**Variation in Practice for Out of Hospital Cardiac Arrest Treated with Percutaneous Coronary Intervention in England and Wales**

**Short running title**: Invasive management of Out of Hospital Cardiac Arrest

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**Abstract**

**Objectives:** We assessed the association between total centre volume, operator volume and Out of Hospital Cardiac Arrest (OHCA) percutaneous coronary intervention (PCI) volume.

**Background:** Variations between OHCA PCI volume, hospital total PCI, and primary PCI volume are not well studied and are unlikely to be clinically justifiable.

**Methods:** Patients undergoing PCI for acute coronary syndrome (ACS) between 1st January 2014 and 31st March 2019 in England and Wales were grouped as OHCA PCI and non-OHCA PCI. Spearman's correlation was used to determine the degree of correlation between each hospital PCI volume and OHCA PCI volume.

**Results:** Out of 250,088 PCI procedures undertaken for ACS, 12,016 (4.8%) were performed for OHCA, and 238,072 (95.2%) were non-OHCA PCI procedures. The OHCA PCI group were younger (mean age (SD) 63.2 (12.3) and 65.6 (12.5, p<0.001), less likely to be female (20.2% vs 26.9%, p<0.001) or Black, Asian and Minority Ethnicity (BAME) (11.5% vs 14.8%, p<0.001) compared to the non-OHCA PCI group. Although there was a degree of correlation between total PCI and OHCA PCI, there was wide variation for both ACS cohort (Spearman correlation R2=0.50) and total PCI volume (Spearman correlation R2=0.60). Furthermore, the correlation between primary PCI volume and OHCA PCI within centres was weak (R2=0.10). Similarly, wide variations between operator PCI volume and OHCA PCI volume were observed.

**Conclusion:** These national data demonstrate wide variation in the practice of OHCA PCI both between centres and individuals. These variations are not expected according to clinical factors and require further investigation.

**Keywords**: Out of Hospital Cardiac Arrest, Percutaneous Coronary Intervention, Mortality, Outcomes, Predictors

**Conflict of interest**

All authors confirm no potential conflict relevant to this manuscript.

**Word count:** 2565 (excluding references, figures and tables)

**Introduction**

Out of Hospital Cardiac Arrest (OHCA) remains a leading cause of morbidity and mortality, with a global incidence of 55 events per 100,000 inhabitants 1. Post mortem studies have revealed that almost two-thirds of OHCA survivors have a primary cardiac aetiology, particularly the presence of significant coronary disease 2-6. Angiographic data of patients presenting with OHCA shows that almost 50% of patients have a complete coronary artery occlusion and up to two-thirds have at least one significant coronary lesion7 8. The management of OHCA patients who are thought to have a cardiac aetiology is contentious9. Specifically, current guidelines and expert opinion universally advocate immediate coronary angiography with a view to percutaneous coronary intervention (PCI) in resuscitated OHCA patients with ECG evidence of ST-elevation myocardial infarction (STEMI). However, such guidelines are less uniform regarding OHCA patients without ST elevation 10 11, with considerable variability in practice around the UK12, particularly regarding the use of invasive coronary angiography and subsequent revascularization 8 9 13. The clinical practice and decision making around invasive management of OHCA are further compounded by randomized trials comparing early versus late angiography and revascularisation rather than angiography versus no angiography14 15.

The threshold for coronary angiography and PCI remains highly variable within UK practice, and this variability is unsatisfactory in terms of equity of access to optimal therapy. Historically, limited data have been available around the clinical and angiographic profile of OHCA patients undergoing PCI in the UK. In 2014, the British Cardiovascular Intervention Society (BCIS) introduced data fields to the national registry regarding the clinical characteristics and management of all patients who sustained an OHCA prior to PCI.

The present analysis describes the clinical and angiographic profile of a national cohort of patients undergoing PCI for OHCA in England and Wales. We assessed variation in practice across centres and individual operators by looking at the proportion of all PCI procedures, number of primary PCI procedures and those performed on patients who had presented with OHCA. Finally, we report clinical outcomes and independent predictors of mortality in patients undergoing PCI following OHCA.

**Methods**

*Study Cohort*

The BCIS database is a national PCI registry that captures almost all PCI activity undertaken in the National Health Service in England and Wales16. Approximately 113 PCI centres and over 700 PCI operators contribute to the registry. The database collects information about the indication for the procedure, clinical characteristics, including important cardiovascular comorbidities, anatomical and procedural characteristics and in-hospital procedural-related complications. Entry of all cases into this database is a mandatory professional responsibility for UK operators. The database is used for auditing and public reporting purposes and also for academic research. Formal ethical approval was not required for this study under current arrangements by the National Health Service (NHS) research governance which allows the anonymized data to be used for research purposes without informed patient consent under section 251 of the National Health Service Act 200617-19. The data that support findings of this study are available from National Institute of Cardiovascular Outcomes Research (NICOR). Restrictions apply to the availability of these data, which were used under license for this study. Data are available from the authors with the permission of NICOR.

*Study population*

All patients aged>18 years undergoing PCI procedures between 1st January 2014 to 31st March 2019 in England and Wales were included in the analysis. As by definition, elective procedures with a stable angina indication would not have been patients with OHCA, all procedures with elective or stable angina indications were excluded. Further exclusions were made based on the missing information about age, sex and OHCA status. The final cohort was divided into an OHCA PCI group and the non-OHCA PCI group. The outcomes of interest were (a) in-hospital mortality; (b) major bleeding defined as a composite of retroperitoneal bleeding, gastrointestinal bleeding, cerebral haemorrhage, platelet or blood transfusion and any access site complication requiring surgery; (c) Major Adverse Cerebrovascular Events (MACCE), a composite of in-hospital mortality, reinfarction and cerebrovascular events. To further elaborate the impact of type of ACS, we performed a sensitivity analysis by stratifying the OHCA PCI group into STEMI and NSTEMI PCI groups.

*Statistical analysis*

Baseline characteristics of the two groups were reported in numbers and percentages, or median and interquartile range, for categorical and continuous variables, respectively. Chi-square test for categorical data and Kruskal Wallis test for continuous data were utilized to compare the characteristics between OHCA and non-OHCA PCI groups. Spearmen's correlation was used to determine the degree of correlation between each hospital's total PCI volume, primary PCI volume, individual operator total PCI volume, primary PCI volume, and OHCA PCI volume. Multiple imputations with chained equations were used to account for any missing assuming that data are missing at random20-22. Age, sex, hospital PCI volume, clinical diagnosis, and in-hospital mortality were registered as regular variables in the imputations model, while all other variables listed in Table 1 were imputed. The variable selection in the model was based on previous studies using the BCIS registry and prior clinical knowledge18 23 24. 10 imputed datasets were generated, which were used to perform all the analyses. Multivariable logistic regression models were used to study the association between OHCA PCI and clinical outcomes. All models included the same variables used in the multiple imputation models and the year of admission. Estimates of odds ratios (ORs) and 95% confidence intervals (95% CIs) were reported. Statistical significance was considered with an alpha of 0.05 in all the 2-sided tests used. Stata version 16.0 was used to perform all the analyses

**Results**

1. *Numbers of procedures*

Between 1st January 2014 to 31st March 2019, 544,431 PCI procedures were undertaken in the UK. 250,088 PCI procedures were included in the final analysis after excluding patients for stable angina and procedures where data were missing for age, sex and OHCA status. Of these, 12,016 (4.8%) were performed for OHCA, and 238,072 (95.2%) were non-OHCA PCI procedures (Supplementary figure 1).

1. *Baseline clinical characteristics*

The OHCA PCI group were younger ((mean age (SD) 63.2 (12.3) and 65.6 (12.5, p<0.001), less likely to be female (20.2% vs 26.9%, p<0.001) or BAME ethnicity (11.5% vs 14.8%, p<0.001) and more likely to be active smokers (36.7% vs 28.9%, p<0.001) compared to the non-OHCA PCI group. The non-OHCA PCI group had higher prevalence of cardiovascular risk factors such as diabetes (22.6% vs 14.9%, p<0.001), hypertension (53.8% vs 39.7%, p<0.001), hypercholesterolemia (52.3% vs 37.6%, p<0.001) and previous AMI (5.1% vs 4.5%) or CABG (6.7% vs 4.5%, p<0.001) (Table 1). Over two-thirds of patients in the OHCA PCI group presented with STEMI (82.1% vs 40.4%, p<0.001), whereas NSTEMI (59.6% vs 17.9%, p<0.001) was a principal diagnosis in the non-OHCA PCI group. Patients in the OHCA PCI group had GCS lower than 9 (56.5% vs 3.6%, p<0.001) and were more likely to be ventilated (68.9% vs 1.1%, p<0.001) than the non-OHCA PCI group. A higher prevalence of cardiogenic shock (33.8% vs 3.2%, p<0.001), use of inotropes (14.1% vs 1.5%, p<0.001) and intra-aortic balloon pump (8.8% vs 1.3%, p<0.001) was observed in the OHCA PCI group. OHCA PCI group had a mean arterial blood gas PH of 7.2 and significantly elevated lactate of 5.2.

The angiographic and anatomical characteristics of OHCA and non-OHCA groups are reported in Table 1. The OHCA PCI group had lower use of intracoronary imaging (OCT or IVUS) and invasive physiological assessment using a pressure wire. OHCA PCI group were also more likely to undergo PCI to the left main stem coronary artery (7.1% vs 5.0%, p<0.001), and multivessel PCI (4.9% vs 3.3%, p<0.001) compared to the non-OHCA PCI group. However, the number of lesions treated, stent used, stent length and diameter were similar in both groups. As determined by TIMI-3 flow at the end of the procedure, the procedural success rate was much lower in the OHCA PCI group (88.2% vs 92.8%, p<0.001)

1. *Variation in characteristics of STEMI and NSTEMI OHCA PCI*

The differences in baseline characteristics, comorbidities and procedural profile of OHCA patients stratified according to the STEMI and NSTEMI OHCA PCI are reported in Table 2. STEMI OHCA PCI group were younger, more likely to be female and of BAME ethnicity. STEMI OHCA PCI group were also more likely to be acidotic (PH 7.2 vs 7.3), had higher concentrations of blood lactate (6.1 vs 4.6) and presented with cardiogenic shock (36.2% vs 22.8%) compared to OHCA non STEMI PCI group.

1. *Relationship between OHCA cases as proportion of overall centre PCI volume and Primary PCI volume*

The proportion of OHCA PCI ranged from 4.7% to 5.3% and from 1.5% to 2.5% in the ACS and overall cohorts, respectively (figure 1). There was significant variation between proportion of OHCA PCI compared to total ACS PCI volume and total PCI volume respectively, across the centres in England and Wales (figure 2, Supplementary figure 2). Higher PCI volume was associated with increased OHCA PCI activity across centres for both ACS cohort (Spearman correlation R2=0.50, p<0.001) and total PCI volume (Spearman correlation R2=0.60, p<0.001) (figure 3, supplementary figure 3). Similar heterogeneity in OHCA PCI volume and total primary PCI volume was noted across all centres with only a weak correlation (R2=0.10, p=0.33) between hospital PPCI volume and OHCA PCI volume (supplementary figure 4).

Supplementary Table 1 shows the differences in characteristics of the OHCA PCI group stratified according to hospital OHCA PCI volume quartiles. Patients undergoing PCI for OHCA in the lowest quartile were older, more likely to be female, BAME ethnicity and presented with NSTEMI or unstable angina. In contrast, the higher quartile hospitals had a higher prevalence of left ventricular systolic dysfunction (LVSD), cardiogenic shock and LMS and CTO PCI.

1. *Relationship between OHCA PCI as proportion of overall PCI volume and Primary PCI volume for individual operators*

There was significant heterogeneity between individual operator total PCI volume and OHCA PCI (spearman's correlation 0.10, p<0.001), as illustrated in supplementary figure 5. Similarly, individual operator primary PCI volume and OHCA PCI were independent with significant variation across the operator volume (spearman's correlation 0.21, p<0.001) (supplementary figure 6).

1. *Factors associated with mortality & other clinical outcomes*

Overall crude mortality (24.7% vs 2.2%, p<0.001), in-hospital MACCE (27.4% vs 3.7%, p<0.001) and bleeding complications (8.1% vs 4.8%, p<0.001) were significantly higher in the OHCA PCI group compared to the non-OHCA PCI group. After adjusting for all the baseline differences in clinical and angiographic characteristics, OHCA PCI was associated with over 30% increase in mortality (OR 1.32 95%CI 1.18-1.47), MACCE (OR 1.21 95%CI 1.09-1.35) but no differences in bleeding complications (OR 0.98 95%CI 0.74-1.29) (Table 3)..

**Discussion**

This analysis of national PCI activity for OHCA patients demonstrates substantial variation in PCI practices both between centres and between individual operators. Specifically, there is only a modest correlation between total or primary PCI volume and OHCA PCI volume amongst the centres. The characteristics of OHCA patients undergoing PCI differs according to whether centres are higher volume or lower volume OHCA PCI centres. These findings indicate unexplained heterogeneity in the standard of clinical care and invasive management across PCI centres and operators.

OHCA patients admitted to hospitals with PCI facilities have increased access to early coronary angiography, specialist input and better outcomes7 25 26. However, there are limited data around the association between hospital overall PCI volume and OHCA PCI volume in contemporary practice. In the present study, we found that the correlation between hospital overall PCI volume and OHCA PCI volume was modest, highlighting the significant heterogeneity in clinical practice across the centres in England and Wales. For instance, some low volume PCI centres had very high OHCA PCI rates and similarly few high volume PCI centres were noted to have modest OHCA PCI rates.

These data cannot be used to explain the underlying reasons for this wide variation in practice. It may be that the reasons are different when considering those with non-ST elevation events compared to those with ST-elevation acute myocardial infarction. Specifically, the literature provides less clear cut evidence of the optimal management of patients without ST-elevation. By contrast, a much more substantial body of evidence describes the optimal care pathway for those with ST-elevation on the initial ECG. Current guidelines recommend immediate coronary angiography followed by revascularization in the survivor of OHCA, particularly those with ST-elevation on the ECG or high suspicion of myocardial ischemia7 11. Therefore, one would expect a much closer association between the number of OHCA PCI cases as a proportion of total PPCI cases undertaken, both by centre and individual. There was no correlation between hospital PPCI volume and OHCA PCI volume in the current study.

In OHCA patients without ST-elevation, the data regarding the clinical benefit of angiography and PCI are discrepant. Two high-quality randomized trials (COACT, TOMAHAWK) have recently demonstrated no overall benefit from undertaking angiography and revascularisation, where appropriate, immediately/very early after admission compared to delaying the angiogram until after a period of stabilization and assessment on intensive care14 15. However, these trials do not inform us as to which of the non-ST elevation patients should be considered for PCI. For example, previous studies have consistently indicated that a significant proportion of patients without ST-elevation have an acutely occluded epicardial vessel6 15. In one single centre series, 21% of the patients with an acutely occluded vessel after OHCA did not have ST elevation27. The lack of definitive data about the value of PCI in non-ST elevation OHCA patients is reflected in the international guidelines, which are less prescriptive about the role of PCI as reflected by our results.

Nevertheless, we might expect that the amount of OHCA PCI by both centres and individuals would correlate strongly with overall PCI and PPCI numbers. This study confirms that this is not the case and demands further scrutiny since the extremes at either end of the spectrum cannot be consistent with optimal patient care. It is possible that some interventionalists or centres are performing such PCI in patients that have little to benefit from such invasive treatment, whilst other interventionalists or centres are denying such patients a potentially beneficial therapy. This discrepant practice demands further attention, as currently survivors of OHCA are often taken to nearest hospital which may not necessarily be PCI centre. Development of a centralized approach in the form of regional cardiac arrest centres, incorporation of appropriate risk stratification and deployment of a full range of support treatment options such as targeted temperature management (TTM), mechanical circulatory support, delivered by a specialist multidisciplinary team may facilitate improved outcomes28-31.

To the best of our knowledge, this is the first national multicentre cohort study of OHCA patients treated with PCI, characterizing these patients' clinical and angiographic profile. We demonstrated the variation in clinical practice across PCI centres based on the hospital overall and PPCI volume and its correlation with OHCA PCI. However, it is important to acknowledge that we could only include patients who had been successfully resuscitated and transferred to PCI centres. We also lacked information about the downtime, hypoxia-induced neurological injury, and recovery extent associated with overall mortality and morbidity. Finally, outcomes of interest were limited to in-hospital outcomes only.

**Conclusion**

This study demonstrates a wide degree of variation between the volume of OHCA PCI in relation to total and PPCI denominator numbers between individual interventionists and centres. This variation is inconsistent with optimal patient care and demands further attention. Development of a national OHCA pathway, risk stratification and centralized cardiac arrest centre approach may help refine the treatment and outcomes of these patients.

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**Figure legends**

**Figure 1A:** Percentage of OHCA PCI over time in acute coronary syndrome cohort performed in UK between 1st January 2014 to 31st March 2019.

OHCA= Out of hospital cardiac arrest, ACS= acute coronary syndrome, PCI= percutaneous coronary intervention

**Figure 2:** Overall proportions of OHCA PCI stratified according to hospital total ACS PCI volume

**Figure 3**: Graphical presentation of overall OHCA PCI versus overall ACS PCI volume for each centre between 2014 to 2019