboratory	3683 (52.7)	
Already in hospital	32 (0.5)	
Intended reperfusion procedure		Not imputed
None	649 (9.0)	
Primary PCI	5939 (82.0)	
Rescue PCI	153 (2.1)	
Thrombolytic treatment	105 (1.5)	
Other coronary intervention	393 (5.4)	
Procedure performed		Not imputed
No angiography	522 (7.4)	
Angiography but no PCI	1017 (14.3)	
Angiography and PCI	5559 (78.3)	
Reason for no angiography		Not imputed
Diagnosis not ACS	35 (11.8)	
Patient refused	11 (3.7)	
Complication before angiography could be performed	22 (7.4)	
Angiography inappropriate because of comorbidity	171 (57.8)	
Technical failure	3 (1.0)	
Laboratory unavailable	8 (2.7)	
Other	46 (15.5)	
Reason for no intervention		Not imputed
Complication before PCI could be performed	37 (3.6)	
Patient refused	5 (0.5)	
PCI felt to be inappropriate	213 (20.9)	
Angiographically normal coronaries/mild disease/infarct-related vessel unclear	342 (33.6)	
Surgical disease	264 (25.9)	
Technical failure	40 (3.9)	
Other	118 (11.6)	

TABLE 9 Overview of participant characteristics for in-hospital mortality cohort (pre-imputation and imputed data sets) (*continued*)

Variable	Pre imputation[a]	After imputation (*N* = 17,604)
Reason treatment not given		Not imputed
None	6650 (48.7)	
Ineligible ECG	4078 (29.9)	
Too late	118 (0.9)	
Risk of haemorrhage	391 (2.9)	
Uncontrolled hypertension	9 (0.1)	
Administrative failure	13 (0.1)	
Elective decision	1078 (7.9)	
Patient refused treatment	8 (0.1)	
Other	1049 (7.7)	
Unknown	249 (1.8)	
Discharge care variables,* n *(%)		
Discharge diagnosis		
ACS	16,476 (95.1)	16,756 (95.2)
Other	843 (4.9)	848 (4.8)
Echocardiography		
No	3948 (26.2)	5069 (28.2)
Yes or planned after discharge	11,140 (73.8)	12,535 (71.2)
Coronary angiography		
Protocol-driven investigation	3974 (25.7)	4422 (25.1)
Symptom-driven investigation	3378 (21.9)	3883 (22.1)
Not performed	8102 (52.4)	9299 (52.8)
Coronary intervention		
PCI	4364 (30.3)	5069 (31.5)
CABG	464 (3.2)	591 (3.4)
Not performed or arranged	9591 (66.5)	11,473 (65.2)

b.p.m., beats per minute; CCU, cardiac care unit; PEA, pulseless electrical activity; SBP, systolic blood pressure; VF, ventricular fibrillation; VT, ventricular tachycardia.
a The *N* for each group is equal to 17,604 minus the number of missing cases (see *Table 7*).
Adapted from Couper *et al.*,[85] with permission from Elsevier. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Reperfusion treatment (pPCI or thrombolysis) was delivered to 62.8% (*n* = 9540) of patients. Of these 9540 patients, the majority received pPCI (pPCI, *n* = 6160, 64.6%; thrombolysis, *n* = 3380, 35.4%). *Figures 7–9* show the percentage of patients receiving reperfusion treatment by year for all patients (see *Figure 7*), STEMI patients (see *Figure 8*) and patients who did not have a STEMI (see *Figure 9*). All figures show an increase in use of reperfusion over time, although this increase is notably higher in the STEMI group than in the group of patients who did not have a STEMI. In all groups, there is a move away from the use of thrombolysis to pPCI over the study period. The point at which the use of pPCI overtakes thrombolysis use is around 2008–9, such that by the end of the study period very few patients received thrombolysis.

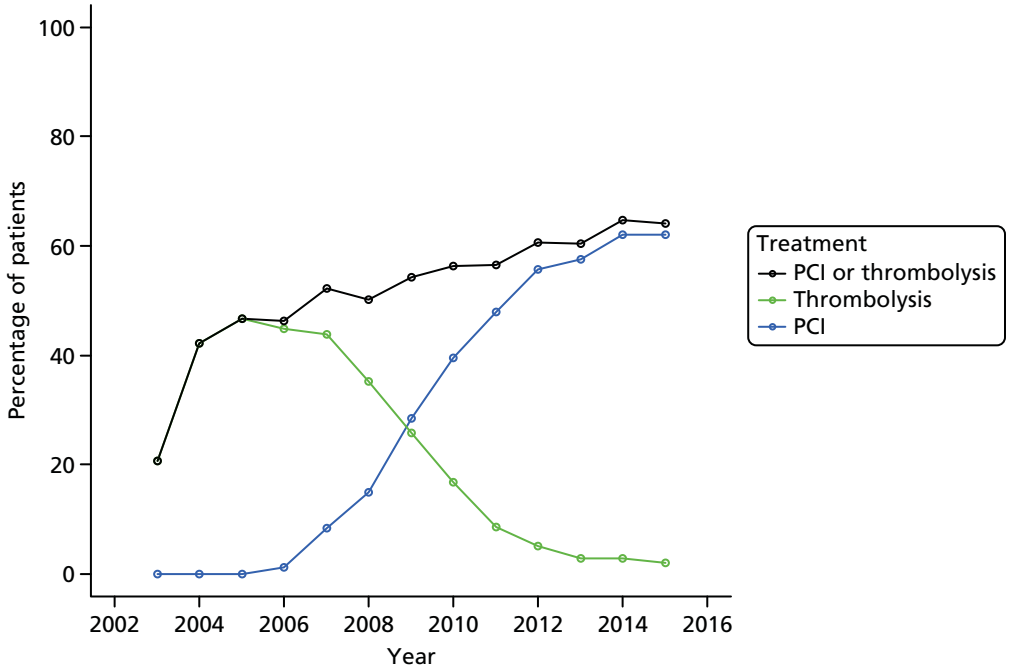

FIGURE 7 Percentage of patients receiving reperfusion treatment by year (all patients). Adapted from Couper *et al.*,[85] with permission from Elsevier. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

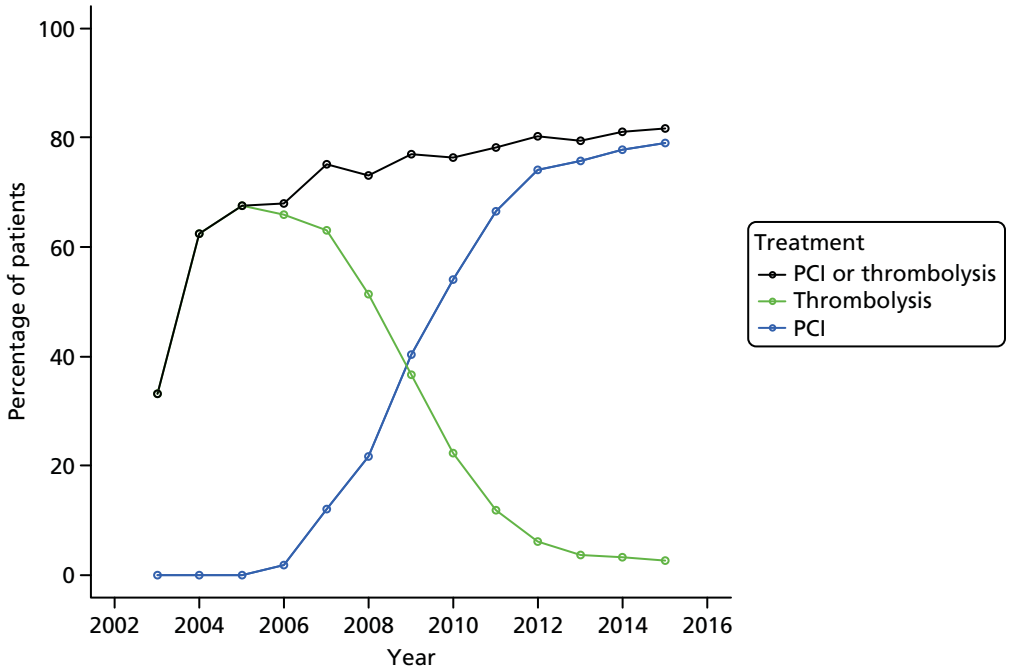

FIGURE 8 Percentage of patients receiving reperfusion treatment by year (patients presenting with STEMI). Adapted from Couper *et al.*,[85] with permission from Elsevier. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

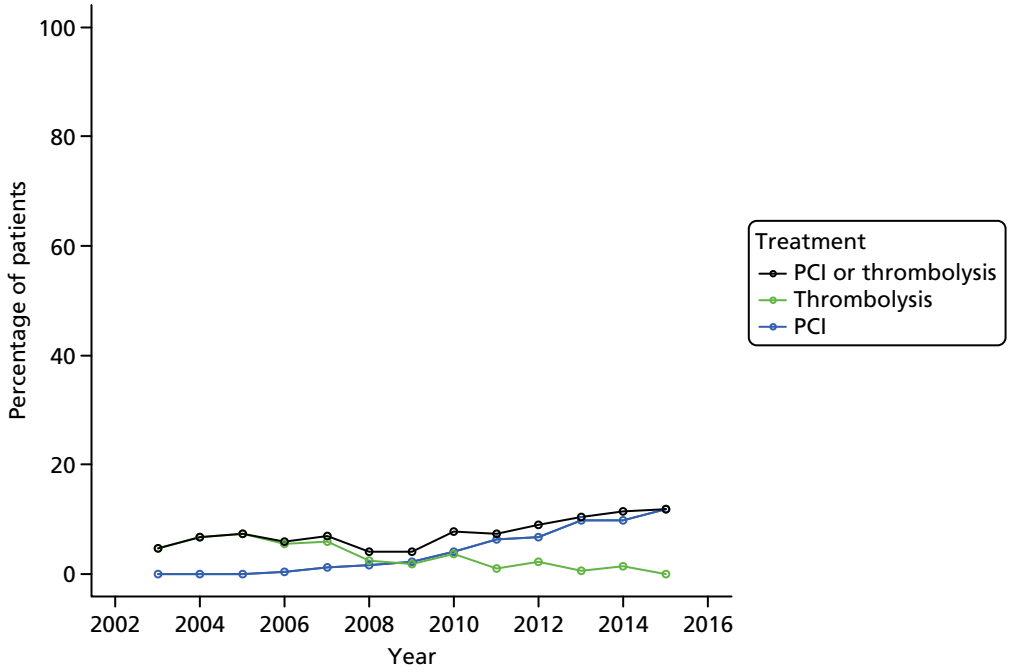

FIGURE 9 Percentage of patients receiving reperfusion treatment by year (patients not presenting with STEMI). Adapted from Couper *et al.*,[85] with permission from Elsevier. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Discharge care variables

In most patients, the discharge diagnosis was ACS ($n = 16,476$, 95.1%). The majority of patients underwent echocardiography during their hospital stay, or this was planned to take place after discharge ($n = 11,140$, 73.8%).

Primary outcome: hospital mortality

Unadjusted analysis

Unadjusted ORs for in-hospital mortality in relation to variables in the imputed data set are presented in *Table 10*. For categorical predictor, the column, Patients, *n* (%), describes the number and percentage of patients in that category who died in hospital.

Demographic variables

Demographic variables associated with increased in-hospital mortality include female sex, increased age, and increased deprivation measured by the IMD score. Ethnicity was not associated with hospital mortality. Demographic variables did not explain much variability in the data set, with age having the highest R^2, at 6%.

Medical history variables

All medical history variables were associated with mortality, except hypertension and previous PCI. Being a smoker and having hypercholesterolaemia were associated with reduced mortality. All other conditions (diabetes mellitus, heart failure, cerebrovascular disease, previous AMI, asthma or COPD, chronic renal failure, peripheral vascular disease, previous angina pectoris and previous CABG) were associated with increased mortality. Medical history variables explained little variability in the data set, with the maximum R^2 being 1.7% for diabetes status.

TABLE 10 Unadjusted ORs for in-hospital mortality

Variable	Patients, *n* (%)	OR (95% CI), *p*-value[a]	RE estimate (R^2, AIC)
Null model			0.433 (0.000, 20242)
Demographic variables			
Age (years)	NA	1.043 (1.040 to 1.046), < 0.001	0.411 (0.060, 19332)
Sex			0.434 (0.013, 20046)
Male	3403 (25.7)	0.577 (0.535 to 0.622), < 0.001	
Female	1644 (37.5)	–	
Ethnicity			0.435 (0.000, 20245)
Asian	235 (29.5)	1.109 (0.918 to 1.339), 0.283	
Black	142 (34.1)	1.022 (0.705 to 1.482), 0.909	
Other	146 (30.7)	1.129 (0.874 to 1.457), 0.353	
White	4524 (28.4)	–	
IMD score	NA	1.005 (1.002 to 1.007), < 0.001	0.431 (0.001, 20228)
Medical history variables			
Smoking status			0.431 (0.013, 20055)
Ever smoked	2704 (24.7)	0.610 (0.564 to 0.661), < 0.001	
Never smoked	2343 (35.2)	–	
Diabetes status			0.430 (0.017, 20015)
Diabetic	1042 (42.9)	2.063 (1.869 to 2.278), < 0.001	
Not diabetic	4005 (26.4)	–	
Hypercholesterolaemia			0.421 (0.007, 20149)
Yes	846 (21.7)	0.648 (0.594 to 0.708), < 0.001	
No	4201 (30.7)	–	
Heart failure			0.425 (0.009, 20138)
Yes	372 (48.9)	2.271 (1.948 to 2.648), < 0.001	
No	4675 (27.8)	–	
Cerebrovascular disease			0.426 (0.006, 20160)
Yes	461 (43.0)	1.878 (1.647 to 2.142), < 0.001	
No	4586 (27.7)	–	
Previous AMI			0.431 (0.002, 20216)
Yes	1039 (33.6)	1.267 (1.161 to 1.381), < 0.001	
No	4008 (27.6)	–	
Asthma or COPD			0.430 (0.002, 20213)
Yes	643 (35.4)	1.362 (1.224 to 1.516), < 0.001	
No	4404 (27.9)	–	
Chronic renal failure			0.429 (0.007, 20161)
Yes	274 (49.4)	2.322 (1.942 to 2.774), < 0.001	
No	4773 (28.0)	–	

TABLE 10 Unadjusted ORs for in-hospital mortality (*continued*)

Variable	Patients, *n* (%)	OR (95% CI), *p*-value[a]	RE estimate (R^2, AIC)
Peripheral vascular disease			0.433 (0.003, 20204)
Yes	241 (41.1)	1.791 (1.503 to 2.135), < 0.001	
No	4806 (28.2)	–	
Previous angina			0.430 (0.002, 20223)
Yes	927 (33.6)	1.245 (1.136 to 1.364), < 0.001	
No	4120 (27.8)	–	
Previous PCI			0.431 (0.000, 20242)
Yes	269 (25.4)	0.893 (0.771 to 1.035), 0.134	
No	4778 (28.9)	–	
Previous CABG			0.432 (0.001, 20238)
Yes	272 (34.4)	1.225 (1.047 to 1.433), 0.011	
No	4775 (28.4)	–	
Hypertension			0.433 (0.000, 20244)
Yes	1835 (28.7)	0.998 (0.930 to 1.072), 0.963	
No	3212 (28.6)	–	
Presenting characteristics of OHCA variables			
Time point of cardiac arrest			0.368 (0.063, 19294)
After ambulance arrival	1034 (14.7)	0.302 (0.279 to 0.327), < 0.001	
Before ambulance arrival	4013 (38.0)	–	
Cardiac arrest rhythm			0.368 (0.104, 18894)
PEA	647 (70.9)	1.024 (0.825 to 1.27), 0.830	
VF/VT	3715 (23.6)	0.139 (0.119 to 0.162), < 0.001	
Asystole	685 (71.1)	–	
Serum glucose (mmol/l)	NA	1.132 (1.120 to 1.144), < 0.001	0.423 (0.083, 18993)
Creatinine (μmol/l)	NA	1.011 (1.009 to 1.013), < 0.001	0.414 (0.070, 19353)
LVEF, *n* (%)			0.475 (0.078, 18947)
Good	891 (15.6)	0.197 (0.150 to 0.260), < 0.001	
Moderate	1490 (23.8)	0.334 (0.264 to 0.422), < 0.001	
Poor	2666 (47.3)	–	
Haemoglobin (g/dl)	NA	0.795 (0.772 to 0.820), < 0.001	0.440 (0.045, 19525)
Serum cholesterol (mmol/l)	NA	0.776 (0.737 to 0.817), < 0.001	0.431 (0.029, 19861)
Admission diagnosis			0.378 (0.019, 20089)
Other diagnosis	259 (36.6)	1.717 (1.555 to 1.894), < 0.001	
Definite MI (other infarction site)	1401 (24.8)	1.142 (1.015 to 1.284), 0.027	
Definite MI (anterior infarction)	1117 (22.1)	–	
SBP at admission (mmHg)	NA	–	0.451 (0.043, 19519)
Linear term[b]		–50.47 (–55.54 to –45.4), < 0.001	
Quadratic term[b]		34.32 (29.57 to 39.07), < 0.001	

continued

TABLE 10 Unadjusted ORs for in-hospital mortality (*continued*)

Variable	Patients, *n* (%)	OR (95% CI), *p*-value[a]	RE estimate (R^2, AIC)
ECG that determined treatment			0.415 (0.005, 20214)
ST segment elevation or LBBB	3290 (26.4)	0.936 (0.845 to 1.037), 0.206	
Other acute abnormality or no acute changes	950 (36.2)	1.239 (1.092 to 1.406), 0.001	
ST segment depression/T-wave changes only	807 (32.2)	–	
Heart rate at admission (b.p.m.)	NA	1.003 (1.002 to 1.005), < 0.001	0.428 (0.002, 20225)
Time of the day of admission (day/night)			0.434 (0.000, 20242)
20.00 to < 08.00 hours	1648 (28.1)	0.942 (0.876 to 1.012), 0.104	
08.00 to < 20.00 hours	3399 (28.9)		
Year	NA	–	0.465 (–0.002, 20177)
Slope (2003–8)		0.955 (0.922 to 0.988), 0.009	
Slope (2009–15)		1.073 (1.046 to 1.100), < 0.001	
Care pathway variables			
Hospital volume (OHCA cases per year)			0.414 (0.006, 20241)
0 to 10 cases	2422 (30.3)	1.510 (0.987 to 2.311), 0.058	
11 to 24 cases	1990 (30.5)	1.766 (1.109 to 2.810), 0.017	
25 to 82 cases	635 (20.5)	–	
Hospital pPCI capability			0.418 (0.003, 20242)
pPCI capable	1858 (23.8)	0.911 (0.811 to 1.023), 0.115	
pPCI incapable	3189 (32.5)	–	
EMS response time (minutes)	NA	0.991 (0.987 to 0.995), < 0.001	0.427 (0.003, 20217)
EMS travel distance (km)	NA	0.977 (0.973 to 0.981), < 0.001	0.420 (0.011, 20113)
Admitting consultant			0.352 (0.056, 19595)
Cardiologist	2188 (20.2)	0.323 (0.296 to 0.353), < 0.001	
Other consultant	2859 (42.2)	–	
Cardiological care during admission			0.332 (0.073, 19388)
Yes	3035 (21.6)	0.275 (0.176 to 0.431), < 0.001	
No	2012 (56.4)	–	
Admission ward			0.272 (0.178, 17490)
Intensive therapy unit	2776 (44.6)	3.405 (2.478 to 4.678), < 0.001	
CCU	1095 (12.2)	0.587 (0.426 to 0.809), 0.001	
Died in ED	345 (99.7)	Not estimable	
General medical ward or other	753 (48.1)	4.050 (2.908 to 5.640), < 0.001	
Cardiac ward – non-CCU	78 (15.5)	–	
Time point of aspirin administration			0.332 (0.140, 18257)
Already on aspirin/antiplatelet drug	992 (34.6)	0.244 (0.214 to 0.278), < 0.001	
Aspirin/antiplatelet given out of hospital	679 (12.0)	0.067 (0.058 to 0.076), < 0.001	
Aspirin/antiplatelet given in hospital	1845 (27.3)	0.176 (0.157 to 0.198), < 0.001	
Not given	1531 (66.6)	–	

TABLE 10 Unadjusted ORs for in-hospital mortality (*continued*)

Variable	Patients, *n* (%)	OR (95% CI), *p*-value[a]	RE estimate (R^2, AIC)
Place where ECG performed			0.413 (0.014, 20096)
In hospital	1623 (37.5)	1.696 (1.466 to 1.963), < 0.001	
Ambulance	3424 (25.8)	–	
Angiotensin-converting enzyme inhibitor (in-hospital use)			0.522 (0.086, 18340)
Yes	454 (8.5)	0.114 (0.101 to 0.127), < 0.001	
No	4593 (37.4)	–	
Loop diuretic (in-hospital use)			0.440 (0.001, 20221)
Yes	1196 (26.7)	0.821 (0.757 to 0.890), < 0.001	
No	3851 (29.4)	–	
Reperfusion treatment and timing			0.363 (0.042, 19719)
Thrombolysis (performed early)	161 (14.9)	0.297 (0.248 to 0.356), < 0.001	
Thrombolysis (performed late)	448 (23.2)	0.502 (0.445 to 0.567), < 0.001	
Thrombolysis (time missing)	116 (31.4)	0.814 (0.643 to 1.030), 0.086	
pPCI (performed early)	755 (17.1)	0.418 (0.376 to 0.465), < 0.001	
pPCI (performed late)	365 (34.3)	1.048 (0.905 to 1.213), 0.532	
pPCI (time missing)	154 (22.9)	0.586 (0.478 to 0.718), < 0.001	
None	3048 (37.8)	–	
Discharge care variables			
Discharge diagnosis			0.432 (0.001, 20239)
ACS	4752 (28.4)	0.824 (0.692 to 0.981), 0.029	
Other	295 (34.8)	–	
Echocardiography			0.489 (0.139, 17925)
Yes or planned	2258 (18.0)	0.139 (0.127 to 0.153), < 0.001	
No	2789 (55.0)	–	
Coronary angiography			0.529 (0.123, 17550)
Protocol driven	510 (11.5)	0.093 (0.081 to 0.107), < 0.001	
Symptom driven	449 (11.6)	0.096 (0.084 to 0.111), < 0.001	
None	4088 (44.0)	–	
Coronary intervention			0.442 (0.074, 18710)
PCI	717 (12.9)	0.177 (0.157 to 0.198), < 0.001	
CABG	12 (2.0)	0.024 (0.010 to 0.056), < 0.001	
None	4318 (37.6)	–	

b.p.m., beats per minute; NA, not applicable; SBP, systolic blood pressure.
a Values describe OR (95% CI), *p*-value, unless stated otherwise.
b Estimates on the logarithmic scale.
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Presenting characteristics for out-of-hospital cardiac arrest

Cardiac arrest following ambulance arrival and an initial cardiac arrest rhythm of VF/VT were both associated with reduced mortality. Increased heart rate, glucose and creatinine were associated with increased mortality. In contrast, increased haemoglobin and cholesterol were associated with reduced mortality. In comparison with ST segment depression/T-wave changes, an ECG with evidence of ST-segment elevation/LBBB was not associated with mortality, but an ECG showing no acute changes or other abnormality was associated with increased mortality. The time of admission was not associated with mortality.

Some presenting characteristics of OHCA variables explain significant variability in the data, including cardiac arrest rhythm ($R^2 = 10.4\%$) and glucose ($R^2 = 8.3\%$)

Care pathway variables

All care pathway variables were associated with an effect on mortality, except hospital PCI capability.

Administration of aspirin, pre-hospital ECG, admission under a cardiologist, cardiological care during admission and reperfusion therapy were associated with reduced mortality. Both increased EMS response time and transfer distance (patient home to hospital) were associated with reduced mortality. Compared with patients treated in the highest volume hospitals, patients treated in mid-volume hospitals (11–24 cases per year) had increased mortality.

Some care pathway predictor variables also explain substantial variability in the data, including admission ward ($R^2 = 17.8\%$) and time point of aspirin administration ($R^2 = 14.0\%$).

Discharge care variables

Echocardiography, coronary angiography and coronary intervention delivery were all associated with reduced mortality. Echocardiography ($R^2 = 13.9\%$) and coronary angiography ($R^2 = 12.3\%$) explained substantial data variability.

Adjusted analysis

The adjusted model for in-hospital mortality is shown in tabular form in *Table 11* and as a caterpillar plot in *Figure 10*. The model consists of 37 predictor variables and explains 36.1% ($R^2 = 0.361$) of the variability in in-hospital mortality across patients. The RE estimate (0.215) and ICC (0.061) are lower than those for the null model, such that the predictor variables explain some variability in in-hospital mortality across hospitals.

TABLE 11 Adjusted analysis for hospital mortality

Variable	Primary analysis; analysis after imputation,[a] OR (95% CI), *p*-value ($n = 17,604$)
Demographic variables	
Age (years)	1.046 (1.042 to 1.051), < 0.001
Sex	
Male	0.877 (0.786 to 0.979), 0.019
Female[b]	
Ethnicity	
Asian	1.022 (0.804 to 1.299), 0.860
Black	0.939 (0.602 to 1.464), 0.780
Other	0.991 (0.723 to 1.358), 0.956
White[b]	
IMD score	1.005 (1.002 to 1.008), 0.003

TABLE 11 Adjusted analysis for hospital mortality (*continued*)

Variable	Primary analysis; analysis after imputation,[a] OR (95% CI), *p*-value ($n = 17,604$)
Medical history variables	
Smoking status	
Ever smoked	0.903 (0.812 to 1.004), 0.059
Never smoked[b]	
Diabetes status	
Diabetic	1.125 (0.981 to 1.290), 0.092
Not diabetic[b]	
Hypercholesterolaemia	
Yes	0.692 (0.615 to 0.779), < 0.001
No[b]	
Heart failure	
Yes	1.318 (1.074 to 1.618), 0.008
No[b]	
Cerebrovascular disease	
Yes	1.299 (1.097 to 1.537), 0.002
No[b]	
Previous AMI	
Yes	1.028 (0.900 to 1.173), 0.685
No[b]	
Asthma or COPD	
Yes	1.247 (1.087 to 1.431), 0.002
No[b]	
Chronic renal failure	
Yes	1.065 (0.841 to 1.350), 0.601
No[b]	
Peripheral vascular disease	
Yes	1.517 (1.208 to 1.904), < 0.001
No[b]	
Previous angina	
Yes	1.011 (0.885 to 1.156), 0.867
No[b]	
Previous PCI	
Yes	1.025 (0.840 to 1.251), 0.806
No[b]	

continued

TABLE 11 Adjusted analysis for hospital mortality (*continued*)

Variable	Primary analysis; analysis after imputation,[a] OR (95% CI), *p*-value ($n = 17,604$)
Previous CABG	
Yes	0.996 (0.811 to 1.222), 0.966
No[b]	
Hypertension	
Yes	0.865 (0.784 to 0.955), 0.004
No[b]	
Presenting characteristics variables	
Time point of cardiac arrest	
After ambulance arrival	0.492 (0.441 to 0.548), < 0.001
Before ambulance arrival[b]	
Cardiac arrest rhythm	
PEA	0.847 (0.658 to 1.088), 0.194
VF/VT	0.217 (0.180 to 0.262), < 0.001
Asystole[b]	
Serum glucose (mmol/l)	1.109 (1.096 to 1.122), < 0.001
Haemoglobin (g/dl)	0.912 (0.878 to 0.946), < 0.001
Serum cholesterol (mmol/l)	0.956 (0.906 to 1.010), 0.108
Admission diagnosis	
Other diagnosis	0.876 (0.750 to 1.024), 0.097
Definite MI – other infarct site	1.022 (0.890 to 1.173), 0.762
Definite MI – anterior infarct[b]	
SBP at admission (mmHg)	
Linear term[c]	–42.15 (–48.35 to –35.96), < 0.001
Quadratic term[c]	17.68 (11.79 to 23.57), < 0.001
ECG that determined treatment	
ST segment elevation or LBBB	1.592 (1.364 to 1.858), < 0.001
ST segment depression or T-wave changes only	0.907 (0.775 to 1.062), 0.227
Other acute abnormality or no acute changes[b]	
Heart rate at admission (b.p.m.)	1.005 (1.004 to 1.007), < 0.001
Time of the day of admission (day/night)	
20.00 to < 08.00 hours	1.091 (0.994 to 1.196), 0.066
08.00 to < 20.00[b] hours	
Year	
Slope (2003–8)	0.947 (0.895 to 1.002), 0.057
Slope (2009–15)	1.044 (1.009 to 1.079), 0.012

TABLE 11 Adjusted analysis for hospital mortality (*continued*)

Variable	Primary analysis; analysis after imputation,[a] OR (95% CI), *p*-value ($n = 17,604$)
Care pathway variables	
Hospital volume (OHCA cases per year)	
0–10 cases	1.033 (0.723 to 1.474), 0.860
11–24 cases	1.259 (0.877 to 1.808), 0.211
25–82 cases[b]	
Hospital pPCI capability	
pPCI capable	1.262 (1.043 to 1.527), 0.017
pPCI incapable[b]	
EMS response time (minutes)	0.999 (0.995 to 1.004), 0.776
EMS travel distance (km)	0.994 (0.989 to 0.999), 0.024
Admitting consultant	
Cardiologist	0.725 (0.641 to 0.822), < 0.001
Other consultant[b]	
Admission ward	
Intensive therapy unit	3.741 (3.331 to 4.202), < 0.001
Died in ED	Not estimable
General ward or other	3.452 (2.941 to 4.051), < 0.001
Cardiac ward – non-CCU	1.212 (0.841 to 1.748), 0.302
CCU[b]	
Place where ECG performed	
In hospital	1.125 (0.970 to 1.304), 0.120
Pre hospital[b]	
Reperfusion treatment and timing	
Thrombolysis (performed early)	0.672 (0.523 to 0.863), 0.002
Thrombolysis (performed late)	0.860 (0.723 to 1.023), 0.088
Thrombolysis (time missing)	0.954 (0.702 to 1.298), 0.766
pPCI (performed early)	0.704 (0.600 to 0.826), < 0.001
pPCI (performed late)	0.941 (0.773 to 1.145), 0.542
pPCI (time missing)	0.690 (0.532 to 0.893), 0.005
None[b]	
RE estimate (adjusted R^2, AIC)	0.215[d] (0.361,[d] 14134[d])

b.p.m., beats per minute; SBP, systolic blood pressure.
a Values describe OR (95% CI), *p*-value, unless stated otherwise.
b Reference category.
c Estimates on the logarithmic scale.
d Median from 25 data sets.
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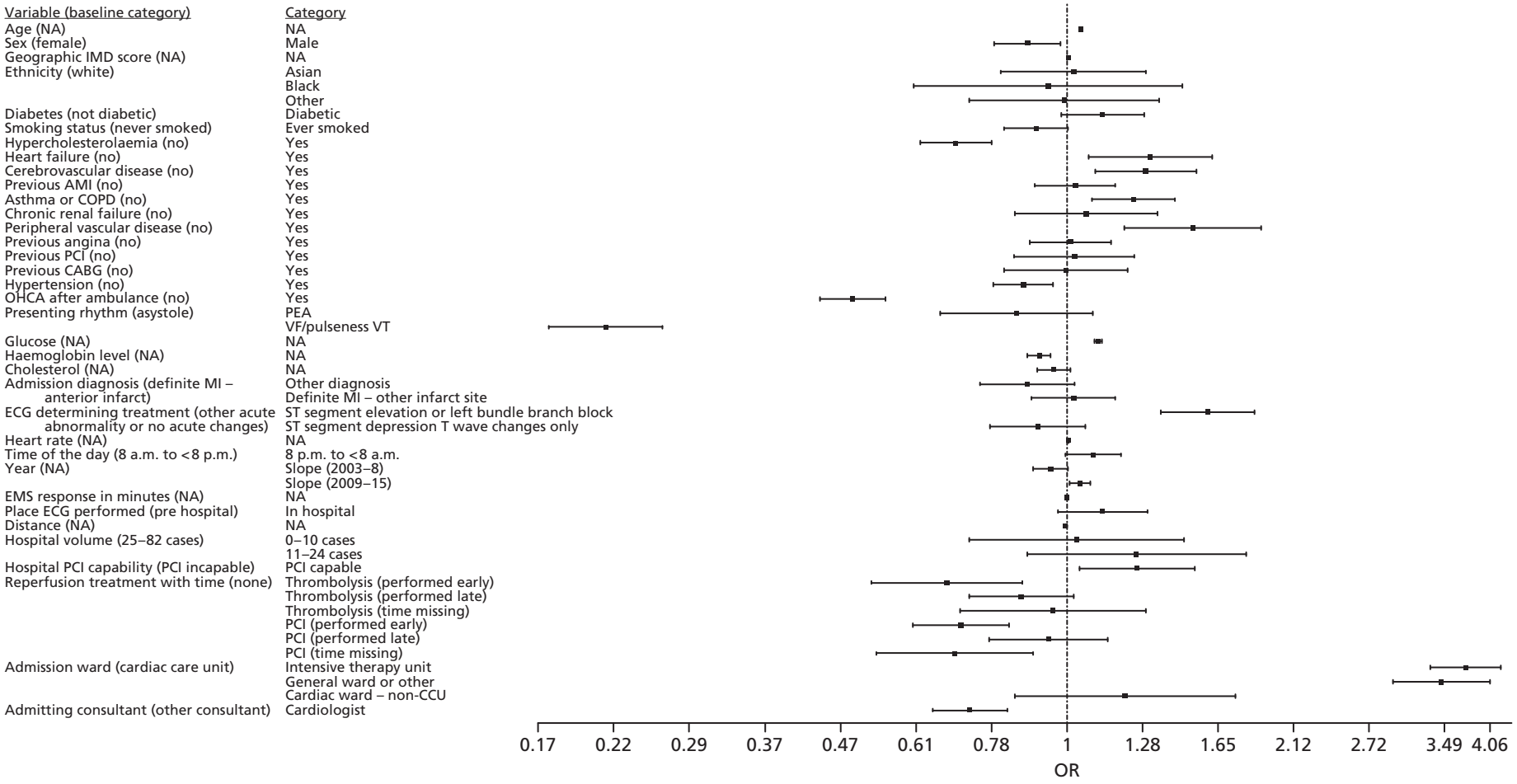

FIGURE 10 Caterpillar plot for OR of in-hospital mortality (adjusted analysis). NA, not applicable.

Demographic variables

As in the unadjusted model, female sex, increased age and increased deprivation measured by the IMD score were associated with increased mortality. As before, ethnicity was not associated with hospital mortality. A model that contains only demographic variables explains 6.8% of variability in the data.

Medical history variables

In the adjusted model, hypercholesterolaemia continued to be associated with reduced mortality. In addition, hypertension was associated with reduced mortality. Heart failure, cerebrovascular disease, asthma or COPD and peripheral vascular disease were associated with increased mortality. Diabetes mellitus, smoking status, previous AMI, chronic renal failure, previous angina pectoris, previous PCI and previous CABG were not associated with mortality.

Presenting characteristics for out-of-hospital cardiac arrest variables

The adjusted analysis showed an association between cardiac arrest following ambulance arrival and an initial cardiac arrest rhythm of VF/VT and reduced mortality.

The admission diagnosis was not associated with mortality, but an ECG showing ST-segment elevation or LBBB, compared with no acute changes, was associated with increased mortality. Increased heart rate and glucose levels were also associated with increased mortality. Increased haemoglobin levels were associated with reduced mortality. Cholesterol levels and time of day were not associated with mortality.

In relation to the year slopes, mortality did not change in the period 2003–8, but there was evidence of increased mortality for each year between 2009 and 2015.

Care pathway variables

Emergency medical service response time, hospital volume and the location where ECG was performed were not associated with survival. Although admission to a pPCI centre seemed to be associated with increased mortality, early pPCI and pPCI where time was missing were associated with reduced mortality. Similarly, early thrombolysis was associated with reduced mortality. Neither late pPCI nor late thrombolysis influenced survival. Each additional kilometre travelled to hospital appeared to be associated with a small decrease in mortality.

Admission under a cardiologist was associated with reduced mortality. The admission ward was associated with mortality, such that, compared with patients admitted to a CCU, those admitted to the intensive therapy unit or general ward tended to have higher mortality.

Sensitivity analyses

Our sensitivity analyses of the primary outcome included a complete-case analysis, 2003–8 data, 2009–15 data, STEMI patients and patients who did not present with a STEMI. These analyses are included in *Table 12*.

Across these analyses, results tended to be more variable and CIs wider because of the smaller sample size. Nevertheless, the directions of effects are broadly similar to primary analysis results where the effect was statistically significant. However, there are noteworthy differences across the data sets. In the complete case and 2009–15 analyses, PEA as the presenting rhythm is associated with a statistically significant reduction in mortality compared with asystole. In the complete-case cohort, the ORs for most reperfusion treatments change direction and indicate harm. This association is statistically significant for thrombolysis (late) and thrombolysis (time missing).

In the cases that did not present with a STEMI, admission during the night (between 20.00 and 07.59 hours) was associated with increased mortality. For the year slope between 2003 and 2008, each year was associated with a reduction in mortality. For hospital PCI capability, the direction of OR changed, suggesting benefit to admission to a PCI centre in this patient group, although this did not reach statistical significance. Importantly in this subgroup, there was no evidence of reduced mortality with the use of a reperfusion treatment.

TABLE 12 Sensitivity analysis for hospital mortality

Variable	OR (95% CI), *p*-value[a]				
	Complete-case analysis ($n = 2284$)	2003–8 data; analysis after imputation ($n = 6075$)	2009–15 data; analysis after imputation ($n = 11,529$)	STEMI patients; analysis after imputation ($n = 12,220$)[b]	Other (not STEMI) patients; analysis after imputation ($n = 4772$)[b]
Demographic variables					
Age (years)	1.047 (1.028 to 1.065), < 0.001	1.048 (1.041 to 1.056), < 0.001	1.046 (1.041 to 1.051), < 0.001	1.048 (1.043 to 1.054), < 0.001	1.048 (1.040 to 1.056), < 0.001
Sex					
Male	0.843 (0.554 to 1.284), 0.427	0.733 (0.597 to 0.900), 0.003	0.961 (0.844 to 1.094), 0.545	0.921 (0.806 to 1.052), 0.226	0.758 (0.621 to 0.925), 0.006
Female[c]					
Ethnicity					
Asian	0.870 (0.330 to 2.292), 0.778	0.931 (0.535 to 1.619), 0.799	1.004 (0.762 to 1.323), 0.977	0.961 (0.725 to 1.275), 0.783	1.167 (0.702 to 1.939), 0.551
Black	Not estimable	1.370 (0.481 to 3.905), 0.556	0.860 (0.528 to 1.399), 0.542	0.833 (0.509 to 1.364), 0.468	1.059 (0.511 to 2.198), 0.877
Other	0.769 (0.085 to 6.956), 0.815	1.056 (0.617 to 1.808), 0.843	0.918 (0.612 to 1.376), 0.677	1.023 (0.726 to 1.440), 0.898	0.871 (0.417 to 1.819), 0.713
White[c]					
IMD score	1.005 (0.994 to 1.017), 0.368	1.006 (1.000 to 1.012), 0.039	1.004 (1.001 to 1.008), 0.026	1.002 (0.998 to 1.006), 0.323	1.010 (1.004 to 1.016), 0.002
Medical history variables					
Smoking status					
Ever smoked	0.927 (0.629 to 1.367), 0.703	0.886 (0.725 to 1.083), 0.239	0.906 (0.798 to 1.030), 0.130	0.875 (0.765 to 1.000), 0.050	1.009 (0.830 to 1.226), 0.927
Never smoked[c]					
Diabetes					
Diabetic	1.446 (0.848 to 2.465), 0.176	1.041 (0.792 to 1.367), 0.773	1.180 (0.999 to 1.394), 0.052	1.162 (0.976 to 1.384), 0.091	1.123 (0.890 to 1.416), 0.329
Not diabetic[c]					
Hypercholesterolaemia					
Yes	0.754 (0.485 to 1.172), 0.210	0.679 (0.539 to 0.855), 0.001	0.684 (0.594 to 0.787), < 0.001	0.669 (0.577 to 0.776), < 0.001	0.684 (0.551 to 0.850), 0.001
No[c]					
Heart failure					
Yes	1.248 (0.552 to 2.820), 0.594	1.235 (0.877 to 1.739), 0.227	1.383 (1.062 to 1.801), 0.016	1.584 (1.178 to 2.128), 0.002	1.192 (0.874 to 1.624), 0.267
No[c]					
Cerebrovascular disease					
Yes	1.364 (0.686 to 2.713), 0.376	1.571 (1.166 to 2.116), 0.003	1.176 (0.958 to 1.445), 0.122	1.075 (0.858 to 1.348), 0.529	1.703 (1.294 to 2.241), < 0.001
No[c]					

TABLE 12 Sensitivity analysis for hospital mortality (*continued*)

Variable	OR (95% CI), *p*-value[a]				
	Complete-case analysis ($n = 2284$)	2003–8 data; analysis after imputation ($n = 6075$)	2009–15 data; analysis after imputation ($n = 11,529$)	STEMI patients; analysis after imputation ($n = 12,220$)[b]	Other (not STEMI) patients; analysis after imputation ($n = 4772$)[b]
Previous AMI					
Yes	1.012 (0.587 to 1.744), 0.966	0.953 (0.758 to 1.198), 0.678	1.076 (0.912 to 1.269), 0.385	0.997 (0.836 to 1.188), 0.971	1.118 (0.899 to 1.39), 0.327
No[c]					
Asthma or COPD					
Yes	0.988 (0.556 to 1.757), 0.968	1.364 (1.064 to 1.750), 0.014	1.202 (1.017 to 1.421), 0.031	1.228 (1.030 to 1.463), 0.022	1.246 (0.975 to 1.591), 0.079
No[c]					
Chronic renal failure					
Yes	1.399 (0.568 to 3.450), 0.465	0.772 (0.487 to 1.223), 0.270	1.168 (0.879 to 1.551), 0.285	0.864 (0.613 to 1.219), 0.406	1.390 (0.969 to 1.995), 0.073
No[c]					
Peripheral vascular disease					
Yes	2.199 (0.961 to 5.034), 0.062	1.444 (0.953 to 2.188), 0.083	1.622 (1.231 to 2.139), 0.001	1.723 (1.286 to 2.309), < 0.001	1.338 (0.903 to 1.981), 0.146
No[c]					
Previous angina					
Yes	1.383 (0.824 to 2.322), 0.219	0.968 (0.769 to 1.218), 0.780	1.021 (0.864 to 1.207), 0.805	1.037 (0.869 to 1.239), 0.684	0.926 (0.743 to 1.154), 0.494
No[c]					
Previous PCI					
Yes	1.307 (0.661 to 2.584), 0.441	1.042 (0.680 to 1.596), 0.850	1.011 (0.803 to 1.272), 0.928	1.051 (0.815 to 1.356), 0.700	0.923 (0.652 to 1.305), 0.649
No[c]					
Previous CABG					
Yes	0.752 (0.348 to 1.629), 0.471	1.458 (0.976 to 2.178), 0.066	0.862 (0.677 to 1.098), 0.229	1.189 (0.894 to 1.583), 0.235	0.830 (0.607 to 1.135), 0.244
No[c]					
Hypertension					
Yes	0.930 (0.624 to 1.385), 0.791	0.857 (0.717 to 1.024), 0.089	0.866 (0.768 to 0.976), 0.019	0.849 (0.752 to 0.960), 0.009	0.866 (0.723 to 1.038), 0.120
No[c]					
Presenting characteristics variables					
Time point of cardiac arrest					
After ambulance arrival	0.467 (0.298 to 0.732), 0.001	0.486 (0.402 to 0.587), < 0.001	0.499 (0.436 to 0.571), < 0.001	0.483 (0.425 to 0.548), < 0.001	0.424 (0.331 to 0.544), < 0.001
Before ambulance arrival[c]					

continued

TABLE 12 Sensitivity analysis for hospital mortality (*continued*)

Variable	OR (95% CI), *p*-value[a]				
	Complete-case analysis (*n* = 2284)	2003–8 data; analysis after imputation (*n* = 6075)	2009–15 data; analysis after imputation (*n* = 11,529)	STEMI patients; analysis after imputation (*n* = 12,220)[b]	Other (not STEMI) patients; analysis after imputation (*n* = 4772)[b]
Cardiac arrest rhythm					
PEA	0.137 (0.05 to 0.375), < 0.001	1.128 (0.720 to 1.769), 0.599	0.727 (0.532 to 0.994), 0.045	0.730 (0.507 to 1.051), 0.091	0.846 (0.573 to 1.248), 0.399
VF/VT	0.090 (0.047 to 0.174), < 0.001	0.240 (0.173 to 0.332), < 0.001	0.202 (0.159 to 0.256), < 0.001	0.189 (0.145 to 0.247), < 0.001	0.231 (0.172 to 0.310), < 0.001
Asystole[c]					
Serum glucose (mmol/l)	1.125 (1.083 to 1.167), < 0.001	1.103 (1.077 to 1.130), < 0.001	1.113 (1.100 to 1.127), < 0.001	1.113 (1.097 to 1.130), < 0.001	1.103 (1.081 to 1.126), < 0.001
Haemoglobin (g/dl)	0.835 (0.758 to 0.920), < 0.001	0.900 (0.825 to 0.982), 0.017	0.919 (0.890 to 0.948), < 0.001	0.920 (0.884 to 0.958), < 0.001	0.892 (0.842 to 0.945), < 0.001
Serum cholesterol (mmol/l)	0.846 (0.721 to 0.992), 0.039	0.970 (0.898 to 1.049), 0.445	0.952 (0.889 to 1.020), 0.160	0.953 (0.892 to 1.017), 0.150	0.980 (0.910 to 1.056), 0.595
Admission diagnosis					
Other diagnosis	1.144 (0.604 to 2.167), 0.679	1.063 (0.763 to 1.479), 0.719	0.797 (0.661 to 0.960), 0.017	1.005 (0.850 to 1.188), 0.956	0.586 (0.329 to 1.043), 0.069
Definite MI – other infarct site	0.988 (0.616 to 1.586), 0.961	1.165 (0.791 to 1.717), 0.440	0.988 (0.858 to 1.137), 0.864	1.029 (0.898 to 1.179), 0.679	1.192 (0.603 to 2.358), 0.614
Definite MI – anterior infarct[c]					
SBP at admission (mmHg)					
Linear term[d]	–7.43 (–15.57 to 0.70), 0.073	–26.62 (–33.3 to –19.9), < 0.001	–33.18 (–39.1 to –27.2), < 0.001	–33.76 (–40.3 to –27.3), < 0.001	–23.45 (–29.6 to –17.3), < 0.001
Quadratic term[d]	8.14 (0.87 to 15.41), 0.028	9.16 (2.96 to 15.36), 0.004	15.18 (9.41 to 20.95), < 0.001	16.96 (11.00 to 22.92), < 0.001	6.42 (0.46 to 12.38), 0.035
ECG that determined treatment					
ST segment elevation or LBBB	1.473 (0.758 to 2.861), 0.253	1.644 (1.266 to 2.135), < 0.001	1.555 (1.283 to 1.884), < 0.001	Only 'ST segment elevation or LBBB' patients included in the analysis	These data were not included
ST segment depression or T-wave changes only	0.532 (0.268 to 1.058), 0.072	0.890 (0.682 to 1.163), 0.394	0.904 (0.743 to 1.099), 0.311		0.859 (0.728 to 1.014), 0.073
Other acute abnormality or no acute changes[c]					
Heart rate at admission (b.p.m.)	1.013 (1.006 to 1.020), < 0.001	1.008 (1.005 to 1.012), < 0.001	1.003 (1.001 to 1.006), 0.003	1.006 (1.004 to 1.008), < 0.001	1.005 (1.002 to 1.008), 0.004
Time of day of admission (day/night)					
20.00 to < 08.00 hours	1.116 (0.764 to 1.629), 0.570	1.120 (0.946 to 1.326), 0.188	1.082 (0.968 to 1.210), 0.164	1.037 (0.926 to 1.163), 0.528	1.203 (1.010 to 1.433), 0.038
08.00 to < 20.00[c] hours					

TABLE 12 Sensitivity analysis for hospital mortality (*continued*)

Variable	OR (95% CI), *p*-value[a]				
	Complete-case analysis ($n = 2284$)	2003–8 data; analysis after imputation ($n = 6075$)	2009–15 data; analysis after imputation ($n = 11,529$)	STEMI patients; analysis after imputation ($n = 12,220$)[b]	Other (not STEMI) patients; analysis after imputation ($n = 4772$)[b]
Year					
Slope (2003–8)	0.616 (0.264 to 1.437), 0.262	0.946 (0.891 to 1.004), 0.068	These data were excluded	0.996 (0.931 to 1.066), 0.916	0.885 (0.810 to 0.968), 0.008
Slope (2009–15)	1.003 (0.873 to 1.152), 0.966	These data were excluded	1.038 (1.004 to 1.074), 0.029	1.038 (0.998 to 1.081), 0.065	1.016 (0.953 to 1.082), 0.632
Care pathway variables					
Hospital volume (OHCA cases)					
0–10 cases	1.726 (0.663 to 4.494), 0.263	0.972 (0.516 to 1.831), 0.931	1.126 (0.771 to 1.643), 0.539	1.229 (0.904 to 1.670), 0.189	0.688 (0.386 to 1.229), 0.207
11–24 cases	2.302 (0.972 to 5.456), 0.058	1.168 (0.607 to 2.247), 0.642	1.276 (0.897 to 1.816), 0.175	1.242 (0.926 to 1.667), 0.148	0.948 (0.534 to 1.681), 0.854
25–82 cases[c]					
Hospital pPCI capability					
pPCI capable	1.001 (0.515 to 1.948), 0.998	1.156 (0.702 to 1.902), 0.569	1.403 (1.101 to 1.789), 0.006	1.584 (1.261 to 1.989), < 0.001	0.849 (0.605 to 1.190), 0.342
pPCI incapable[c]					
EMS response time (minutes)	1.015 (1.000 to 1.031), 0.058	0.998 (0.988 to 1.008), 0.703	1.000 (0.994 to 1.005), 0.861	1.000 (0.995 to 1.005), 0.996	0.997 (0.987 to 1.007), 0.589
EMS travel distance (km)	0.988 (0.967 to 1.011), 0.301	0.999 (0.989 to 1.009), 0.810	0.992 (0.986 to 0.998), 0.009	0.992 (0.986 to 0.998), 0.012	0.997 (0.987 to 1.008), 0.612
Admitting consultant					
Cardiologist	0.676 (0.418 to 1.094), 0.111	0.739 (0.604 to 0.904), 0.003	0.694 (0.590 to 0.816), < 0.001	0.794 (0.680 to 0.927), 0.003	0.615 (0.494 to 0.766), < 0.001
Other consultant[c]					
Admission ward					
Intensive therapy unit	3.833 (2.374 to 6.188), < 0.001	4.632 (3.744 to 5.732), < 0.001	3.461 (3.009 to 3.982), < 0.001	3.267 (2.852 to 3.742), < 0.001	5.239 (4.107 to 6.685), < 0.001
Died in ED	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable
General ward or other	5.554 (2.882 to 10.70), < 0.001	3.461 (2.670 to 4.487), < 0.001	3.601 (2.910 to 4.457), < 0.001	3.549 (2.884 to 4.368), < 0.001	3.575 (2.642 to 4.838), < 0.001
Cardiac ward – non-CCU	4.952 (1.432 to 17.13), 0.012	2.012 (0.925 to 4.374), 0.078	1.127 (0.748 to 1.699), 0.567	1.148 (0.728 to 1.810), 0.552	1.588 (0.861 to 2.929), 0.138
CCU[c]					
Place where ECG performed					
In hospital	1.127 (0.717 to 1.771), 0.604	1.257 (0.931 to 1.697), 0.136	1.049 (0.909 to 1.211), 0.513	1.127 (0.956 to 1.329), 0.154	1.088 (0.878 to 1.348), 0.439
Pre hospital[c]					

continued

TABLE 12 Sensitivity analysis for hospital mortality (*continued*)

Variable	OR (95% CI), *p*-value[a]				
	Complete-case analysis ($n = 2284$)	2003–8 data; analysis after imputation ($n = 6075$)	2009–15 data; analysis after imputation ($n = 11,529$)	STEMI patients; analysis after imputation ($n = 12,220$)[b]	Other (not STEMI) patients; analysis after imputation ($n = 4772$)[b]
Reperfusion treatment and timing					
Thrombolysis (performed early)	1.199 (0.396 to 3.631), 0.749	0.676 (0.488 to 0.936), 0.180	0.791 (0.502 to 1.248), 0.314	0.714 (0.550 to 0.926), 0.011	0.501 (0.121 to 2.071), 0.340
Thrombolysis (performed late)	2.114 (1.035 to 4.318), 0.040	0.849 (0.666 to 1.083), 0.188	0.920 (0.706 to 1.199), 0.536	0.893 (0.741 to 1.075), 0.231	0.939 (0.480 to 1.837), 0.854
Thrombolysis (time missing)	28.03 (3.038 to 258.6), 0.003	0.833 (0.537 to 1.292), 0.414	0.995 (0.620 to 1.597), 0.982	0.940 (0.672 to 1.315), 0.717	1.248 (0.500 to 3.117), 0.635
pPCI (performed early)	1.176 (0.598 to 2.312), 0.639	0.449 (0.208 to 0.968), 0.041	0.685 (0.576 to 0.815), < 0.001	0.618 (0.518 to 0.737), < 0.001	0.802 (0.430 to 1.498), 0.490
pPCI (performed late)	0.811 (0.377 to 1.743), 0.592	1.924 (0.969 to 3.819), 0.062	0.894 (0.724 to 1.103), 0.294	0.836 (0.675 to 1.035), 0.100	0.967 (0.479 to 1.952), 0.926
pPCI (time missing)	1.149 (0.341 to 3.875), 0.822	0.506 (0.117 to 2.183), 0.361	0.661 (0.504 to 0.867), 0.003	0.610 (0.463 to 0.802), < 0.001	1.496 (0.593 to 3.773), 0.393
None[c]					
RE estimate (adjusted R^2, AIC)	0.192 (0.296, 1042)	0.311[e] (0.399,[e] 4608[e])	0.192[e] (0.346,[e] 9539[e])	0.118[e] (0.354,[e] 9471[e])	0.378[e] (0.365,[e] 4133[e])

b.p.m., beats per minute; SBP, systolic blood pressure.
a Values describe OR (95% CI), *p*-value, unless stated otherwise.
b Data for 612 patients missing prior to imputation for ECG that determined treatment, so not included in analysis.
c Reference category.
d Estimates on the logarithmic scale.
e Median from 25 data sets.
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Secondary outcome: neurological outcome at discharge

Adjusted analysis

The adjusted analysis for neurological outcome at discharge is presented in *Table 13*. The results of the analysis are similar to those reported for the primary outcome (in-hospital mortality), although there are a few important differences.

In the baseline demographic category, sex was found not to be predictive of neurological outcome. In the care pathway category, the location where the ECG was performed did influence outcome, such that in-hospital ECG was associated with a poorer outcome. In contrast to the primary outcome analysis, there was no evidence of an association between transfer distance or admission to a pPCI centre and neurological outcome. Finally, in this analysis there was a statistically significant association between late thrombolysis and improved neurological outcome.

Sensitivity analyses

In sensitivity analyses, there was a similar pattern to that observed in the primary outcome sensitivity analyses in that the reduced sample sizes led to greater variability in results and wider CIs (*Table 14*). However, the results in the sensitivity analyses were broadly similar to those reported in the analysis of the whole cohort.

TABLE 13 Adjusted analysis for neurological outcome

Variable	Analysis after imputation, OR (95% CI), *p*-value (*n* = 15,286)
Demographic variables	
Age (years)	1.030 (1.026 to 1.034), < 0.001
Sex	
Male	0.955 (0.860 to 1.061), 0.391
Female[a]	
Ethnicity	
Asian	1.138 (0.904 to 1.433), 0.271
Black	1.054 (0.697 to 1.594), 0.804
Other	1.009 (0.757 to 1.345), 0.952
White[a]	
IMD score	1.003 (1.000 to 1.007), 0.032
Medical history variables	
Smoking status	
Ever smoked	0.941 (0.843 to 1.051), 0.281
Never smoked[a]	
Diabetes status	
Diabetic	1.003 (0.875 to 1.150), 0.964
Not diabetic[a]	
Hypercholesterolaemia	
Yes	0.714 (0.638 to 0.800), < 0.001
No[a]	
Heart failure	
Yes	1.358 (1.096 to 1.682), 0.005
No[a]	
Cerebrovascular disease	
Yes	1.227 (1.034 to 1.456), 0.019
No[a]	
Previous AMI	
Yes	1.005 (0.881 to 1.147), 0.940
No[a]	
Asthma or COPD	
Yes	1.171 (1.022 to 1.342), 0.023
No[a]	
Chronic renal failure	
Yes	1.031 (0.806 to 1.319), 0.807
No[a]	
Peripheral vascular disease	
Yes	1.560 (1.240 to 1.961), < 0.001
No[a]	

continued

TABLE 13 Adjusted analysis for neurological outcome (*continued*)

Variable	Analysis after imputation, OR (95% CI), *p*-value (*n* = 15,286)
Previous angina	
Yes	0.932 (0.816 to 1.065), 0.303
No[a]	
Previous PCI	
Yes	0.986 (0.811 to 1.199), 0.888
No[a]	
Previous CABG	
Yes	1.027 (0.833 to 1.265), 0.806
No[a]	
Hypertension	
Yes	0.820 (0.745 to 0.903), < 0.001
No[a]	
Presenting characteristics variables	
Time point of cardiac arrest	
After ambulance arrival	0.428 (0.387 to 0.473), < 0.001
Before ambulance arrival[a]	
Cardiac arrest rhythm	
PEA	0.842 (0.629 to 1.125), 0.244
VF/VT	0.263 (0.212 to 0.324), < 0.001
Asystole[a]	
Serum glucose (mmol/l)	1.092 (1.080 to 1.104), < 0.001
Haemoglobin (g/dl)	0.930 (0.904 to 0.957), < 0.001
Serum cholesterol (mmol/l)	0.961 (0.920 to 1.004), 0.077
Admission diagnosis	
Other diagnosis	0.880 (0.756 to 1.023), 0.097
Definite MI – other infarct site	1.020 (0.896 to 1.161), 0.769
Definite MI – anterior infarct[a]	
SBP at admission (mmHg)	
Linear term[b]	–34.37 (–40.31 to –28.43), < 0.001
Quadratic term[b]	16.27 (10.73 to 21.80), < 0.001
ECG that determined treatment	
ST segment elevation or LBBB	1.528 (1.310 to 1.782), < 0.001
ST segment depression T-wave changes only	0.966 (0.828 to 1.128), 0.662
Other acute abnormality or no acute changes[a]	
Heart rate (b.p.m.)	1.004 (1.002 to 1.006), < 0.001
Time of the day of admission (day/night)	
20.00 to < 08.00 hours	1.020 (0.933 to 1.115), 0.662
08.00 to < 20.00[a] hours	

TABLE 13 Adjusted analysis for neurological outcome (*continued*)

Variable	Analysis after imputation, OR (95% CI), *p*-value ($n = 15,286$)
Year	
Slope (2003–8)	0.985 (0.936 to 1.037), 0.575
Slope (2009–15)	1.054 (1.020 to 1.089), 0.002
Care pathway variables	
Hospital volume (OHCA cases per year)	
0–10 cases	0.942 (0.671 to 1.323), 0.731
11–24 cases	1.113 (0.788 to 1.574), 0.543
25–82 cases[a]	
Hospital pPCI capability	
pPCI capable	1.030 (0.859 to 1.235), 0.748
pPCI incapable[a]	
EMS response time (minutes)	1.000 (0.996 to 1.004), 0.900
EMS travel distance (km)	0.996 (0.991 to 1.001), 0.122
Admitting consultant	
Cardiologist	0.743 (0.658 to 0.838), < 0.001
Other consultant[a]	
Admission ward	
Intensive therapy unit	3.797 (3.399 to 4.241), < 0.001
Died in ED	Not estimable
General ward or other	2.992 (2.541 to 3.522), < 0.001
Cardiac ward – non-CCU	1.092 (0.781 to 1.526), 0.607
CCU[a]	
Place where ECG performed	
In hospital	1.164 (1.024 to 1.324), 0.020
Pre hospital[a]	
Reperfusion treatment and timing	
Thrombolysis (performed early)	0.661 (0.528 to 0.826), < 0.001
Thrombolysis (performed late)	0.811 (0.686 to 0.959), 0.014
Thrombolysis (time missing)	0.899 (0.663 to 1.220), 0.495
pPCI (performed early)	0.678 (0.582 to 0.791), < 0.001
pPCI (performed late)	0.912 (0.752 to 1.107), 0.352
pPCI (time missing)	0.830 (0.644 to 1.070), 0.151
None[a]	
RE estimate (adjusted R^2, AIC)	0.206[c] (0.352,[c] 14455[c])

b.p.m., beats per minute; SBP, systolic blood pressure.
a Reference category.
b Estimates on the logarithmic scale.
c Median from 25 data sets.

TABLE 14 Sensitivity analyses for neurological outcome

Variable	OR (95% CI), *p*-value				
	Complete-case analysis ($n = 2109$)	2003–8 data; analysis after imputation ($n = 5292$)	2009–15 data; analysis after imputation ($n = 9994$)	STEMI patients; analysis after imputation ($n = 10,701$)[a]	Other (not STEMI) patients; analysis after imputation ($n = 4045$)[a]
Demographic variables					
Age (years)	1.017 (1.004 to 1.031), 0.010	1.025 (1.018 to 1.031), < 0.001	1.034 (1.029 to 1.039), < 0.001	1.033 (1.028 to 1.038), < 0.001	1.028 (1.020 to 1.035), < 0.001
Sex					
Male	1.200 (0.845 to 1.706), 0.308	0.807 (0.675 to 0.965), 0.019	1.054 (0.924 to 1.202), 0.433	0.986 (0.866 to 1.122), 0.829	0.897 (0.734 to 1.096), 0.287
Female[b]					
Ethnicity					
Asian	2.295 (1.137 to 4.632), 0.020	0.960 (0.595 to 1.551), 0.868	1.159 (0.882 to 1.525), 0.289	1.133 (0.858 to 1.495), 0.379	1.259 (0.764 to 2.073), 0.366
Black	2.361 (0.387 to 14.41), 0.352	1.026 (0.356 to 2.958), 0.962	1.044 (0.666 to 1.637), 0.850	1.065 (0.649 to 1.749), 0.803	1.003 (0.499 to 2.015), 0.993
Other	2.084 (0.625 to 6.951), 0.232	0.973 (0.595 to 1.591), 0.912	0.951 (0.655 to 1.381), 0.792	1.008 (0.729 to 1.393), 0.964	0.991 (0.508 to 1.936), 0.980
White[b]					
IMD score	1.005 (0.996 to 1.015), 0.262	1.004 (0.999 to 1.009), 0.149	1.004 (1.000 to 1.008), 0.050	1.004 (1.000 to 1.008), 0.069	1.003 (0.997 to 1.009), 0.383
Medical history variables					
Smoking status					
Ever smoked	1.134 (0.833 to 1.544), 0.423	1.002 (0.832 to 1.205), 0.987	0.904 (0.793 to 1.030), 0.129	0.942 (0.824 to 1.077), 0.383	0.960 (0.792 to 1.163), 0.675
Never smoked[b]					
Diabetes status					
Diabetic	0.804 (0.508 to 1.272), 0.351	0.883 (0.691 to 1.128), 0.319	1.067 (0.900 to 1.265), 0.458	1.035 (0.869 to 1.231), 0.701	0.978 (0.775 to 1.233), 0.851
Not diabetic[b]					
Hypercholesterolaemia					
Yes	0.766 (0.541 to 1.084), 0.133	0.753 (0.612 to 0.926), 0.007	0.674 (0.588 to 0.774), < 0.001	0.672 (0.584 to 0.773), < 0.001	0.772 (0.627 to 0.952), 0.015
No[b]					
Heart failure					
Yes	1.167 (0.559 to 2.438), 0.681	1.261 (0.899 to 1.769), 0.179	1.422 (1.069 to 1.892), 0.016	1.619 (1.186 to 2.210), 0.002	1.271 (0.923 to 1.748), 0.141
No[b]					
Cerebrovascular disease					
Yes	1.036 (0.569 to 1.886), 0.909	1.417 (1.058 to 1.898), 0.019	1.141 (0.921 to 1.412), 0.227	1.190 (0.947 to 1.494), 0.135	1.317 (0.997 to 1.740), 0.053
No[b]					

TABLE 14 Sensitivity analyses for neurological outcome (*continued*)

Variable	OR (95% CI), *p*-value				
	Complete-case analysis ($n = 2109$)	2003–8 data; analysis after imputation ($n = 5292$)	2009–15 data; analysis after imputation ($n = 9994$)	STEMI patients; analysis after imputation ($n = 10,701$)[a]	Other (not STEMI) patients; analysis after imputation ($n = 4045$)[a]
Previous AMI					
Yes	0.967 (0.618 to 1.513), 0.883	0.898 (0.724 to 1.115), 0.331	1.070 (0.904 to 1.267), 0.433	0.947 (0.794 to 1.129), 0.544	1.062 (0.857 to 1.316), 0.583
No[b]					
Asthma or COPD					
Yes	1.240 (0.792 to 1.940), 0.347	1.311 (1.035 to 1.662), 0.025	1.119 (0.946 to 1.325), 0.190	1.106 (0.933 to 1.312), 0.246	1.320 (1.031 to 1.690), 0.028
No[b]					
Chronic renal failure					
Yes	1.950 (0.851 to 4.469), 0.115	0.720 (0.458 to 1.132), 0.155	1.155 (0.851 to 1.567), 0.354	0.857 (0.603 to 1.218), 0.389	1.239 (0.850 to 1.806), 0.265
No[b]					
Peripheral vascular disease					
Yes	1.745 (0.800 to 3.808), 0.162	1.442 (0.972 to 2.140), 0.069	1.672 (1.255 to 2.228), < 0.001	1.663 (1.241 to 2.226), 0.001	1.477 (0.991 to 2.201), 0.056
No[b]					
Previous angina					
Yes	1.196 (0.782 to 1.828), 0.409	0.968 (0.777 to 1.205), 0.771	0.905 (0.763 to 1.073), 0.251	0.920 (0.770 to 1.098), 0.356	0.941 (0.757 to 1.169), 0.582
No[b]					
Previous PCI					
Yes	1.060 (0.597 to 1.885), 0.842	0.958 (0.642 to 1.430), 0.834	0.981 (0.778 to 1.237), 0.874	1.065 (0.828 to 1.369), 0.624	0.848 (0.605 to 1.189), 0.338
No[b]					
Previous CABG					
Yes	0.789 (0.404 to 1.542), 0.488	1.311 (0.881 to 1.950), 0.182	0.923 (0.718 to 1.186), 0.530	1.151 (0.856 to 1.549), 0.352	0.934 (0.685 to 1.275), 0.668
No[b]					
Hypertension					
Yes	0.936 (0.684 to 1.280), 0.678	0.765 (0.649 to 0.901), 0.001	0.852 (0.756 to 0.961), 0.009	0.823 (0.731 to 0.925), 0.001	0.799 (0.668 to 0.954), 0.013
No[b]					
Presenting characteristics variables					
Time point of cardiac arrest					
After ambulance arrival	0.625 (0.443 to 0.883), 0.008	0.423 (0.358 to 0.499), < 0.001	0.426 (0.375 to 0.484), < 0.001	0.413 (0.367 to 0.464), < 0.001	0.459 (0.367 to 0.573), < 0.001
No[b]					

continued

TABLE 14 Sensitivity analyses for neurological outcome (*continued*)

Variable	OR (95% CI), *p*-value				
	Complete-case analysis ($n = 2109$)	2003–8 data; analysis after imputation ($n = 5292$)	2009–15 data; analysis after imputation ($n = 9994$)	STEMI patients; analysis after imputation ($n = 10,701$)[a]	Other (not STEMI) patients; analysis after imputation ($n = 4045$)[a]
Cardiac arrest rhythm					
PEA	0.267 (0.103 to 0.691), 0.006	1.046 (0.638 to 1.716), 0.858	0.707 (0.488 to 1.023), 0.066	0.730 (0.484 to 1.103), 0.135	0.851 (0.546 to 1.326), 0.476
VF/VT	0.154 (0.081 to 0.294), < 0.001	0.301 (0.212 to 0.427), < 0.001	0.230 (0.175 to 0.303), < 0.001	0.230 (0.170 to 0.310), < 0.001	0.279 (0.201 to 0.388), < 0.001
Asystole[b]					
Serum glucose (mmol/l)	1.104 (1.069 to 1.140), < 0.001	1.073 (1.052 to 1.095), < 0.001	1.104 (1.090 to 1.118), < 0.001	1.097 (1.083 to 1.112), < 0.001	1.080 (1.059 to 1.101), < 0.001
Haemoglobin (g/dl)	0.938 (0.867 to 1.014), 0.109	0.929 (0.878 to 0.983), 0.010	0.935 (0.907 to 0.964), < 0.001	0.929 (0.898 to 0.961), < 0.001	0.935 (0.887 to 0.984), 0.011
Serum cholesterol (mmol/l)	0.884 (0.784 to 0.997), 0.045	0.955 (0.898 to 1.016), 0.145	0.965 (0.908 to 1.026), 0.257	0.961 (0.911 to 1.014), 0.145	0.976 (0.914 to 1.043), 0.475
Admission diagnosis					
Other diagnosis	0.696 (0.415 to 1.167), 0.170	1.098 (0.832 to 1.448), 0.509	0.795 (0.659 to 0.959), 0.017	1.024 (0.865 to 1.211), 0.786	0.464 (0.265 to 0.814), 0.007
Definite MI – other infarct site	0.649 (0.451 to 0.933), 0.019	1.168 (0.867 to 1.574), 0.308	0.971 (0.848 to 1.113), 0.672	1.024 (0.893 to 1.174), 0.735	0.870 (0.453 to 1.670), 0.675
Definite MI – anterior infarct[b]					
SBP at admission (mmHg)					
Linear term[c]	–9.88 (–16.36 to -3.41), 0.003	–22.11 (–28.2 to –16.0), < 0.001	–26.35 (–32.2 to –20.5), < 0.001	–27.12 (–33.3 to –21.0), < 0.001	–19.67 (–25.2 to –14.1), < 0.001
Quadratic term[c]	2.73 (–3.33 to 8.79), 0.378	7.63 (1.80 to 13.46), 0.010	14.79 (9.24 to 20.34), < 0.001	15.37 (9.85 to 20.88), < 0.001	6.24 (0.53 to 11.95), 0.032
ECG that determined treatment					
ST segment elevation or LBBB	1.348 (0.768 to 2.368), 0.298	1.379 (1.078 to 1.763), 0.010	1.653 (1.357 to 2.014), < 0.001	Only 'ST segment elevation or LBBB' patients included in the analysis	These data were excluded
ST segment depression T-wave changes only	1.171 (0.678 to 2.024), 0.572	0.836 (0.650 to 1.077), 0.165	1.067 (0.875 to 1.301), 0.524		0.928 (0.788 to 1.092), 0.368
Other acute abnormality or no acute changes[b]					
Heart rate at admission (b.p.m.)	1.007 (1.001 to 1.013), 0.017	1.006 (1.003 to 1.009), < 0.001	1.002 (1.000 to 1.005), 0.049	1.005 (1.002 to 1.007), < 0.001	1.003 (1.000 to 1.007), 0.048
Time of day of admission (day/night)					
20.00 to < 08.00 hours	1.011 (0.750 to 1.362), 0.944	1.033 (0.884 to 1.206), 0.686	1.020 (0.913 to 1.140), 0.721	0.989 (0.887 to 1.104), 0.846	1.082 (0.911 to 1.284), 0.369
08.00 to < 20.00[b] hours					

TABLE 14 Sensitivity analyses for neurological outcome (*continued*)

Variable	OR (95% CI), *p*-value				
	Complete-case analysis ($n = 2109$)	2003–8 data; analysis after imputation ($n = 5292$)	2009–15 data; analysis after imputation ($n = 9994$)	STEMI patients; analysis after imputation ($n = 10,701$)[a]	Other (not STEMI) patients; analysis after imputation ($n = 4045$)[a]
Year					
Slope (2003–8)	0.983 (0.512 to 1.889), 0.960	0.987 (0.936 to 1.040), 0618	These data were excluded	1.008 (0.947 to 1.072), 0.807	0.970 (0.892 to 1.055), 0.479
Slope (2009–15)	0.948 (0.850 to 1.056), 0.331	These data were excluded	1.050 (1.015 to 1.086), 0.004	1.046 (1.006 to 1.088), 0.023	1.041 (0.978 to 1.109), 0.205
Care pathway variables					
Hospital volume (OHCA cases per year)					
0–10 cases	1.176 (0.596 to 2.319), 0.640	1.115 (0.653 to 1.904), 0.690	0.874 (0.586 to 1.302), 0.507	1.128 (0.812 to 1.569), 0.473	0.597 (0.347 1.027), 0.062
11–24 cases	1.335 (0.735 to 2.424), 0.342	1.155 (0.663 to 2.011), 0.611	1.131 (0.776 to 1.648), 0.523	1.097 (0.793 to 1.516), 0.576	0.945 (0.553 1.614), 0.835
25–82 cases[b]					
Hospital pPCI capability					
pPCI capable	0.678 (0.402 to 1.142), 0.144	0.896 (0.579 to 1.386), 0.620	1.037 (0.811 to 1.327), 0.771	1.307 (1.047 to 1.631), 0.018	0.617 (0.448 0.850), 0.003
pPCI incapable[b]					
EMS response time (minutes)	1.006 (0.992 to 1.019), 0.420	0.999 (0.990 to 1.008), 0.857	1.000 (0.996 to 1.005), 0.918	1.002 (0.997 to 1.006), 0.501	0.997 (0.987 1.007), 0.513
EMS travel distance (km)	1.006 (0.990 to 1.022), 0.479	0.998 (0.988 to 1.008), 0.668	0.995 (0.989 to 1.001), 0.103	0.994 (0.989 to 1.000), 0.066	0.997 (0.987 1.008), 0.605
Admitting consultant					
Cardiologist	0.899 (0.613 to 1.319), 0.588	0.718 (0.601 to 0.858), < 0.001	0.758 (0.644 to 0.892), 0.001	0.777 (0.668 to 0.903), 0.001	0.671 (0.547 0.823), < 0.001
Other consultant[b]					
Admission ward					
Intensive therapy unit	3.153 (2.179 to 4.562), < 0.001	3.899 (3.228 to 4.711), < 0.001	3.815 (3.330 to 4.370), < 0.001	3.560 (3.130 to 4.050), < 0.001	4.255 (3.426 5.284), < 0.001
Died in ED	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable
General ward or other	2.857 (1.640 to 4.976), < 0.001	2.482 (1.947 to 3.166), < 0.001	3.704 (2.959 to 4.636), < 0.001	3.096 (2.511 to 3.818), < 0.001	2.729 (2.047 3.640), < 0.001
Cardiac ward – non-CCU	1.654 (0.592 to 4.624), 0.337	2.042 (1.073 to 3.885), 0.030	0.944 (0.634 to 1.403), 0.774	1.114 (0.722 to 1.720), 0.625	1.165 (0.667 2.036), 0.591
CCU[b]					
Place where ECG performed					
In hospital	1.475 (1.019 to 2.135), 0.040	1.201 (0.951 to 1.517), 0.124	1.135 (0.980 to 1.314), 0.090	1.154 (0.986 to 1.351), 0.074	1.128 (0.927 1.374), 0.229
Pre hospital[b]					

continued

TABLE 14 Sensitivity analyses for neurological outcome (*continued*)

Variable	OR (95% CI), *p*-value				
	Complete-case analysis ($n = 2109$)	2003–8 data; analysis after imputation ($n = 5292$)	2009–15 data; analysis after imputation ($n = 9994$)	STEMI patients; analysis after imputation ($n = 10,701$)[a]	Other (not STEMI) patients; analysis after imputation ($n = 4045$)[a]
Reperfusion treatment and timing					
Thrombolysis (performed early)	0.867 (0.410 to 1.831), 0.708	0.677 (0.513 to 0.892), 0.006	0.656 (0.420 to 1.025), 0.064	0.735 (0.580 to 0.930), 0.010	0.363 (0.094 1.398), 0.141
Thrombolysis (performed late)	0.562 (0.307 to 1.028), 0.062	0.793 (0.635 to 0.990), 0.041	0.870 (0.662 to 1.142), 0.315	0.852 (0.711 to 1.022), 0.084	0.948 (0.495 1.818), 0.873
Thrombolysis (time missing)	10.695 (1.46 to 78.41), 0.020	0.882 (0.594 to 1.311), 0.535	0.901 (0.539 to 1.504), 0.690	0.888 (0.634 to 1.243), 0.488	0.997 (0.411 2.418), 0.996
pPCI (performed early)	0.670 (0.400 to 1.123), 0.129	0.586 (0.323 to 1.065), 0.079	0.658 (0.553 to 0.782), < 0.001	0.623 (0.523 to 0.741), < 0.001	0.707 (0.392 1.274), 0.249
pPCI (performed late)	0.567 (0.305 to 1.055), 0.073	1.806 (0.956 to 3.413), 0.068	0.853 (0.690 to 1.053), 0.138	0.837 (0.678 to 1.033), 0.097	0.581 (0.296 1.144), 0.116
pPCI (time missing)	2.156 (0.758 to 6.132), 0.150	0.315 (0.069 to 1.439), 0.136	0.802 (0.611 to 1.052), 0.111	0.746 (0.567 to 0.982), 0.037	1.843 (0.744 4.564), 0.187
None[b]					
RE estimate (Adjusted R^2, AIC)	0.138 (0.256 to 1505)	0.217[d] (0.358[d] to 5064[d])	0.232[d] (0.351,[d] 9421[d])	0.159[d] (0.352,[d] 9892[d])	0.339[d] (0.319,[d] 4135[d])

b.p.m., beats per minute; SBP, systolic blood pressure.
a Excludes cases where ECG that determined treatment field was missing in pre-imputation data set.
b Reference category.
c Estimates on the logarithmic scale.
d Median from 25 data sets.

There were a few results of note. In relation to admission to a PCI centre, this, counterintuitively, was associated with worse outcome for STEMI patients but improved outcome for other cases. Furthermore, reperfusion treatment was found to be of no benefit in the cohort of patients who did not have a STEMI.

Secondary outcome: time to all-cause mortality

Overview of cohort

The analysis of time to all-cause mortality included the 12,483 patients who survived to hospital discharge for whom data were available on outcome.

The characteristics of this cohort are included in *Table 15* for both the pre-imputation and the imputed data sets. As was the case for the in-hospital mortality patient cohort, the pre-imputation and imputed data sets for the time to all-cause mortality patient cohorts are similar. Furthermore, the imputed data sets for both hospital mortality and time to all-cause mortality cohorts are broadly similar (*Tables 9* and *15*).

The key, albeit small, differences between cohorts typically relate to variables that were associated with hospital mortality. For example, patients in the time to all-cause mortality cohort tended to be slightly younger [mean age 65.3 (SD 13.2) years vs. 63.3 (SD 12.8) years], were more likely to be male (75.1% v 78.2% patients), less likely to have a comorbidity (e.g. heart failure, 5.0% vs. 3.5% of patients), more likely to have a cardiac arrest after ambulance arrival (39.9% vs. 47.7% of patients), initial rhythm was more likely to be VF/VT (89.6% vs. 95.9% of patients) and were more likely to have received reperfusion treatment (62.9% vs. 68.4% of patients).

TABLE 15 Overview of participant characteristics for time to all-cause mortality cohort (pre-imputation and imputed data sets)

Variable	Pre-imputation[a]	Imputed data set ($N = 12,483$)
Demographic variables,* n *(%)		
Age (years)		
Range	20–114	20–114
Mean (SD)	63.3 (12.82)	63.3 (12.82)
Median (IQR)	63.3 (54–73)	63.3 (54–73)
Sex		
Female	2715 (21.8)	2721 (21.8)
Ethnicity		
White	10,234 (93.9)	11,340 (90.8)
Asian	361 (3.3)	541 (4.3)
Black	93 (0.9)	273 (2.2)
Other	187 (1.7)	329 (2.6)
IMD score		
Range	0.72–85.59	0.72–85.59
Mean (SD)	21.98 (15.80)	22.00 (15.76)
Median (IQR)	17.4 (10.1–30.3)	17.5 (10.1–30.2)
Medical history variables,* n *(%)		
Smoking status		
Ever smoked	7244 (66.0)	8157 (65.3)
Never smoked	3726 (34.0)	4326 (34.7)
Diabetes status		
Diabetic	1266 (10.9)	1385 (11.1)
Not diabetic	10,298 (89.1)	11,098 (88.9)
Hypercholesterolaemia		
Yes	3055 (27.6)	3055 (24.5)
Heart failure		
Yes	388 (3.5)	388 (3.1)
Cerebrovascular disease		
Yes	610 (5.4)	610 (4.9)
Previous AMI		
Yes	2048 (17.8)	2048 (16.4)
Asthma or COPD		
Yes	1170 (10.5)	1170 (9.4)
Chronic renal failure		
Yes	281 (2.5)	281 (2.3)
Peripheral vascular disease		
Yes	346 (3.1)	346 (2.8)

continued

TABLE 15 Overview of participant characteristics for time to all-cause mortality cohort (pre-imputation and imputed data sets) (*continued*)

Variable	Pre-imputation[a]	Imputed data set (*N* = 12,483)
Previous angina		
Yes	1827 (16.1)	1827 (14.6)
Previous PCI		
Yes	791 (7.0)	791 (6.3)
Previous CABG		
Yes	517 (4.5)	517 (4.1)
Hypertension		
Yes	4551 (39.9)	4551 (36.5)
Presenting characteristics of OHCA variables,* n *(%)		
Time point of cardiac arrest		
Before ambulance arrival	6503 (52.3)	6528 (52.3)
After ambulance arrival	5935 (47.7)	5955 (47.7)
Cardiac arrest rhythm		
Asystole	249 (2.1)	276 (2.2)
PEA	237 (2.0)	259 (2.1)
VF/VT	11,254 (95.9)	11,948 (95.7)
Serum glucose (mmol/l)		
Range	1–48.5	1–59
Mean (SD)	10.07 (4.20)	10.07 (4.30)
Median (IQR)	9.1 (7.0–12.0)	9.1 (7.0–12.0)
Creatinine (μmol/l)		
Range	1–1219	1–1219
Mean (SD)	99.35 (42.10)	101.98 (44.93)
Median (IQR)	94 (78–112)	95 (78–115)
LVEF		
Good	2534 (39.8)	5140 (41.2)
Moderate	2692 (42.3)	4927 (39.5)
Poor	1138 (17.9)	2416 (19.4)
Haemoglobin (g/dl)		
Range	5–21.60	5–21.60
Mean (SD)	13.81 (1.92)	13.70 (1.98)
Median (IQR)	14.0 (12.7–15.0)	14.0 (12.5–15.0)
Serum cholesterol (mmol/l)		
Range	1–18	1–20.50
Mean (SD)	4.87 (1.39)	4.79 (1.45)
Median (IQR)	4.8 (3.9–5.7)	4.7 (3.8–5.7)

TABLE 15 Overview of participant characteristics for time to all-cause mortality cohort (pre-imputation and imputed data sets) (*continued*)

Variable	Pre-imputation[a]	Imputed data set (*N* = 12,483)
Admission diagnosis		
Definite MI – anterior infarction	3087 (30.3)	4023 (32.2)
Definite MI – other infarction site	2766 (27.2)	4122 (33.0)
Other initial diagnosis	4323 (42.5)	4338 (34.8)
SBP at admission (mmHg)		
Range	50–230	50–230
Mean (SD)	128.51 (27.57)	128.61 (27.90)
Median (IQR)	127 (110–145)	127 (110–145)
ECG that determined treatment		
ST segment elevation or LBBB	9000 (74.0)	9137 (73.2)
ST segment depression or T-wave changes only	1587 (13.0)	1677 (13.4)
Other acute abnormality or no acute changes	1575 (13.0)	1669 (13.4)
Heart rate at admission (b.p.m.)		
Range	25–180	25–180
Mean (SD)	88.34 (23.77)	88.42 (23.96)
Median (IQR)	85 (72–101)	85 (72–102)
Time of the day of admission (day/night)		
08.00 to < 20.00 hours	8290 (66.4)	8290 (66.4)
Killip class		Not imputed
Basal crepitations and/or elevated venous pressure	590 (14.2)	
Pulmonary oedema	217 (5.2)	
Cardiogenic shock	443 (10.6)	
No evidence of heart failure	2913 (70.0)	
Not applicable	0 (0)	
Care pathway variables,* n *(%)		
Hospital volume (OHCA cases per year)		
1–10 cases	5507 (44.1)	5507 (44.1)
11–24 cases	4509 (36.1)	4509 (36.1)
25–82 cases	2467 (19.8)	2467 (19.8)
Hospital pPCI capability		
pPCI capable	5937 (47.6)	5937 (47.6)
pPCI incapable	6546 (52.4)	6546 (52.4)
EMS response time (minutes)		
Range	0–180	0–180
Mean (SD)	11.99 (12.44)	11.86 (12.41)
Median (IQR)	9.00 (5–14)	8.00 (5–14)

continued

TABLE 15 Overview of participant characteristics for time to all-cause mortality cohort (pre-imputation and imputed data sets) (*continued*)

Variable	Pre-imputation[a]	Imputed data set (*N* = 12,483)
EMS travel distance (km)		
Range	0–242	0–242
Mean (SD)	11.90 (10.50)	12.29 (10.80)
Median (IQR)	8.78 (4.22–16.79)	9.27 (4.34–17.42)
Admitting consultant		
Cardiologist	8506 (69.2)	8615 (69.0)
Other consultant	3794 (30.8)	3868 (31.0)
Cardiological care during admission		
Yes	9243 (96.8)	10,597 (84.9)
Admission ward		
CCU	7742 (62.7)	7803 (62.5)
Cardiac ward – non-CCU	422 (3.4)	425 (3.4)
Intensive therapy unit	3393 (27.5)	3437 (27.5)
General medical ward or other	789 (6.4)	817 (6.5)
Died in ED	0 (0)	1 (0)
Time point of aspirin administration		
Already on aspirin/antiplatelet drug	1744 (15.0)	1867 (15.0)
Aspirin/antiplatelet given pre-hospital	4706 (40.5)	5016 (40.2)
Aspirin/antiplatelet given in-hospital	4512 (38.8)	4857 (38.9)
Not given	661 (5.7)	743 (6.0)
Place where ECG performed		
Pre hospital	8166 (77.9)	9084 (72.8)
In hospital	2317 (22.1)	3399 (27.2)
Thienopyridine inhibitor (in-hospital use)		
Yes	849 (12.1)	
Angiotensin-converting enzyme inhibitor (in-hospital use)		
Yes	4876 (46.0)	4876 (39.1)
Loop diuretic (in-hospital use)		
Yes	3286 (31.4)	3286 (26.3)
Reperfusion treatment and timing		
None	3482 (31.6)	4929 (39.6)
Thrombolysis (performed early)	919 (8.3)	919 (7.4)
Thrombolysis (performed late)	1479 (13.4)	1479 (11.8)
Thrombolysis (time missing)	254 (2.3)	254 (2.0)
pPCI (performed early)	3665 (33.3)	3665 (29.4)
pPCI (performed late)	698 (6.3)	698 (5.6)
pPCI (time missing)	519 (4.7)	519 (4.2)

TABLE 15 Overview of participant characteristics for time to all-cause mortality cohort (pre-imputation and imputed data sets) (*continued*)

Variable	Pre-imputation[a]	Imputed data set (*N* = 12,483)
Assessment at non-intervention hospital		Not imputed
No contact with non-interventional hospital	6117 (77.3)	
Patient remains in ambulance	25 (0.3)	
ED	1433 (18.1)	
Acute assessment unit	25 (0.3)	
CCU/cardiac facility	157 (2.0)	
Self-referral	27 (0.3)	
Already in hospital	83 (1.0)	
Other	47 (0.6)	
Assessment at intervention centre		Not imputed
Assessed in ED	1447 (27.2)	
Acute assessment unit	28 (0.5)	
CCU/cardiac facility	932 (17.5)	
Catheter laboratory	2902 (54.5)	
Already in hospital	18 (0.3)	
Intended reperfusion procedure		Not imputed
None	412 (7.5)	
Primary PCI	4558 (82.8)	
Rescue PCI	123 (2.2)	
Thrombolytic treatment	83 (1.5)	
Other coronary intervention	331 (6.0)	
Procedure performed		Not imputed
No angiography	217 (4.0)	
Angiography but no PCI	705 (13.1)	
Angiography and PCI	4461 (82.9)	
Reason for no angiography		Not imputed
Diagnosis not ACS	21 (15.0)	
Patient refused	9 (6.4)	
Complication before angiography could be performed	14 (10.0)	
Angiography inappropriate because of comorbidity	52 (37.1)	
Technical failure	2 (1.4)	
Laboratory unavailable	7 (5.0)	
Other	35 (25.0)	
Reason for no intervention		Not imputed
Complication before PCI could be performed	15 (2.1)	
Patient refused	5 (0.7)	

continued

TABLE 15 Overview of participant characteristics for time to all-cause mortality cohort (pre-imputation and imputed data sets) (*continued*)

Variable	Pre-imputation[a]	Imputed data set (*N* = 12,483)
PCI felt to be inappropriate	112 (16.0)	
Angiographically normal coronaries/mild disease/infarct related vessel unclear	255 (36.5)	
Surgical disease	209 (29.9)	
Technical failure	24 (3.4)	
Other	78 (11.2)	
Reason treatment not given		Not imputed
None	5115 (55.0)	
Ineligible ECG	2629 (28.3)	
Too late	69 (0.7)	
Risk of haemorrhage	224 (2.4)	
Uncontrolled hypertension	3 (0.03)	
Administrative failure	8 (0.1)	
Elective decision	456 (4.9)	
Patient refused treatment	6 (0.1)	
Other	610 (6.6)	
Unknown	185 (2.0)	
Discharge care variables,* n *(%)		
Discharge diagnosis		
ACS	11,865 (95.6)	11,935 (95.6)
Other	547 (4.4)	548 (4.4)
Echocardiography		
No	1866 (16.6)	2237 (17.9)
Yes or planned after discharge	9344 (83.4)	10,246 (82.1)
Coronary angiography		
Protocol driven investigation	3502 (32.1)	3921 (31.4)
Symptom driven investigation	2959 (27.1)	3440 (27.6)
Not performed	4442 (40.7)	5122 (41.0)
Coronary intervention		
PCI	3734 (36.8)	4758 (38.1)
CABG	456 (4.5)	595 (4.8)
Not performed or arranged	5964 (58.7)	7130 (57.1)
Followed up by cardiologist		
No cardiology follow up	612 (6.7)	1771 (14.2)
Cardiologist	8498 (93.3)	10,712 (85.8)
Cardiac rehabilitation		
No	1000 (9.4)	1456 (11.7)
Yes	9683 (90.6)	11,027 (88.3)

TABLE 15 Overview of participant characteristics for time to all-cause mortality cohort (pre-imputation and imputed data sets) (*continued*)

Variable	Pre-imputation[a]	Imputed data set (*N* = 12,483)
Discharged on beta-blocker		
No	977 (9.9)	3639 (29.2)
Yes	8844 (90.1)	8844 (70.8)
Discharged on angiotensin-converting enzyme inhibitor		
No	862 (8.8)	3585 (28.7)
Yes	8898 (91.2)	8898 (71.3)
Discharged on statin		
No	483 (4.9)	3144 (25.2)
Yes	9339 (95.1)	9339 (74.8)
Discharged on antiplatelet		
Dual antiplatelet	5652 (59.3)	5929 (47.5)
Single antiplatelet	3576 (37.5)	4338 (34.7)
No antiplatelet	307 (3.2)	2216 (17.8)
Smoking cessation advice		Not imputed
Non-smoker	6522 (71.5)	
No	179 (2.0)	
Yes	2417 (26.5)	
Dietary advice on discharge		Not imputed
No	556 (8.0)	
Not applicable	583 (8.3)	
Yes	5838 (83.7)	

b.p.m., beats per minute; SBP, systolic blood pressure.
a Sample size = 12,483 minus missing data.

In relation to discharge variables, most patients were discharged on the following drugs: a statin (*n* = 9339, 95.1%), angiotensin-converting-enzyme (ACE) inhibitor (*n* = 8898, 91.2%), antiplatelet therapy (dual therapy, *n* = 5652, 59.3%; monotherapy, *n* = 3576, 37.5%) and beta-blocker (*n* = 8844, 90.1%). In addition, patients were usually followed up by a cardiologist (*n* = 8498, 93.3%) and received cardiac rehabilitation (*n* = 9683, 90.6%).

Unadjusted analysis

The unadjusted analysis of time to all-cause mortality is included in *Table 16*.

Among demographic variables, both increased age and female sex were associated with worse outcome. Ethnicity was not associated with outcome. In contrast to other outcomes, although there was a trend to worse outcome as deprivation increased, this did not reach statistical significance in this analysis.

For medical history variables, most medical conditions (previous AMI, heart failure, chronic renal failure, previous angina pectoris, diabetes mellitus, cerebrovascular disease, hypertension, asthma or COPD, peripheral vascular disease, previous CABG and previous PCI) were associated with an increased mortality. For smoking status, the ever smoked category was associated with reduced mortality. Hypercholesterolaemia was not associated with mortality.

TABLE 16 Unadjusted analysis for time to all-cause mortality

Variable	Imputed data set	
	HR (95% CI), *p*-value	RE estimate (AIC)
Demographic variables		
Age (years)	1.075 (1.070 to 1.079), < 0.001	0.040 (1364)
Sex		0.068 (63)
Male	0.744 (0.672 to 0.823), < 0.001	
Female		
Ethnicity		0.067 (32)
Asian	0.797 (0.583 to 1.092), 0.158	
Black	1.017 (0.654 to 1.582), 0.940	
Other	0.883 (0.629 to 1.239), 0.471	
White		
IMD score	1.003 (1.000 to 1.006), 0.086	0.069 (35)
Medical history variables		
Smoking status		0.067 (70)
Ever smoked	0.742 (0.672 to 0.819), < 0.001	
Never smoked		
Diabetes status		0.067 (135)
Diabetic	1.909 (1.692 to 2.154), < 0.001	
Not diabetic		
Hypercholesterolaemia		0.069 (32)
Yes	0.998 (0.897 to 1.110), 0.969	
No		
Heart failure		0.064 (238)
Yes	3.861 (3.304 to 4.512), < 0.001	
No		
Cerebrovascular disease		0.065 (116)
Yes	2.224 (1.908 to 2.593), < 0.001	
No		
Previous AMI		0.059 (300)
Yes	2.405 (2.180 to 2.654), < 0.001	
No		
Asthma or COPD		0.067 (78)
Yes	1.623 (1.423 to 1.852), < 0.001	
No		
Chronic renal failure		0.068 (192)
Yes	4.107 (3.421 to 4.929), < 0.001	
No		

TABLE 16 Unadjusted analysis for time to all-cause mortality (*continued*)

Variable	Imputed data set	
	HR (95% CI), *p*-value	RE estimate (AIC)
Peripheral vascular disease		0.069 (73)
Yes	2.105 (1.717 to 2.582), < 0.001	
No		
Previous angina		0.061 (176)
Yes	1.978 (1.781 to 2.197), < 0.001	
No		
Previous PCI		0.071 (43)
Yes	1.361 (1.148 to 1.613), < 0.001	
No		
Previous CABG		0.065 (66)
Yes	1.797 (1.499 to 2.153), < 0.001	
No		
Hypertension		0.069 (81)
Yes	1.390 (1.269 to 1.522), < 0.001	
No		
Presenting characteristics of OCHA variables		
Time point of cardiac arrest		0.066 (57)
After ambulance arrival	0.791 (0.722 to 0.867), < 0.001	
Before ambulance arrival		
Cardiac arrest rhythm		0.065 (115)
PEA	1.193 (0.850 to 1.675), 0.308	
VF/VT	0.472 (0.371 to 0.600), < 0.001	
Asystole		
Serum glucose (mmol/l)	1.031 (1.017 to 1.046), < 0.001	0.067 (66)
Creatinine (μmol/l)	1.004 (1.002 to 1.005), < 0.001	0.074 (162)
Haemoglobin (g/dl)	0.823 (0.797 to 0.851), < 0.001	0.076 (350)
Serum cholesterol (mmol/l)	0.760 (0.727 to 0.794), < 0.001	0.073 (273)
Admission diagnosis		0.030 (264)
Other diagnosis	2.373 (2.070 to 2.720), < 0.001	
Definite MI (other infarction site)	1.362 (1.147 to 1.616), < 0.001	
Definite MI (anterior infarction)		
SBP at admission (mmHg)	0.998 (0.996 to 1.000), 0.035	0.071 (38)
ECG that determined treatment		0.043 (148)
ST segment elevation or LBBB	0.615 (0.544 to 0.694), < 0.001	
Other acute abnormality or no acute changes	1.102 (0.948 to 1.280), 0.205	
ST segment depression or T-wave changes only		

continued

TABLE 16 Unadjusted analysis for time to all-cause mortality (*continued*)

Variable	Imputed data set	
	HR (95% CI), *p*-value	RE estimate (AIC)
Heart rate at admission (b.p.m.)	1.001 (0.999 to 1.003), 0.322	0.069 (33)
Time of the day of admission		0.070 (38)
20.00 to < 08.00 hours	0.884 (0.803 to 0.974), 0.012	
08.00 to < 20.00 hours		
Year	0.987 (0.973 to 1.002), 0.087	0.063 (34)
Care pathway variables		
Hospital volume (OHCA cases per year)		0.051 (42)
0–10 cases	1.330 (1.090 to 1.623), 0.005	
11–24 cases	1.081 (0.872 to 1.341), 0.476	
25–82 cases		
Hospital pPCI capability		0.032 (65)
pPCI capable	0.703 (0.629 to 0.785), < 0.001	
pPCI incapable		
EMS response time (minutes)	0.999 (0.995 to 1.004), 0.784	0.069 (32)
EMS travel distance (km)	0.992 (0.987 to 0.997), 0.003	0.062 (43)
Admitting consultant		0.049 (57)
Cardiologist	0.765 (0.692 to 0.845), < 0.001	
Other consultant		
Admission ward		0.071 (97)
Intensive therapy unit	1.050 (0.943 to 1.170), 0.373	
General medical ward or other	1.917 (1.647 to 2.232), < 0.001	
Cardiac ward – non CCU	1.590 (1.188 to 2.127), 0.002	
CCU		
Place where ECG performed		0.062 (51)
In hospital	1.282 (1.125 to 1.460), < 0.001	
Pre hospital		
Reperfusion treatment and timing		0.028 (269)
Thrombolysis (performed early)	0.393 (0.320 to 0.481), < 0.001	
Thrombolysis (performed late)	0.553 (0.479 to 0.639), < 0.001	
Thrombolysis (time missing)	0.604 (0.438 to 0.832), 0.002	
pPCI (performed early)	0.455 (0.399 to 0.519), < 0.001	
pPCI (performed late)	0.451 (0.348 to 0.585), < 0.001	
pPCI (time missing)	0.828 (0.635 to 1.079), 0.161	
None		

TABLE 16 Unadjusted analysis for time to all-cause mortality (*continued*)

Variable	Imputed data set	
	HR (95% CI), *p*-value	RE estimate (AIC)
Discharge variables		
Discharge diagnosis		0.069 (52)
ACS	0.627 (0.517 to 0.761), < 0.001	
Other diagnosis		
Echocardiography		0.065 (54)
Done or planned	0.763 (0.679 to 0.857), < 0.001	
No		
Coronary angiography		0.088 (222)
Protocol driven	0.542 (0.478 to 0.614), < 0.001	
Symptom driven	0.475 (0.411 to 0.549), < 0.001	
None		
Followed up by cardiologist		0.046 (192)
Yes	0.493 (0.430 to 0.567), < 0.001	
No		
Cardiac rehabilitation		0.071 (256)
Yes	0.401 (0.350 to 0.461), < 0.001	
No		
Discharged on beta-blocker		0.047 (187)
Yes	0.545 (0.496 to 0.598), < 0.001	
No		
Discharged on angiotensin-converting enzyme inhibitor		0.050 (182)
Yes	0.547 (0.498 to 0.601), < 0.001	
No		
Discharged on statin		0.054 (124)
Yes	0.609 (0.553 to 0.672), < 0.001	
No		
Discharged on aspirin		0.050 (116)
Yes	0.618 (0.559 to 0.682), < 0.001	
No		
Discharged on thienopyridine inhibitor or ticagrelor		0.042 (89)
Yes	0.674 (0.605 to 0.752), < 0.001	
No		
Antiplatelet therapy on discharge		0.034 (148)
Dual antiplatelet	0.497 (0.435 to 0.568), < 0.001	
Single antiplatelet	0.780 (0.691 to 0.882), < 0.001	
No antiplatelet		

b.p.m., beats per minute; SBP, systolic blood pressure.

For presenting characteristics, most results were similar to the unadjusted in-hospital mortality with factors such as cardiac arrest following ambulance arrival, initial rhythm of VF/VT, and increased haemoglobin levels associated with improved survival. There was an association between admission between 20.00 and 07.59 and improved outcome.

For care pathway variables, results were again similar to the unadjusted in-hospital mortality analysis. Factors such as reperfusion therapy (both pPCI and thrombolysis) and admission under a cardiologist were associated with reduced mortality. However, in this cohort, patient admission to very low volume hospitals was associated with worse outcome, while admission to a PCI centre was associated with improved outcome. Importantly, the need to be admitted to an intensive care unit did not influence long-term outcome.

Discharge interventions such as drugs (antiplatelet therapy, statins, ACE inhibitor, beta-blockers) were all associated with improved outcome. Similarly, follow-up by a cardiologist and cardiac rehabilitation were associated with improved outcome.

Adjusted analysis

The results for the adjusted analysis are included as *Table 17*.

For demographic variables, increased age and deprivation were predictive of increased mortality, but ethnicity and sex were not associated with mortality.

In the adjusted model, only four medical history variables (previous AMI, heart failure, diabetes mellitus, and asthma or COPD) were associated with worse outcome. In addition, the effect estimate for smoking status changed direction in this model so the ever smoked category became associated with increased mortality. The remaining medical conditions were not associated with outcome.

In the presenting characteristics of OHCA variable section, laboratory values (haemoglobin, cholesterol, glucose, creatinine) were associated with the outcome, although the effect size was small. There was a trend towards improved outcome when the arrest occurred after ambulance arrival, although this did not reach statistical significance. In this model, time of day of admission was not associated with outcome. The year slope suggested worse outcome over time.

None of the care pathway variables was associated with time to all-cause mortality. Although, generally, the effect estimate direction was the same as in previous models, the estimate was closer to one and the result was not statistically significant.

The discharge care variables that do not predict hazard of death are echocardiography, discharge diagnosis, antiplatelet prescription and statin prescription. The provision of coronary angiography, cardiology follow-up and cardiac rehabilitation were associated with reduced the risk of mortality. Similarly, discharge on beta-blocker or ACE inhibitor were associated with improved outcome.

Sensitivity analyses

We undertook a complete-case analysis of 1381 (11.1% of cohort) patients with complete data (*Table 17*). The results were broadly similar to the adjusted analysis of the imputed data set, although some effects switched direction and/or became non-significant. For example, in the imputed data set, the HR for previous AMI was 1.394 (95% CI 1.2 to 1.6), but the HR was 0.850 (95% CI 0.5 to 1.5) in the complete-case analysis.

TABLE 17 Adjusted analysis for time to all-cause mortality

Predictor variable	HR (95% CI), *p*-value	
	Primary analysis: analysis after imputation ($n = 12,483$)	Complete-case analysis ($n = 1381$)
Demographic variables		
Age (years)	1.061 (1.055 to 1.066), < 0.001	1.080 (1.059 to 1.102), < 0.001
Sex		
Male	1.062 (0.942 to 1.197), 0.328	1.373 (0.841 to 2.243), 0.205
Female[a]		
Ethnicity		
Asian	0.999 (0.722 to 1.381), 0.994	0.875 (0.307 to 2.495), 0.802
Black	0.888 (0.562 to 1.403), 0.610	1.064 (0.137 to 8.284), 0.953
Other	0.875 (0.613 to 1.250), 0.464	1.742 (0.388 to 7.816), 0.469
White[a]		
IMD score	1.007 (1.003 to 1.010), < 0.001	1.012 (1.000 to 1.024), 0.053
Medical history variables		
Smoking status		
Ever smoked	1.122 (1.006 to 1.251), 0.039	1.435 (0.958 to 2.149), 0.080
Never smoked[a]		
Diabetes status		
Diabetic	1.163 (1.008 to 1.342), 0.038	1.394 (0.822 to 2.362), 0.217
Not diabetic[a]		
Heart failure		
Yes	1.428 (1.196 to 1.705), < 0.001	2.926 (1.373 to 6.238), 0.005
No[a]		
Cerebrovascular disease		
Yes	1.132 (0.963 to 1.331), 0.132	1.750 (1.017 to 3.009), 0.043
No[a]		
Previous AMI		
Yes	1.394 (1.232 to 1.576), < 0.001	0.850 (0.497 to 1.453), 0.553
No[a]		
Asthma or COPD		
Yes	1.266 (1.102 to 1.454), 0.001	1.366 (0.805 to 2.319), 0.248
No[a]		
Chronic renal failure		
Yes	1.163 (0.922 to 1.467), 0.204	1.298 (0.534 to 3.156), 0.565
No[a]		

continued

TABLE 17 Adjusted analysis for time to all-cause mortality (*continued*)

Predictor variable	HR (95% CI), *p*-value	
	Primary analysis: analysis after imputation (*n* = 12,483)	Complete-case analysis (*n* = 1381)
Peripheral vascular disease		
Yes	1.163 (0.937 to 1.443), 0.171	1.149 (0.474 to 2.786), 0.759
No[a]		
Previous angina		
Yes	1.012 (0.892 to 1.147), 0.856	0.980 (0.583 to 1.647), 0.939
No		
Previous PCI		
Yes	1.034 (0.856 to 1.248), 0.731	1.441 (0.725 to 2.865), 0.298
No[a]		
Previous CABG		
Yes	0.960 (0.788 to 1.169), 0.683	1.152 (0.539 to 2.464), 0.715
No[a]		
Presenting characteristics of patients and OHCA variables		
Time point of cardiac arrest		
After ambulance arrival	0.907 (0.815 to 1.010), 0.074	0.849 (0.548 to 1.315), 0.463
Before ambulance arrival[a]		
Cardiac arrest rhythm		
PEA	1.099 (0.774 to 1.560), 0.597	0.922 (0.167 to 5.102), 0.926
VF/VT	0.772 (0.598 to 0.998), 0.048	0.821 (0.226 to 2.975), 0.764
Asystole[a]		
Serum glucose (mmol/l)	1.017 (1.003 to 1.032), 0.019	0.991 (0.941 to 1.044), 0.737
Creatinine (μmol/l)	1.001 (1.000 to 1.002), 0.005	1.011 (1.006 to 1.017), < 0.001
Haemoglobin (g/dl)	0.942 (0.908 to 0.977), 0.001	0.862 (0.775 to 0.959), 0.006
Serum cholesterol (mmol/l)	0.925 (0.879 to 0.973), 0.003	0.987 (0.845 to 1.152), 0.866
Admission diagnosis		
Other diagnosis	1.300 (1.086 to 1.556), 0.004	1.079 (0.529 to 2.197), 0.835
Definite MI – other infarct site	1.167 (0.977 to 1.395), 0.089	0.909 (0.571 to 1.447), 0.688
Definite MI – anterior infarct[a]		
SBP at admission (mmHg)	0.997 (0.995 to 0.999), 0.007	0.997 (0.991 to 1.004), 0.451
ECG determining treatment		
ST segment elevation or LBBB	1.039 (0.888 to 1.216), 0.635	1.234 (0.634 to 2.401), 0.536
ST segment depression or T-wave changes only	0.992 (0.852 to 1.155), 0.919	0.775 (0.382 to 1.574), 0.481
Other acute abnormality or No acute changes[a]		
Heart rate at admission (b.p.m.)	1.004 (1.002 to 1.006), < 0.001	1.005 (0.997 to 1.013), 0.200

TABLE 17 Adjusted analysis for time to all-cause mortality (*continued*)

Predictor variable	HR (95% CI), *p*-value	
	Primary analysis: analysis after imputation ($n = 12,483$)	Complete-case analysis ($n = 1381$)
Time of day of admission (day/night)		
20.00 to < 08.00 hours	1.016 (0.919 to 1.123), 0.761	1.416 (0.967 to 2.072), 0.074
08.00 to < 20.00[a] hours		
Year	1.045 (1.019 to 1.071), 0.001	1.036 (0.902 to 1.190), 0.618
Care pathway variables		
Hospital volume (OHCA cases per year)		
0–10 cases	0.998 (0.800 to 1.247), 0.989	1.125 (0.548 to 2.312), 0.748
1–24 cases	1.067 (0.863 to 1.318), 0.550	0.970 (0.538 to 1.748), 0.918
25–82 cases[a]		
Hospital pPCI capability		
pPCI capable	0.919 (0.762 to 1.108), 0.375	0.834 (0.442 to 1.572), 0.574
pPCI incapable[a]		
EMS response time (minutes)	1.001 (0.997 to 1.005), 0.653	0.998 (0.979 to 1.018), 0.867
EMS travel distance (km)	1.000 (0.994 to 1.006), 0.985	0.995 (0.975 to 1.014), 0.585
Admitting consultant		
Cardiologist	1.120 (0.992 to 1.266), 0.068	0.866 (0.505 to 1.486), 0.602
Other consultant[a]		
Admission ward		
Intensive therapy unit	1.022 (0.897 to 1.166), 0.741	0.840 (0.477 to 1.477), 0.544
General ward or other	1.212 (1.026 to 1.431), 0.024	1.302 (0.541 to 3.133), 0.557
Cardiac ward – non-CCU	1.192 (0.896 to 1.585), 0.229	1.107 (0.344 to 3.566), 0.864
CCU[a]		
Place where ECG performed		
In hospital	0.912 (0.799 to 1.042), 0.175	1.198 (0.679 to 2.114), 0.533
Pre hospital[a]		
Reperfusion treatment and timing		
Thrombolysis (performed early)	0.895 (0.703 to 1.140), 0.371	0.434 (0.130 to 1.448), 0.175
Thrombolysis (performed late)	0.925 (0.773 to 1.108), 0.399	0.685 (0.316 to 1.484), 0.337
Thrombolysis (time missing)	1.025 (0.733 to 1.434), 0.833	[b]
pPCI (performed early)	0.972 (0.798 to 1.185), 0.782	0.936 (0.480 to 1.826), 0.846
pPCI (performed late)	0.833 (0.621 to 1.118), 0.224	0.502 (0.162 to 1.556), 0.233
pPCI (time missing)	1.171 (0.873 to 1.571), 0.293	3.278 (1.089 to 9.865), 0.035
None[a]		

continued

TABLE 17 Adjusted analysis for time to all-cause mortality (*continued*)

Predictor variable	HR (95% CI), *p*-value	
	Primary analysis: analysis after imputation (*n* = 12,483)	Complete-case analysis (*n* = 1381)
Discharge care variables		
Discharge diagnosis		
ACS	1.168 (0.942 to 1.447), 0.156	1.604 (0.366 to 7.036), 0.531
Other diagnosis[a]		
Echocardiography		
Done or planned	0.973 (0.859 to 1.102), 0.663	1.135 (0.607 to 2.120), 0.692
No[a]		
Coronary angiography		
Protocol driven	0.678 (0.592 to 0.777), < 0.001	0.980 (0.618 to 1.555), 0.931
Symptom driven	0.657 (0.563 to 0.767), < 0.001	1.066 (0.640 to 1.776), 0.806
None[a]		
Followed by a cardiologist		
Yes	0.704 (0.586 to 0.844), < 0.001	0.374 (0.180 to 0.776), 0.008
No[a]		
Cardiac rehabilitation		
Yes	0.640 (0.541 to 0.757), < 0.001	0.737 (0.340 to 1.597), 0.439
No[a]		
Discharged on beta-blocker		
Yes	0.833 (0.725 to 0.956), 0.010	0.824 (0.460 to 1.474), 0.514
No[a]		
Discharged on ACE inhibitor		
Yes	0.780 (0.677 to 0.899), 0.001	0.673 (0.373 to 1.216), 0.190
No[a]		
Discharged on statin		
Yes	1.004 (0.843 to 1.195), 0.967	0.343 (0.149 to 0.791), 0.012
No[a]		
Antiplatelet therapy on discharge		
Dual antiplatelet	0.823 (0.654 to 1.034), 0.094	1.291 (0.483 to 3.452), 0.610
Single antiplatelet	1.055 (0.887 to 1.253), 0.545	1.268 (0.458 to 3.513), 0.648
No antiplatelet[a]		
RE estimate (median AIC)	0.033[c] (2084)[c]	0.000 (155)

b.p.m., beats per minute; SBP, systolic blood pressure.
a Reference category.
b The two patients in this category were recategorised to the category 'Thrombolysis (performed late)' to enable model convergence.
c Median from 25 imputed data sets.

Chapter 5 Discussion

Summary of findings

In this cohort study, we included data from 17,604 patients who had an OHCA secondary to ACS between 2003 and 2015, and who were included in the MINAP data set. The study showed evidence of variability in survival between hospitals. Among hospitals with at least 60 cases over the study period, hospital survival rates ranged from 34% to 89% (overall survival rate was 71.3%). Modelling that adjusted for patient and treatment characteristics could account for only 36.1% of this variability.

We used an imputed data set to identify modifiable and non-modifiable factors associated with our three outcomes (in-hospital mortality, neurological outcome and time to all-cause mortality).

For our primary outcome (in-hospital mortality), variables associated with reduced mortality outcome included male sex, hypercholesterolaemia, hypertension, OHCA after ambulance arrival, increased haemoglobin level, systolic blood pressure and heart rate, increased distance to hospital, arrest rhythm of VF/VT, reperfusion treatment and admission under a cardiologist. Factors associated with increased mortality included increased age, increased deprivation, heart failure, cerebrovascular disease, peripheral vascular disease, asthma/COPD, increased glucose level, ECG showing ST elevation or LBBB and treatment in a PCI centre. Key factors unrelated to outcome included ethnicity, admission diagnosis, time of day of admission, hospital volume and place where ECG was performed. In sensitivity analyses, results were similar to the main analysis. In patients who had a STEMI, reperfusion treatment was associated with improved outcome, although, paradoxically, treatment in a pPCI centre was associated with worse outcome. In contrast, for patients who did not have a STEMI, both reperfusion treatment and treatment in a pPCI centre had no association with outcome.

For neurological outcome, the results of the adjusted analysis were similar to those of our primary outcome of in-hospital mortality. However, pre-hospital ECG, compared with in-hospital ECG, was associated with improved outcome. Furthermore, neither treatment in a pPCI centre nor EMS transport distance was associated with outcome. In sensitivity analyses, treatment in a pPCI centre was associated with worse outcome for STEMI patients, but improved outcome in other patients. Reperfusion treatment in patients who did not have a STEMI was not associated with outcome.

The analysis of time to all-cause mortality included only patients who survived to hospital discharge. In this analysis, demographic variables (age, deprivation) and past medical history (heart failure, cerebrovascular disease, diabetes mellitus, asthma or COPD, smoking status) were associated with outcome. Some presenting OHCA characteristic variables were associated with outcome (haemoglobin, glucose, creatinine, diagnosis). However, none of the care pathway variables was associated with long-term mortality, suggesting that in-hospital treatment influences hospital survival but not long-term mortality following survival to hospital discharge. Discharge interventions, such as drug therapy (beta-blocker, ACE inhibitor), cardiology follow-up and cardiac rehabilitation, did influence outcome, although antiplatelet therapy did not influence the long-term outcome.

Modifiable factors

The decision as to where to transport a patient following successful resuscitation from OHCA is challenging. For pre-hospital clinicians, the decision requires careful consideration of the potential benefits to the patient of access to specialist services and clinical teams at a large centre versus the risk of longer transport times. In our analysis, we used categorisation as a pPCI centre and hospital volume as markers of large, specialist centres. In our analysis, neither of these factors was associated with improved outcome and our primary analysis found that admission to a pPCI centre was associated with worse outcome.

In other health areas, such as trauma, surgery and critical care, increased patient volume is associated with improved outcomes at a hospital level.[86–89] In MI, there appears to be similar evidence of a relationship between increased hospital volume and improved patient outcome.[90,91] Furthermore, in patients treated with pPCI, increased hospital PCI volume is also associated with improved survival, although there is no association in patients treated with thrombolytics.[37,38,92] Based on such data, the British Cardiovascular Intervention Society recommend that hospitals must undertake at least 100 pPCIs per year to function as a pPCI centre.[72]

For OHCA, however, there is inconsistency between studies as to the relationship between hospital volume and its effect on patient outcome.[93–98] For example, Schober *et al.*[94] included 2238 OHCA patients admitted to seven hospitals in Vienna, Austria, and found that the highest volume centre reported the highest survival rate. In contrast, Cudnik *et al.*[93] analysed data from 4125 patients with OHCA of cardiac origin admitted to 155 US hospitals, but found no association between volume and patient outcome. Instead of volume, it may be that for OHCA patients it is the specialist services (e.g. critical care, PCI) that are available at the treating hospital, rather than its volume, that are most associated with patient outcome.[30,34,98–103] For example, Stub *et al.*[34] scored 111 North American hospitals based on the availability of coronary angiography, targeted temperature management and use of delayed prognostication, and correlated these performance measures with 3252 OHCA cases from the Resuscitation Outcomes Consortium. In an adjusted analysis, the authors reported that the highest performing hospitals reported the highest rates of hospital survival and survival with good neurological outcome.

This correlates with our finding that, although admission to a pPCI centre may be associated with increased mortality, the actual delivery of reperfusion treatment appeared to be the most important modifiable factor associated with improved survival in this patient cohort, particularly when delivered early. In our patient cohort, over 50% of patients received reperfusion treatment. Both early thrombolysis and primary PCI seemed to significantly reduce the risk of in-hospital death across all cases, although sensitivity analyses suggested that this effect was limited to STEMI cases. This supports current recommendations that resuscitated OHCA patients with a STEMI should be considered for reperfusion.[73,74,104] In contrast, guidelines for OHCA patients who do not have a STEMI recommend that these patients may be considered for reperfusion once non-cardiac causes for the OHCA have been ruled out.[74,104,105] This is seemingly driven by evidence that these OHCA patients with cardiac arrest resulting from a cardiac cause frequently have an occluded coronary vessel.[16,99,106,107] However, observational studies of the effect of PCI following OHCA in patients who have not had a STEMI have produced mixed results, with some finding evidence of a survival benefit while others report that there is no effect on survival.[16,107–110]

Over the course of our study, we noted that the use of thrombolysis decreased as the use of pPCI increased, such that overall there was an increase in the use of reperfusion treatment. In 2015, three-quarters of patients presenting with a STEMI in the context of OHCA received pPCI. In contrast, less than 15% of patients who did not present with a STEMI received pPCI. This is consistent with data from across the MINAP data set and correlates with data showing that pPCI is the preferred reperfusion strategy in STEMI.[48,111,112]

Following successful resuscitation, the management of OHCA patients may be complex owing to post-cardiac-arrest syndrome.[21] This is evidenced in an observational study of 248 post-cardiac-arrest patients transferred by a critical care transfer team in which a critical clinical event occurred in 23% of patients and 6% suffered a rearrest.[113] There is therefore a possible risk associated with prolonged transportation. Counterintuitively, our primary outcome analysis suggested that for each kilometre travelled, mortality reduced (OR of death 0.994, 95% CI 0.989–0.999). The explanation for this finding is unclear, particularly as it contrasts with a previous observational study of 10,315 critically ill patients transported by English Ambulance Services between 1997 and 2001, which found that each additional 10 km travelled was associated with an absolute increase in mortality of 1%.[114] Importantly, however, this study excluded OHCA patients. International data from OHCA patients suggests that there is no association (benefit or harm) between distance or time travelled and patient outcome.[115–117]

There are a number of possible explanations for this unexpected finding. The first is that the analysis was based on the assumption that cardiac arrests included in the analysis occurred in the home. We chose this approach, as MINAP records only the patient's home postcode rather than the location of the cardiac arrest. This approach seemed reasonable as other studies show that most cardiac arrests occur in the home, although we are unable to test this in our population.[5,24] Interestingly, the median transport distance reported in this study was only slightly longer than that reported in the study by Nicholl *et al.*[114] (median 5 km vs. 8 km). Second, this may be a type I statistical error, particularly given the small effect size and the associated 95% CI, which was close to 1. Notably, our reported point estimate was similar to the point estimates reported in other studies.[115,116] A third explanation is that this is a true effect due to patients being transferred longer distances to specialist centres for treatment, which were associated with improved outcome, but the effect was confounded by other variables. In Cudnik *et al.*'s[115] observational study of 7540 patients who had suffered an OHCA resulting from a cardiac cause, there was evidence of an association between being transferred to the nearest hospital, rather than a more distant hospital, and increased mortality.[115]

In this study, the use of pre-hospital ECG was not associated with improved survival in the analysis of the primary outcome, but was associated with improved neurological survival in our secondary analysis. The use of pre-hospital ECG is recommended by international guidelines to triage the patient to a specialist centre for pPCI in the event that the ECG shows a STEMI.[73,104] A previous study demonstrated how the use of pre-hospital ECG was associated with increased timeliness of pPCI and reduced mortality.[51]

Synthesising these data surrounding pPCI centre, reperfusion treatment, hospital volume, pre-hospital ECG and EMS transport distance is challenging. However, it would seem reasonable to suggest patients in this cohort should receive a pre-hospital ECG following ROSC in order to triage them to appropriate care. If there is an indication for reperfusion treatment, then it would be reasonable to transfer the patient to a specialist centre to receive this treatment. If there is uncertainty as to the cause of the cardiac arrest and the patient's ECG does not show ST elevation, then the patient may be transferred to the nearest hospital with appropriate facilities to meet the patient's care needs (e.g. critical care, cardiology services), which may also be beneficial for relatives. Several clinical trials are planned or in progress to address the role of pPCI among patients with NSTEMI, which should help to reduce uncertainty about how best to manage this patient group (e.g. Patterson *et al.*[42]).

In patients who survived to leave hospital, discharge interventions were strongly associated with long-term mortality, such as discharge on a beta-blocker and ACE inhibitor and referral to coronary rehabilitation. These interventions are recommended in current guidelines.[73,105] In contrast, antiplatelet therapy and statins on discharge were not associated with long-term mortality in our study. The reason for this finding is unclear as there is good evidence that they are effective in reducing long-term mortality following MI.[118,119] This may be partly explained by a selection bias, as patients with a better long-term prognosis, as indicated by blood pressure and renal function, may be more likely to be prescribed beta-blockers and ACE inhibitors, whereas prescription of antiplatelets and statins may be less influenced by these factors. We also acknowledge that our antiplatelet analysis may have been affected by the non-availability of pre-2009 thienopyridine inhibitor data. Furthermore, a large proportion of patients received both aspirin and statins on discharge, so our analyses may have had insufficient power to reliably detect a difference between groups.

The findings from this study inform the recent National Framework[120] to improve care of people with OHCA in England. The framework recommends that patients who achieve ROSC are transferred to recognised centres of care that have the expertise and facilities to provide round-the-clock access to cardiac catheterisation and an intensive care unit. Although the present study did not find evidence of improved outcomes based on PCI capability or hospital volume, no harm was seen from increasing transfer distance from scene to hospital.

Non-modifiable factors

In our study, a number of demographic and medical history variables were associated with both in-hospital and long-term mortality. Our finding that women were less likely to survive than men conflicts with the results of a recently published systematic review, which compared male and female survival following cardiac arrest.[121] The meta-analysis of 409,323 patients from 13 studies reported that women were more likely to survive cardiac arrest (OR for survival 1.10, 95% CI 1.03 to 1.20), despite having worse baseline characteristics such as increased age and being more likely to have a cardiac arrest at home and be in a non-shockable rhythm. A sensitivity analysis that was limited to OHCA resulting from a cardiac cause produced similar findings.

In contrast, female sex in the MI literature is usually associated with worse outcome.[122–125] Women who present with MI are typically older and have more comorbidities, but there is also evidence that women are less likely to receive evidence-based interventions such as a pre-hospital ECG or PCI, which may explain the apparent discrepancy in outcome.[51,122–124,126,127] In our study, we did not examine sex differences in relation to demographics or treatment delivery.

Our study found that social deprivation was associated with increased hospital mortality and time to all-cause mortality. This finding has been reported previously in both the MI and cardiac arrest literature.[128–134] However, this relationship is likely to be complex given that factors such as race and lifestyle may be associated with both socioeconomic class and risk of cardiovascular disease.[135,136] As is the case with sex, this difference in survival may be partly explained by differences in treatment, such that patients who are more socially deprived are less likely to receive key interventions such as bystander CPR and PCI.[130,132,134,137–140] For example, an observational study of OHCA undertaken in the north-east of England reported that bystander CPR rates ranged from 14.5% in the most deprived areas to 23.2% in the least deprived areas.[138] The studies that describe a relationship between PCI and social deprivation were undertaken in health systems that are markedly different from the UK, such that the generalisability of these data to the UK setting is unclear. Indeed, a Scottish study found no evidence of an association between socioeconomic class and use of coronary angiography and intervention following MI.[141] Our analysis found that social deprivation was associated with mortality even after adjustment for baseline and treatment variables, suggesting that the precise mechanism by which social deprivation is associated with mortality is likely to be complex.

Study strengths and limitations

The key strength of our study was the use of robust statistical methods on a large national audit data set to answer an important research question. The inclusion of > 17,000 patients has enabled us to draw important conclusions about factors that may explain variability in survival following OHCA attributable to ACS.

Nevertheless, the study has a number of limitations.

First, our study examined a cohort of patients who had OHCA secondary to ACS. Our cohort included 17,604 patients, of whom 12,557 (71.3%) survived to hospital discharge. Identification of patients with ACS following OHCA as ECG findings may be non-specific or difficult to interpret reliably. Over the period of our study, a total of 1,127,140 individual admissions were included in the MINAP data set. Extrapolating epidemiological data from the National Out of Hospital Cardiac Arrest registry shows that, over the same period, there were approximately 210,000 OHCA of presumed cardiac cause that were treated by English ambulance services, of which approximately 54,100 (26%) achieved ROSC and 16,600 (8%) survived to hospital discharge. In our cohort, 6225 patients were admitted to an intensive care unit. Over a similar period (2004–14), there were 29,621 patients admitted to UK intensive care units following OHCA due to any cause.[142] For this reason, the findings of this study cannot be reliably extrapolated to either patients who have an OHCA secondary to other conditions or patients with myocardial ischaemia who do not have an OHCA.

Second, the primary purpose of MINAP is the collection of data on myocardial ischaemia for audit purposes to assess quality of care. It was not, however, developed for the primary purpose of research, nor was it intended to be an audit to assess quality of care in OHCA patients. As such, despite MINAP capturing a large data set, it does not record certain key data relating to both the cardiac arrest event and hospital treatment. These important missing data items include the location of the cardiac arrest, use of bystander CPR, whether or not the arrest was monitored or witnessed, and intensive care treatments such as the use of targeted temperature management.[12] There is an urgent need to link the MINAP data set with other relevant data sets, such as the Out of Hospital Cardiac Arrest Outcomes project and the Intensive Care National Audit and Research Centre case mix programme, to provide more detailed information about this patient group.[143,144]

Third, owing to regulations regarding the release of patient-identifiable data, we experienced restrictions in what data could be released by NICOR. For example, we were not permitted data on the day of the week of hospital admission, nor were we able to link hospital characteristics to the study data set. The study group was concerned by a lack of clarity as to precisely what combinations of data could be released and would welcome the development of guidance around this issue.

Fourth, we are aware of differences between hospitals in relation to the methods used to identify patients. Anecdotally, some hospitals include only patients admitted to the CCU or who are managed by a cardiology consultant, while other hospitals take an active approach to identify all patients with ACS (e.g. follow-up of all positive troponin results reported by the hospital pathology laboratory). This leads to under-reporting of patients, particularly patients who do not have a STEMI.[48,145] This issue has been recognised by MINAP in annual reports.[48] The number of cardiac arrests per year has been relatively static for the last 10 years, yet we observed that the number of cases recorded in MINAP more than doubled over this period. Interestingly, the largest rise in cases was among patients who had a STEMI, which is the group reported by MINAP to be most reliably reported. The precise reason for this increase in cases is unclear, but may be improved case ascertainment or, alternatively, increasing cardiac intervention among this cohort. As such, there is a high risk of ascertainment bias, particularly in the early years of data capture, and this may explain some of the unexplained variability in survival between hospitals.

Finally, and most importantly, this was an observational study. Despite the use of statistical techniques to adjust for known potential confounders, our results may have been affected by unmeasured residual confounders (such as those outlined in point two above) for which we were unable to adjust. This is exemplified by the variable 'time point of aspirin administration' in which, in unadjusted analyses, the OR associated with giving aspirin prior to hospital arrival compared with not giving aspirin was 0.067 (95% CI 0.06 to 0.08). In contrast, the ISIS-2 clinical trial of aspirin in AMI reported that aspirin reduced vascular deaths by 23%.[146] On this basis, we concluded that the variable was likely to be heavily confounded (e.g. patient's consciousness level and associated ability to take aspirin) and, thus, not included in the modelling. The extent to which other variables may have been confounded is unknown. As such, consideration should be given to testing our key findings in robust clinical trials.

Patient and public involvement

Our clinical academic team was fortunate to be joined by two patient and public involvement (PPI) representatives who ensured that the interests of patients were central to all study decision-making from the inception of the project. This included the incorporation of neurological outcome as an outcome, as it was considered important to patients and is often under-reported in the cardiac arrest literature.[54] Bob Ewings and John Long sat as full members of the study team. Our experience in this project highlighted the value in engaging PPI representatives at an early stage of the study design with ongoing active involvement throughout the study period.

Chapter 6 Conclusions

The number of patients captured in the MINAP database following OHCA has doubled over the last decade, with > 2000 cases recorded in 2014. The proportion of patients treated with reperfusion therapy increased from 20% to 60%. This was primarily attributable to an increase in the proportion of STEMI patients treated with PCI since 2006 and a concurrent reduction in the proportion treated with thrombolysis. The overall rate of survival to discharge was 71.3% of patients, but there was variability in survival between hospitals (range 34–89%; median 71.4%, IQR 60.7–76.9%). Survival with favourable neurological outcome occurred in 59.1% of cases, which also varied between hospitals (range 13–84%; median 58.9%, IQR 44.2–66.8%).

Multivariate analysis of patient demographics, medical history, presenting characteristics and care pathway captured in the MINAP database was able to explain 36% of variation in outcome. The majority of patients underwent 12-lead ECG prior to hospital admission. The present study found no evidence that the location where the ECG was recorded affected outcome. Nevertheless, pragmatically, ECG prior to transfer to hospital facilitates informs decision-making about the most appropriate destination hospital and presents the opportunity to provide an early alert to the receiving hospital.

The evaluation of modifiable factors in the patient journey produced conflicting results. Although there was no evidence to suggest harm from increased transfer distances, centre volume and specialist services (PCI) either had no effect or were associated with worse outcomes. Early reperfusion, whether by thrombolysis or PCI, was associated with improved outcomes, primarily in patients with evidence of STEMI.

Recommendations for future research

Our research has identified the need for further research in the following areas:

1. The clinical effectiveness and cost-effectiveness of an invasive reperfusion strategy in patients with resuscitated OHCA of cardiac cause who have not had a STEMI.
2. Factors affecting the decision to use an invasive perfusion strategy by cardiologists following OHCA.
3. Factors that influence survival following OHCA using observational data from multiple data sets (e.g. MINAP and Out of Hospital Cardiac Arrest Outcomes project).
4. The differences in characteristics and decision-making processes of clinicians at high- and low-performing hospitals.
5. The risk of adverse clinical events (e.g. rearrest) associated with prolonged transportation following OHCA.
6. Paramedic experiences of decision-making (pre-hospital ECG, transfer destination) in relation to patient care following ROSC.

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Contributions of authors

Keith Couper (Research Fellow) was responsible for the co-ordination of the project and for drafting/revising the final report. He contributed to data analysis and interpretation.

Peter K Kimani (Assistant Professor of Statistics and Epidemiology) was responsible for the statistical analysis, including imputation and modelling, and data interpretation. He contributed to the development of the concept of the project and drafting/revising the final report. He provided expertise on imputation and modelling.

Chris P Gale (Associate Professor of Cardiovascular Health Sciences) contributed to the development of the concept of the project and project design, data analysis and interpretation and drafting/revising the final report. He provided expertise on the MINAP data set and cardiovascular care.

Tom Quinn (Professor of Cardiovascular Nursing) contributed to the development of the concept of the project and project design, data analysis and interpretation and drafting/revising the final report. He provided expertise on the MINAP data set, OHCA and cardiovascular care.

Iain B Squire (Professor of Cardiovascular Medicine) contributed to the development of the concept of the project and project design, data analysis and interpretation and drafting/revising the final report. He provided expertise on the MINAP data set and cardiovascular care.

Andrea Marshall (Principal Research Fellow) contributed to the development of the concept of the project and project design, data analysis and interpretation and drafting/revising the final report. She provided expertise on imputation and modelling.

John JM Black (Consultant in Emergency Medicine and Medical Director of the NHS Ambulance Trust) contributed to the development of the concept of the project and project design, data analysis and interpretation and drafting/revising the final report. He provided expertise on OHCA and pre-hospital/emergency care.

Matthew W Cooke (Professor of Clinical Systems Design) contributed to the development of the concept of the project and project design, data analysis and interpretation and drafting/revising the final report. He provided expertise on pre-hospital/emergency care and clinical systems.

Bob Ewings (PPI Representative) contributed to the development of the concept of the project and project design, data analysis and interpretation and drafting/revising the final report.

John Long (PPI Representative) contributed to the development of the concept of the project and project design, data analysis and interpretation and drafting/revising the final report.

Gavin D Perkins (Professor of Critical Care Medicine) was responsible for the development of the concept of the project and project design, and contributed to analysis and interpretation of the data and drafting/revising the final report. He provided expertise on OHCA, pre-hospital/emergency care and critical care.

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Data sharing statement

This study is secondary research that used data from the MINAP. As such, the data are not suitable for sharing beyond those contained in the report. Further information can be obtained from the corresponding author.

Patient data

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety, and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it's important that there are safeguards in place to make sure that it is stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives You can find out more about the background to this citation here: https://understandingpatientdata.org.uk/data-citation.

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Appendix 1 Overview of the Myocardial Ischaemia National Audit Project data fields and their use in the study

Field name	MINAP field number	Response options	Variable used	Used in modelling		
				In-hospital mortality	Neurological outcome	Time to all-cause mortality
MINAP data set						
Hospital identifier	1.01	–	Supplied as anonymised identifier – used to categorise patients by hospital and in case identification to identify duplicate cases	–	–	–
Patient case record number	1.02	–	Not used/supplied	–	–	–
NHS number	1.03	–	Supplied as anonymised identifier – used in case identification to identify duplicate cases	–	–	–
Patient surname	1.04	–	Not used/supplied	–	–	–
Patient forename	1.05	–	Not used/supplied	–	–	–
Patient date of birth	1.06	–	Supplied as age at time of event	✓	✓	✓
Patient sex	1.07	Not known, male, female, not specified	Yes	✓	✓	✓
Patient administration status	1.09	NHS, private, amenity, unknown	Not used/supplied	–	–	–
Patient postcode	1.10	–	Supplied as northings–eastings – used to calculate distance to hospital	✓	✓	✓
GP/PCT code	1.11	–	Not supplied	–	–	–
Patient ethnicity	1.13	White, black, Asian, mixed, not stated, other, unknown	Yes	✓	✓	✓
Initial diagnosis	2.01	Definite MI, ACS, chest pain? Cause, other initial diagnosis	Merged with field 2.36	✓	✓	✓
ECG determining treatment	2.03	No acute changes, ST segment elevation, LBBB, ST segment depression, T-wave changes only, other acute abnormality, unknown	Yes	✓	✓	✓
Where was aspirin/other antiplatelet given?	2.04	Already on aspirin/antiplatelet drug, aspirin/antiplatelet drug given out of hospital, aspirin/antiplatelet drug given after arrival in hospital, aspirin/antiplatelet contraindicated, not given, unknown	Reported in unadjusted analyses. Not used in modelling as unadjusted result suggested heavily confounded	–	–	–

Field name	MINAP field number	Response options	Variable used	Used in modelling		
				In-hospital mortality	Neurological outcome	Time to all-cause mortality
Previous AMI	2.05	No, yes, unknown	Yes	✓	✓	✓
Previous angina	2.06	No, yes, unknown	Yes	✓	✓	✓
Hypertension	2.07	No, yes, unknown	Yes	✓	✓	–
Hypercholesterolaemia	2.08	No, yes, unknown	Yes	✓	✓	–
Peripheral vascular disease	2.09	No, yes, unknown	Yes	✓	✓	✓
Cerebrovascular disease	2.10	No, yes, unknown	Yes	✓	✓	✓
Asthma or COPD	2.11	No, yes, unknown	Yes	✓	✓	✓
Chronic renal failure	2.12	No, yes, unknown	Yes	✓	✓	✓
Heart failure	2.13	No, yes, unknown	Yes	✓	✓	✓
Cardiac markers raised	2.14	No, yes, unknown	Yes	–	–	–
Serum cholesterol (mmol/l)	2.15	–	Yes	✓	✓	✓
Smoking status	2.16	Never smoked, ex-smoker, current smoker, non smoker – smoking history unknown, unknown	Yes	✓	✓	✓
Diabetes	2.17	Not diabetic, diabetes (dietary control), diabetes (oral medicine), diabetes (insulin), insulin plus oral medication, unknown	Yes	✓	✓	✓
Previous PCI	2.18	No, yes, unknown	Yes	✓	✓	✓
Previous CABG	2.19	No, yes, unknown	Yes	✓	✓	✓
SBP (mmHg)	2.20	–	Yes	✓	✓	✓
Heart rate (b.p.m.)	2.21	–	Yes	✓	✓	✓
Admitting consultant	2.22	Cardiologist, other general physician, other, unknown	Yes	✓	✓	✓
Place first 12-lead ECG performed	2.23	Ambulance, in hospital, other health-care facility, unknown	Yes	✓	✓	✓
Beta-blocker use	2.24	No, yes, unknown	Not used/supplied	–	–	–

Field name	MINAP field number	Response options	Variable used	Used in modelling		
				In-hospital mortality	Neurological outcome	Time to all-cause mortality
Angiotensin-converting enzyme inhibitor or ARB use	2.25	No, yes, unknown	Not used/supplied	–	–	–
Statin use	2.26	No, yes, unknown	Not used/supplied	–	–	–
Serum glucose (mmol/l)	2.28	–	Yes	✓	✓	✓
Height	2.29	–	Not used/supplied	–	–	–
Weight	2.30	–	Not used/supplied	–	–	–
LVEF	2.31	Good, moderate, poor, not assessed, unknown	Yes	–	–	–
Family history of CHD	2.32	No, yes, unknown	Not used/supplied	–	–	–
Cardiological care during admission	2.33	No, yes, unknown	Yes	–	–	–
Creatinine	2.34	–	Yes	–	–	✓
Haemoglobin (g/dl)	2.35	–	Yes	✓	✓	✓
Site of infarction	2.36	Anterior, inferior, posterior, lateral, indeterminate, unknown	See field 2.01	–	–	–
ECG QRS complex duration	2.37	QRS complex duration ≥ 120 millisecond, QRS complex duration < 120 millisecond, unknown	Not used/supplied	–	–	–
Thienopyridine inhibitor use	2.38	No, yes, unknown	Not used/supplied	–	–	–
Admission method	2.39	Direct admission via emergency service, self presenter to this hospital, already in this hospital, inter-hospital transfer for specific treatment, repatriation after coronary intervention, other, unknown	Not used/supplied	–	–	–
Patient location at time of STEMI	2.40	Onset of STEMI while patient not in hospital (ST elevation on first ECG), ST elevation first recorded on a subsequent ECG in (or before arrival at) a non-interventional hospital, ST elevation first recorded on a subsequent ECG in (or before arrival at) the interventional hospital, not applicable, unknown	Not used/supplied	–	–	–

Field name	MINAP field number	Response options	Variable used	Used in modelling		
				In-hospital mortality	Neurological outcome	Time to all-cause mortality
Killip class	2.41	No evidence of heart failure, basal crepitations and/or elevated venous pressure, pulmonary oedema, cardiogenic shock, not applicable, unknown	Yes	–	–	–
Stress echo	2.42	No, yes, planned after discharge, not indicated, unknown	Not used/supplied	–	–	–
Date/time of symptom onset	3.01	–	Not used/supplied	–	–	–
Date/time of call for help	3.02	–	Used to determine EMS response time with fields 3.03/3.04 See field 3.39	✓	✓	✓
Date/time of arrival of first responder	3.03	–	See field 3.02	–	–	–
Date/time of arrival of ambulance	3.04	–	See field 3.02	–	–	–
Ambulance job number	3.05	–	Not supplied	–	–	–
Date/time of arrival at hospital	3.06	–	Time, month and year supplied Analyses included term for year slope. Time categroised as day or night	✓	✓	✓
Reason reperfusion treatment not given	3.08	None, ineligible ECG, too late, risk of haemorrhage, uncontrolled hypertension, administrative failure, elective decision, patient refused treatment, other, unknown	Yes	–	–	–
Date/time of reperfusion treatment	3.09	–	See field 3.39	–	–	–

Field name	MINAP field number	Response options	Variable used	Used in modelling		
				In-hospital mortality	Neurological outcome	Time to all-cause mortality
Delay before treatment	3.10	No, sustained hypertension, clinical concern about recent cerebrovascular event or surgery, delay obtaining consent, initial ECG ineligible, cardiac arrest, obtaining consent for therapeutic trial, hospital administrative failure, ambulance procedural delay, other, ambulance, 12-lead ECG not diagnostic of STEMI, consideration of primary PCI, ambulance administrative delay, catheterisation laboratory access delayed, delay in activating catheterisation laboratory team, pre-PCI complication, equipment failure, convalescent STEMI	Not used/supplied	–	–	–
Where was initial reperfusion treatment given?	3.11	No reperfusion attempted, before admission to hospital, in A&E, in CCU (direct admission), in CCU (slowtrack), elsewhere in hospital, catheterisation laboratory, unknown	Not used/supplied	–	–	–
Cardiac arrest date/time – first arrest only	3.13		Used in case identification	–	–	–
Cardiac arrest location	3.14	No arrest, before ambulance arrival, after ambulance arrival, A&E, CCU, medical ward, elsewhere in hospital, catheterisation laboratory	Yes	✓	✓	✓
Arrest presenting rhythm	3.15	Asystole, VF/pulseless VT, PEA, unknown	Yes	✓	✓	✓
Outcome of arrest	3.16	No return of circulation, ROSC but died in hospital, discharged from hospital (with neurological deficit), discharged from hospital (no neurological deficit), resuscitation not attempted, transferred to another hospital, unknown	Used in case identification and for neurological outcome	–	–	–
Admission ward	3.17	CCU, acute admissions unit, general medical ward, intensive therapy unit, other, died in A&E, cardiac ward (non CCU), stepdown ward, unknown	Yes	✓	✓	✓

Field name	MINAP field number	Response options	Variable used	Used in modelling		
				In-hospital mortality	Neurological outcome	Time to all-cause mortality
Peak troponin	3.19	–	Not used/supplied	–	–	–
Unfractionated heparin	3.20	No, yes, unknown	Not used/supplied	–	–	–
Low-molecular-weight heparin	3.21	No, yes, unknown	Not used/supplied	–	–	–
Thienopyridine platelet inhibitor	3.22	No, yes, unknown	Not used/supplied	–	–	–
IV 2b/3a agent	3.24	No, yes, unknown	Not used/supplied	–	–	–
IV beta-blocker	3.25	No, yes, unknown	Not used/supplied	–	–	–
Calcium channel blocker	3.27	No, yes, unknown	Not used/supplied	–	–	–
IV nitrate	3.28	No, yes, unknown	Not used/supplied	–	–	–
Oral nitrate	3.29	No, yes, unknown	Not used/supplied	–	–	–
Potassium channel modulator	3.30	No, yes, unknown	Not used/supplied	–	–	–
Warfarin	3.31	No, yes, unknown	Not used/supplied	–	–	–
Angiotensin-converting enzyme inhibitor or ARB	3.32	No, yes, unknown	Yes	–	–	–
Thiazide diuretic	3.33	No, yes, unknown	Not used/supplied	–	–	–
Loop diuretic	3.34	No, yes, unknown	Yes	–	–	–
Thrombolytic drug	3.36	Streptokinase, alteplase, reteplase, tenecteplase	See field 3.39	–	–	–
Troponin assay	3.37	Troponin I, troponin T, high-sensitivity troponin T, high-sensitivity troponin I, unknown	Not used/supplied	–	–	–
Fondaparinux	3.38	No, yes, unknown	Not used/supplied	–	–	–
Initial reperfusion treatment	3.39	None, thrombolytic treatment, pPCI in house, referred for consideration for pPCI elsewhere, pPCI already was performed at the interventional hospital, unknown	Used with fields 3.04, 3.06, 3.09, 3,36 to determine nature and timing of reperfusion treatment	✓	✓	✓

Field name	MINAP field number	Response options	Variable used	Used in modelling		
				In-hospital mortality	Neurological outcome	Time to all-cause mortality
Additional reperfusion treatment	3.40	None, rescue PCI in house, referred for rescue PCI elsewhere, facilitated PCI, additional dose of thrombolytic	Not used/supplied	–	–	–
Inpatient management of hyperglycaemia/diabetes	3.41	None, glucose insulin regime, insulin pump, multidose insulin, other pre-admission insulin regime, oral medication only, diet only, unknown	Not used/supplied	–	–	–
Diabetic therapy at discharge	3.42	None, multidose insulin regime, other insulin regime, oral medication, insulin plus oral medication, diet only, not applicable, unknown	Not used/supplied	–	–	–
Oral beta-blocker	3.43	No, yes, unknown	Not used/supplied	–	–	–
Aldosterone antagonist	3.44	No, yes, unknown	Not used/supplied	–	–	–
Bivalirudin	3.45	No, yes, contraindicated, not indicated, unknown	Not used/supplied	–	–	–
Date/time of arrival at non-interventional hospital	3.46	–	Not used/supplied	–	–	–
Assessment at non-interventional hospital	3.47	No contact with a non-interventional hospital, patient remains in ambulance, A&E, acute assessment unit, CCU/cardiac facility, self referral, already in hospital, other, unknown	Yes	–	–	–
Assessment at interventional centre	3.48	Assessed in A&E, acute assessment unit, CCU/cardiac facility, catheterisation laboratory, already in hospital, unknown	Yes	–	–	–
Intended reperfusion procedure	3.49	None, primary PCI, rescue PCI, thrombolytic treatment, other coronary intervention, unknown	Yes	–	–	–
Procedure performed	3.50	No angiography, angiography but no PCI, angiography and PCI, unknown	Yes	–	–	–

Field name	MINAP field number	Response options	Variable used	Used in modelling		
				In-hospital mortality	Neurological outcome	Time to all-cause mortality
Why was no angiogram performed?	3.51	Not applicable, diagnosis not ACS, patient refused, patient died, complication before angiography could be performed, angiography inappropriate because of comorbidity, technical failure, laboratory unavailable, other, unknown	Yes	–	–	–
Why was no intervention performed?	3.52	Not applicable, patient refused, patient died, complication before PCI could be performed, PCI felt to be inappropriate, angiographically normal coronaries/mild disease/infarct-related vessel unclear, surgical disease, technical failure, other, unknown	Yes	–	–	–
Date/time of start of insulin infusion	3.53	–	Not supplied	–	–	–
Date of discharge	4.01	–	Used to determine outcomes	–	–	–
Discharge diagnosis	4.02	MI (ST elevation), threatened MI, ACS (troponin positive)/NSTEMI, ACS (troponin negative), chest pain of uncertain cause, MI (unconfirmed), other diagnosis, Takotsubo cardiomyopathy, PCI related MI	Yes	–	–	✓
Bleeding complications	4.03	None, intracranial bleed, retroperitoneal haemorrhage, any bleed with Hb fall of > 50 g, any bleed with Hb fall of > 30 g and < 50 g, any bleed with Hb fall of < 30 g, unknown	Not supplied	–	–	–
Death in hospital	4.04	No, from MI, from complication of treatment, other non-cardiac-related cause, other cardiac cause, unknown	Used to determine outcome	–	–	–
Discharged on beta-blocker	4.05	No, yes, contraindicated, patient declined treatment, not applicable, not indicated, unknown	Yes	–	–	✓

Field name	MINAP field number	Response options	Variable used	Used in modelling		
				In-hospital mortality	Neurological outcome	Time to all-cause mortality
Discharged on angiotensin-converting enzyme inhibitor or ARB	4.06	No, yes, contraindicated, patient declined treatment, not applicable, not indicated, unknown	Yes	–	–	✓
Discharged on statin	4.07	No, yes, contraindicated, patient declined treatment, not applicable, not indicated, unknown	Yes	–	–	✓
Discharged on aspirin	4.08	No, yes, contraindicated, patient declined treatment, not applicable, not indicated, unknown	Used to determine antiplatelet therapy strategy on discharge with fields 4.27/4.31	–	–	✓
Cardiac rehabilitation	4.09	No, yes, patient declined, not indicated, unknown	Yes	–	–	✓
Exercise test	4.10	No, yes, planned after discharge, not indicated, unknown	Not supplied	–	–	–
Echocardiography	4.11	No, yes, planned after discharge, not indicated, unknown	Yes	–	–	✓
Radionuclide study	4.12	No, yes, planned after discharge, not indicated, unknown	Not supplied	–	–	–
Coronary angiography	4.13	Protocol-driven investigation performed in this hospital, symptom-driven investigation performed in this hospital, protocol-driven investigation performed at another hospital, symptom-driven investigation performed at another hospital, planned after discharge, not applicable, patient refused, not performed, unknown	Yes	–	–	✓
Coronary intervention	4.14	PCI, CABG, PCI planned after discharge, CABG planned after discharge, not applicable, patient refused, not performed or arranged, unknown	Yes	–	–	–
Date/time of referral for investigation/intervention	4.15	–	Not used/supplied	–	–	–

Field name	MINAP field number	Response options	Variable used	Used in modelling		
				In-hospital mortality	Neurological outcome	Time to all-cause mortality
Discharge destination	4.16	Home, other hospital, convalescence, death, other speciality in same hospital, unknown	Not used/supplied	–	–	–
Daycase transfer date	4.17	–	Not supplied	–	–	–
Angiogram date/time	4.18	–	Not used/supplied	–	–	–
Local intervention date	4.19	–	Not used/supplied	–	–	–
Interventional centre code	4.20	–	Not supplied	–	–	–
Referring hospital code	4.21	–	Not supplied	–	–	–
Followed up by	4.23	Cardiologist, non cardiologist, no follow up, not applicable, unknown	Yes	–	–	✓
Reinfarction	4.24	No, yes, unknown	Not used/supplied	–	–	–
Date of return to referring hospital	4.26	–	Not supplied	–	–	–
Discharged on a thienopyridine inhibitor	4.27	No, yes, contraindicated, patient declined treatment, not applicable, not indicated, unknown	See field 4.08	–	–	–
Discharged on an aldosterone antagonist	4.28	No, yes, contraindicated, patient declined treatment, not applicable, not indicated, unknown	Not supplied	–	–	–
What procedure was performed at the interventional hospital	4.29	No angiography or primary reperfusion treatment performed, angiography only, primary angioplasty, rescue angioplasty, CABG, thrombolytic treatment, unknown	Not used/supplied	–	–	–
Delay to performance of angiogram	4.30	None, delay due to comorbid clinical condition/competing clinical issue, capacity issues, patient preference, other, unknown	Not used/supplied	–	–	–
Discharged on ticagrelor	4.31	No, yes, contraindicated, patient declined treatment, not applicable, not indicated, unknown	See field 4.08	–	–	–

Field name	MINAP field number	Response options	Variable used	Used in modelling		
				In-hospital mortality	Neurological outcome	Time to all-cause mortality
High risk NSTEMI	4.32	No, yes, unknown	Not supplied	–	–	–
Smoking cessation advice given	5.1	No, yes, planned in rehabilitation, not applicable, unknown	Yes	–	–	–
Dietary advice given during this admission	5.2	No, yes, planned in rehabilitation, not applicable, unknown	Yes	–	–	–
ONS data						
Survival status and days to censorship	–	–	Yes	–	–	–
IMD score	–	–	Yes	✓	✓	✓
Other data items						
Hospital northings–eastings	–	–	See field 1.10	–	–	–
Mini-GRACE score	–	–	Derived from other supplied fields	–	–	–
PCI centre	–	–	Determined using field 3.39 for each hospital	✓	✓	✓
Cardiac arrest volume	–	–	Yes	✓	✓	✓

A&E, accident and emergency; ARB, angiotensin receptor blocker; b.p.m., beats per minute; CHD, coronary heart disease; GP, general practitioner; Hb, haemoglobin; IV, intravenous; PCT, primary care trust; SBP, systolic blood pressure.

Appendix 2 Imputation iteration performance: models of convergence

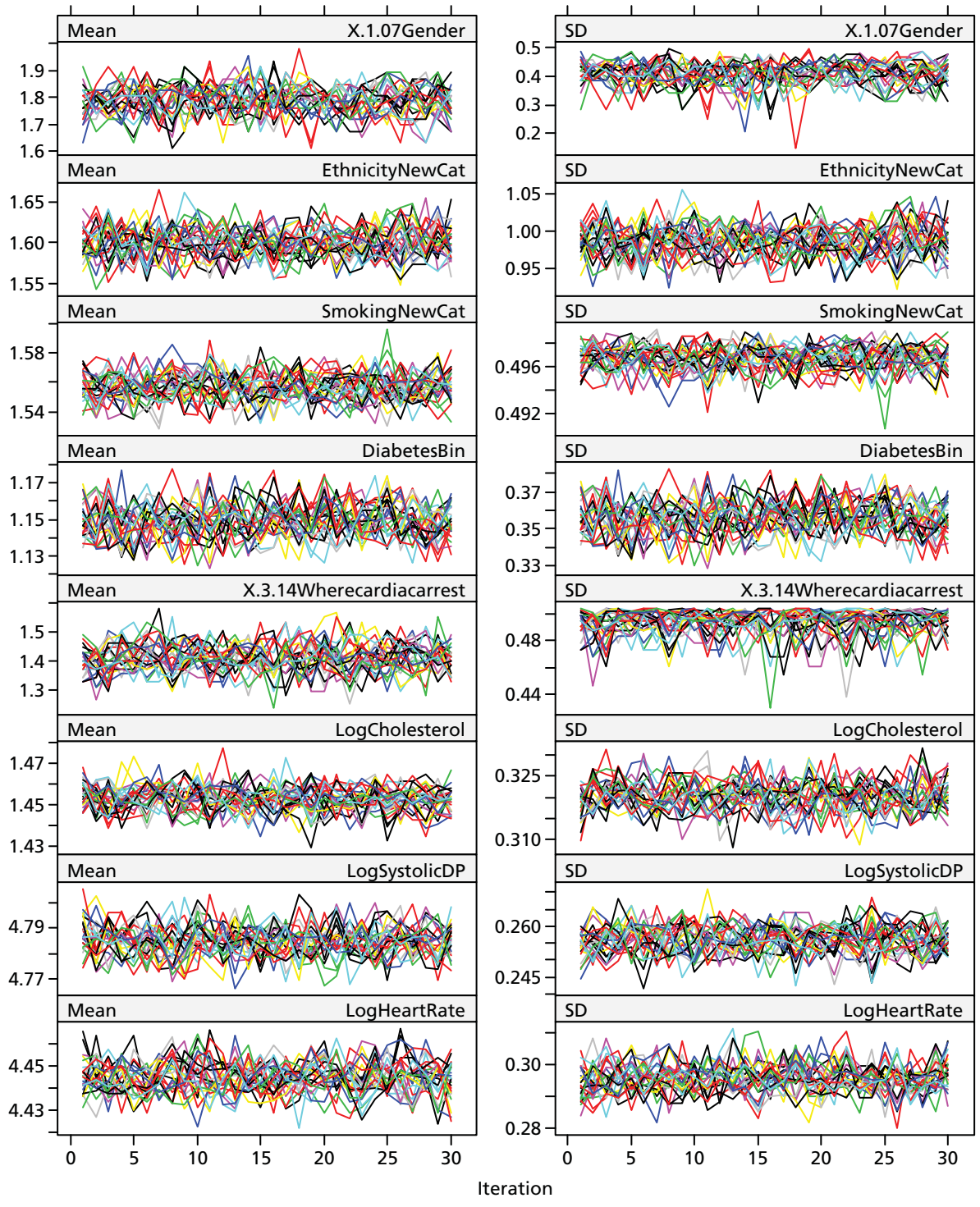

FIGURE 11 Imputation iteration performance: models of convergence – first group of variables.

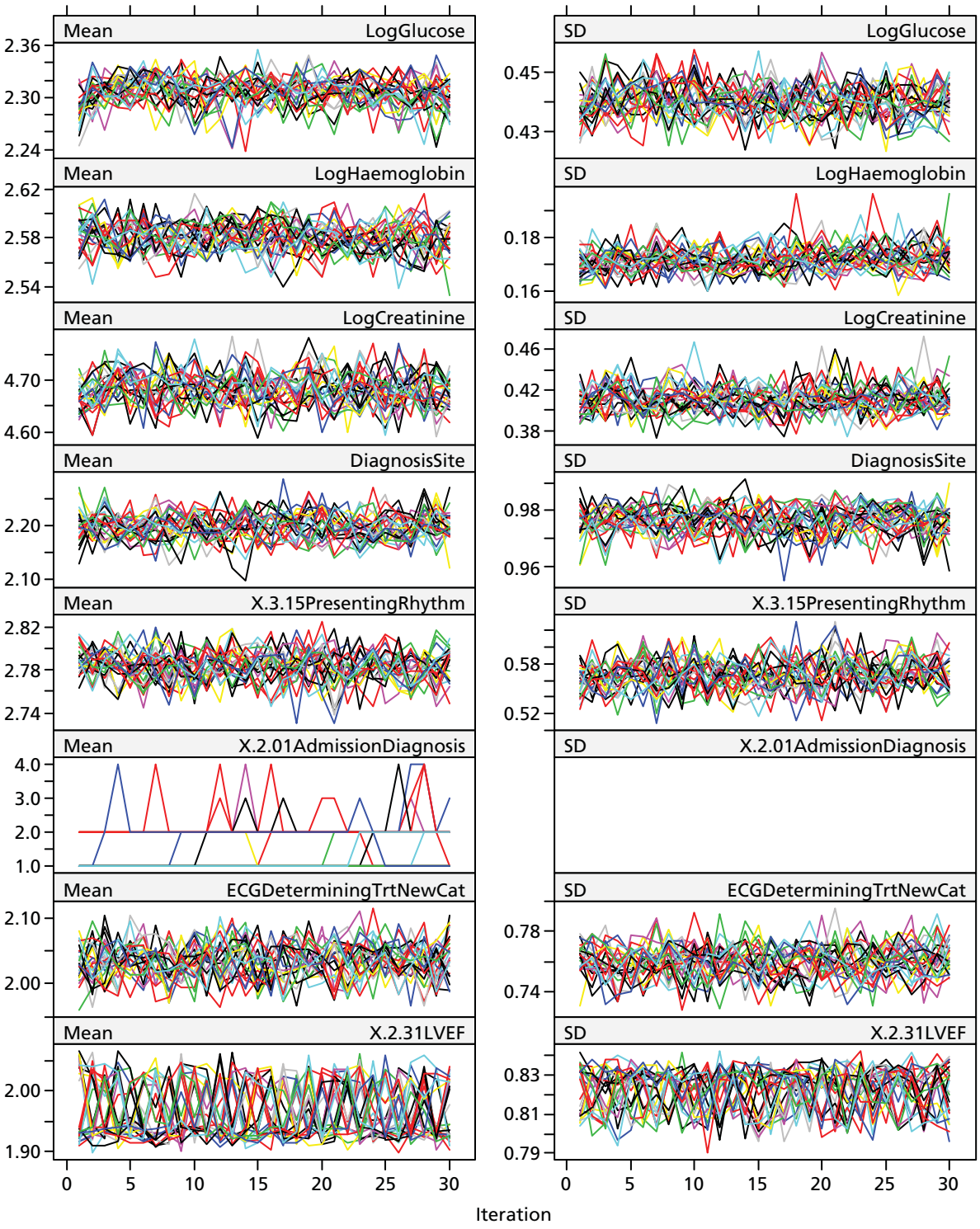

FIGURE 12 Imputation iteration performance: models of convergence – second group of variables.

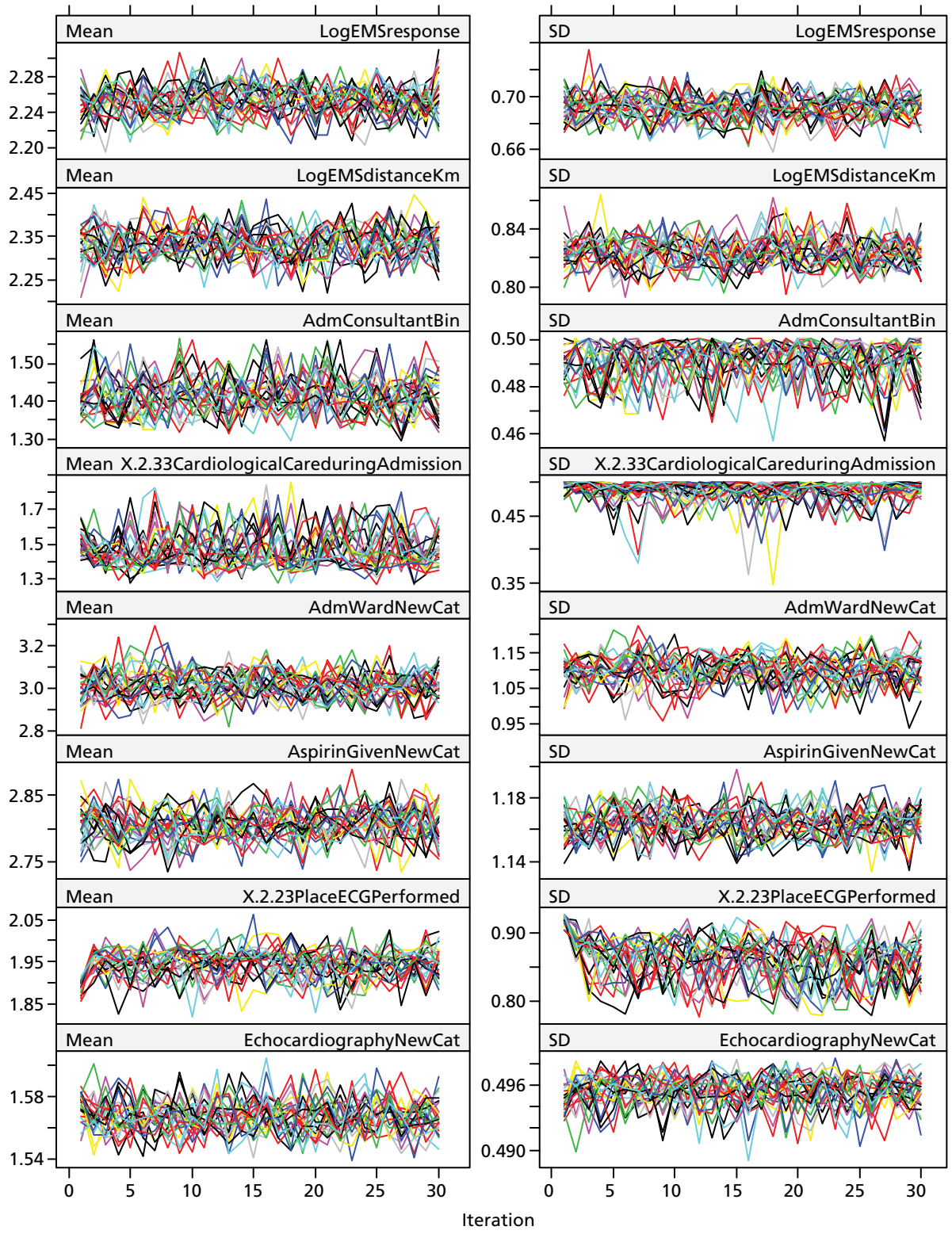

FIGURE 13 Imputation iteration performance: models of convergence – third group of variables.

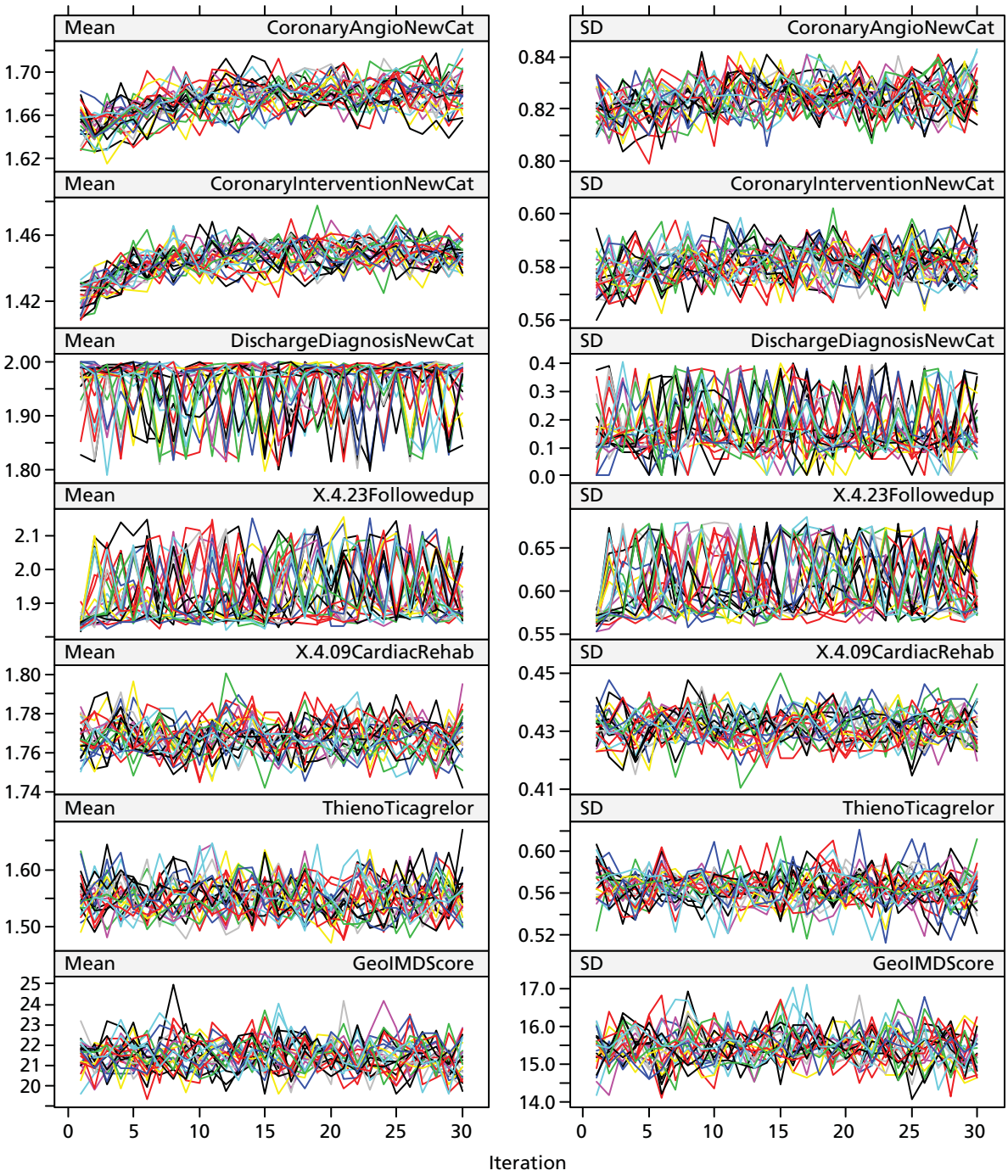

FIGURE 14 Imputation iteration performance: models of convergence – fourth group of variables.

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