Primary Percutaneous Coronary Intervention for ST-elevation myocardial infarction (STEMI): consultant-led protocols for treatment are not associated with excess out of hours mortality

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Primary Percutaneous Coronary Intervention for ST-elevation myocardial infarction (STEMI): consultant-led protocols for treatment are not associated with excess out of hours mortality

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Article Summary

Article Focus:

- Recent emerging evidence has suggested that patients admitted during the to hospital out of hours have a higher mortality than those admitted during the normal working day. Whether this is true for patients with ST-Elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PPCI) is unclear.
- The optimum delivery of PPCI requires an integrated network of hospitals, following a multidisciplinary, consultant-led, protocol-driven approach. We investigated whether such a strategy was effective in providing equally effective in-hospital and long-term outcomes for STEMI patients treated by PPCI within normal working hours compared with those treated out of-hours.

Key Messages:

- A consultant-led protocol for provision of PPCI for treatment of STEMI is not associated with an increase in mortality for patients treated out of hours compared to in hours.
- Delivery of primary PCI with a multidisciplinary, consultant-led, protocol-driven approach delivers safe and effective treatment for patients regardless of the time of presentation.
- Similar strategies could be implemented for other acute medical conditions to improve outcomes 'out of hours' without involving complete replication of weekday hospital services at the weekend.

Strengths and Limitations of the Current Study

- The strength of this study is that it assesses outcome in a large contemporary cohort of consecutive patients undergoing PPCI for STEMI in a regional Heart Attack Centre centre, therefore, the results are likely to be widely generalisable. The large cohort also ensures that all-cause mortality can be used as the primary end point, which has the advantage of being entirely objective.
- This study is a consecutive but retrospective observational analysis from a single centre's experience. We cannot account for the effects of residual confounding factors or selection bias that we have been unable to control for.

Abstract

Objectives

Timely delivery of primary percutaneous coronary intervention (PPCI) is the treatment of choice for STEMI. Optimum delivery of PPCI requires an integrated network of hospitals, following a multidisciplinary, consultant-led, protocol-driven approach. We investigated whether such a strategy was effective in providing equally effective in-hospital and long-term outcomes for STEMI patients treated by PPCI within normal working hours compared with those treated out of-hours.

Design: Observational study

Setting: Large PPCI centre in London.

Participants: 3347 STEMI patients were treated with PPCI between 2004 and 2012. The follow-up median was 3.3 years (IQR: 1.2-4.6 years).

Primary and secondary outcome measures: The primary end-point was long-term major adverse cardiac events (MACE) with all cause mortality a secondary endpoint.

Results

Of the 3347 STEMI patients, 1299 patients (38.8%) underwent PPCI during a weekday between 08:00 and 18:00 (routine-hours group) and 2048 (61.2%) underwent PPCI on a weekday between 18:00 and 08:00 or a weekend (out-of-

hours group).

There were no differences in baseline characteristics between the two groups with comparable door to balloon times (IHs 67.8mins vs OOHs 69.6mins, p=0.709), call to balloon times (IHs 116.63 vs OOHs 127.15mins, p=0.60) and procedural success. In hospital mortality rates were comparable between the two groups (IHs 3.6% vs OFHs 3.2%) with timing of presentation not predictive of outcome (HR 1.25 (95%CI 0.74-2.11). Over the follow-up period there were no significant differences in rates of mortality (IHs 7.4% vs. OFHs 7.2%, p=0.442) or MACE (IHs 15.4% vs. OFHs 14.1%, p=0.192) between the two groups. After adjustment for confounding variables using multivariate analysis, timing of presentation was not an independent predictor of mortality (HR 1.04 95%CI: 0.78-1.39).

Conclusion

This large registry study demonstrates that the delivery of PPCI with a multidisciplinary, consultant-led, protocol-driven approach delivers safe and effective treatment for patients regardless of the time of presentation.

Keywords: Primary PCI, In-Hours, Out of Hours, myocardial infarction

Background

There is increasing evidence suggesting that patients admitted during the weekend have a higher mortality than those admitted during the week [1].This excess mortality is thought to be strongly associated with the lack of cover of senior doctors (consultant level), during the weekends [2] and has led to debate around redesigning healthcare provision to eliminate reduced staffing at the weekends.

Primary percutaneous coronary intervention (PPCI) is the accepted gold standard for the treatment of ST-segment elevation myocardial infarction (STEMI) as recognized in all recent guidelines [3-5], and needs to be available at all hours (24/7). The delivery of PPCI services represents a significant logistical challenge, especially as many patients with STEMI present outside of usual hospital working hours (0800 to 1700) and at weekends. Whether patients with STEMI presenting outside of usual hospital working hours have inferior outcomes when compared with patients that present during the working day is still unclear.

Previous studies have demonstrated differing results in outcome after PPCI during 'in-hours' compared to 'out of hours'. Some studies showing no association with adverse outcomes and timing [6-12], whereas other studies suggested higher rates of mortality after PPCI during 'out of hours' compared to 'in hours' [13-16]. It is difficult to compare these studies directly because of

differences in patient characterises and variability in other treatment provided to patients – for example, some of these studies also used fibrinolysis [8, 12, 14, 15, 17].

The aim this study was therefore to clarify the relative outcomes of patients with STEMI presenting to a UK regional PPCI centre outside of usual hospital working hours with patients presenting during usual working hours.

Methods

This was an observational cohort study of 3347 consecutive patients undergoing PPCI in a high volume centre between January 2004 and July 2012. These patients were divided into two groups based on the timing of PPCI. Those undergoing PPCI during usual hospital working hours, designated 'in-hours' group (IH) (between 0800 and 1700 Monday to Friday) and those undergoing PPCI outside of usual hospital working hours, designated 'out of hours group' (OOH) (i.e. between 1701 and 0759 Monday to Friday and from 1701 Friday to 0759 Monday).

Service arrangement

The London Chest hospital (LCH) is the tertiary heart attack center for the North-East region of London and receives patients with STEMI for primary PCI in an unselected manner. This includes patients with cardiogenic shock and post cardiac arrest, including intubated and ventilated patients. The hospital serves a well developed network of 6 local district general hospitals covering a

population of 1.6 million people and includes close working with the London Ambulance Service. Patients are taken directly to the cardiac catheterization laboratory 24 hours a day with all cases performed by/under supervision of a consultant. Out of hours the catheterization laboratory is covered by an 'on-call team'. The on-call team is composed of an interventional cardiologist, a senior cardiology trainee, two cardiac catheterization laboratory nurses, a cardiac physiologist, and a radiographer. Aside from the senior cardiology trainee who is resident in hospital out of hours, all the on-call team members are non-resident. Out of hours there are also reduced trainees covering the patients care post procedure and other non-cardiac hospital services are also reduced with lower levels of staffing in radiology, pathology and anaesthetics (ITU) (All of these services follow a similar consultant lead service out of hours).

PPCI pathway

During out of hours the on-call team members are contacted immediately upon acceptance of a patient for PPCI. The on-call team members will be in the hospital within 15-40 minutes of the original call and the catheterization laboratory will be ready to take the patient as soon as they arrive. In the majority of cases, the on-call team will be in the hospital before the arrival of the patient. During routine-working hours, the on-call team is in the hospital and the catheterization laboratories are fully functioning. Upon accepting a patient, the catheterization laboratory coordinators inform the on-call interventional cardiologist and cardiology trainee and the next available free catheterization laboratory is identified. The patient is taken to the catheterization laboratory

and PPCI is performed by the interventional cardiologist who is working in that laboratory. Standard PPCI protocol for our institution includes pre-loading with 300mg aspirin, 300mg or 600mg clopidogrel and GPIIb/IIIA inhibitors unless contraindicated. Aspiration thombectomy was performed at the operator's discretion.

Data was entered prospectively into the clinical database at the time of PPCI including patient characteristics, procedural factors and procedural complications. Successful primary PCI result was defined as final Thrombolysis In Myocardial Infarction flow grade 3 and residual stenosis <30% in the infarct-related artery at the end of the procedure. Post-discharge complications and further revascularisation procedures were entered retrospectively from the electronic patient record and cardiac surgical database. Major Adverse Cardiac Events were defined as death, recurrent myocardial infarction (defined as 'new ischaemic pain with new ST elevation, or ischaemic ECG changes and further elevation of enzymes (increase of creatine kinase-MB to ≥ 2 times the reference value or rise in Troponin T >30ng/l (99th centile <10ng/l)), whether treated with further revascularisation therapy or not') and target vessel revascularisation. MACE events (identified from patient notes and electronic records) were adjudicated by 3 independent physicians who were not involved in the procedure and were unaware of the patient's PPCI timing (in versus out of hours). All-cause mortality was recorded to 11th September 2012 from the UK Office of National Statistics. A retrospective data quality audit of 100 randomly selected medical records established that 94.8% of data fields, including complications, were entered correctly into the database.

Ethics

The data were collected as part of a mandatory national cardiac audit and all patient identifiable fields were removed prior to analysis. The local ethics committee advised us that formal ethical approval was not required.

Statistical analysis

Continuous variables are presented as mean±SD, categorical variables as absolute number and percentages. Normality of distribution of continuous variables was assessed using the Shapiro-Wilkes test. Normally distributed continuous variables were compared with unpaired t-tests, and non-normally distributed variables were compared with the Mann-Whitney test. Categorical variables were compared using the $\chi 2$-test or Fisher's exact test when appropriate. Kaplan Meier curves were used to represent survival and cumulative incidence of events over follow-up, with the log rank test used for evidence of a statistically significant difference between the groups. Time was measured from the first admission for a procedure to outcome (all cause mortality). The association of timing of PPCI (OOH vs IH) with 30-day mortality was assessed using logistic regression analysis, and long-term mortality using Cox regression analyses. The proportional hazard assumption was satisfied for all outcomes evaluated. Finally, a non-parsimonious logistic regression model with procedural timing as the dependent variable was constructed incorporating all baseline clinical and procedural characteristics listed in table 1 and table 2 to generate a propensity score (ie the predicted probability of procedural timing for

each patient), which ranged between 0 and 1, for each patient. We the subdivided our cohort into quintiles based on propensity score so that comparisons could be made between patients with similar baseline probabilities of mortality[18]. The rates of 30-day and 5-year mortality in the IH vs OOH groups in each quintile were compared. Risk ratios (RRs) for mortality were calculated for each quintile, as well as an overall Mantel-Hantzel RR for the stratified analysis.

Results

Within our study population of 3347 patients 1299 (38.8%) PPCIs were performed In-Hours (IHs) and 2048 (61.2%) PPCIs were performed Out-of-Hours (OOHs).

Patient characteristics (Table 1)

Table 1 demonstrates the baseline characteristics between the two groups. There were no differences in baseline characteristics between the IHs group versus the OOHs group.

Procedural Characteristics and Outcomes (Table 2)

There was no difference in access route or target vessel intervention between the two groups. Although the Door to Balloon time were slightly longer in the OOHs group compared to the IHs group, this difference was not statistically significant (Figure 1). In addition, there was no statistically significant difference in the Call to Balloon time between the two groups. There were higher rates of glycoprotein IIb/IIIa inhibitor use in the OOHs group compared to the IHs group. Procedural success rates and use of thrombectomy were similar between the two groups.

Early Outcomes (Table 3)

There were no differences in in-hospital MACE rates (IH 4.5% vs OOH 5.0%; p=0.644). There was no difference in either 30-day MACE rates (IH 6.3% vs OOH 5.8%; p=0.580) or 30 day mortality rates (IH 4.4% vs OOH 4.0%; p=0.613) between the groups.

Predictors of early Outcome (Table 4)

In terms of early (30 day) all-cause mortality and MACE events, Out of hours PPCI was not an independent predictor of mortality (HR 0.74 (95% CI: 0.42-1.29) and MACE events (HR 0.81 (95% CI 0.54-1.22). However, as expected, reduced renal function, shock, low EF and procedural success were independent predictors of early outcome (Table 4).

Long term Outcome (Figures 2-4)

Patients were followed-up for a median of 3.0 years (IQR range: 1.2-4.6 years). MACE event rates were not different between the groups at 1 year (IH 11.8% vs OOH 11.3%; p=0.757) or 3 years (14.2% vs 13.2%; p=0.489). Mortality rates at 1 year (IH 6.3% vs OOH 6.2%; p=0.934) and 3 years (OOH 7.1% vs 7.3%; p=0.938) were not different between the groups.

Predictors of Long term Outcome

Timing of PPCI (out-of-hours vs in-hours) was not a univariate predictor of all cause mortality (unadjusted hazard ratio 1.04 (95% confidence intervals 0.78-1.39) (Figure 5). Incorporation of timing of PPCI into a multivariate cox model did not change this (adjusted hazard ratio 1.03 (95% confidence intervals 0.70-1.50) (Figure 6). In addition, timing of PPCI was also not an independent predictor of MACE (unadjusted hazard ratio 0.93 (95% confidence intervals 0.76-1.14).

Stratification of risk by propensity score (Long term Outcome) (Table 5)

Analysis of patients stratified into quintiles using propensity score showed that higher risk patients were less likely to undergo PPCI out-of-hours (68.2% in Q1 v 57.8% in Q5; table 5). There was no significant difference in long-term mortality between IH and OOH in any of the propensity score quintiles (Overall Mantel Haenszel HR 1.09 (0.77-1.55)).

Discussion

We report both short-term and long-term outcomes after PPCI for STEMI in a large contemporary cohort of patients presenting in and out of usual hospital working hours at a regional UK heart attack centre. We have found that the timing of presentation to hospital does not affect mortality after STEMI. Importantly there was no difference in effective treatment delivery as evidenced by door-to-balloon and call-to-balloon times between patients presenting in-hours and those presenting out-of-hours. That rapid reperfusion can be achieved despite reduced staffing levels is likely to be the key to the equivalent outcomes of our OOH population.

It was first recognised in the 1970s that throughout the Western world mortality is up to 10% higher in patients admitted to acute hospitals at the weekend than during the week [6, 19] with cardiovascular disease one of the main causes of this excess mortality [19]. In particular, there has been focus towards studies that have suggested increased mortality (due to delayed care) in patients with severe medical conditions who are admitted during weekends [6]. Kostis et al also found higher mortality in patients with myocardial infarctions admitted on weekends [14].

Interest in patient management and safety outside normal working hours, has increased recently following a report by Dr Foster Intelligence that showed increased mortality in UK hospitals at the weekend [20], and suggested a clear association between this excess and reduced numbers of senior doctors in

hospitals. Our study clearly shows that the availability of a consultant-led, protocol-driven service at all times of day abolishes the excess out-of hours risk for myocardial infarction - one of the main causes of in-hospital mortality.

Hospital staffing is often reduced out-of-hours compared to normal working hours, which has been linked to increased mortality. In our study despite reduced staffing levels and support services at weekends there was no excess in adverse outcomes suggesting that suitable seniority and experience of the medical care on site is crucial rather than exact replication of weekday service provision. The clear consultant-led protocol that we adopt at our high volume institution is key to providing a standardised management strategy for patients whether it is 'in hours' or 'out of hours'. We propose that this system could be adapted to other acute medical emergencies such as upper gastrointestinal bleeds, diabetic ketoacidosis and acute cerebrovascular accidents.

Providing a 24/7 service for PPCI is a challenge for both hospitals, medical personnel and the emergency medical services. Recent studies have found that up to two third of STEMI patients are admitted to a PPCI centre outside normal working hours [2] – this was also the case for our series. A finding in the Dr Foster report [20] was that the creation of networks through rationalisation of services in parts of the UK may improve outcomes at weekends, a strategy appropriate for a population such as London. Our study shows that the creation of one such network for Primary PCI in the North East of London is safe and leads to improved outcomes. Similar strategies could be implemented for other acute

medical conditions to improve outcomes 'out of hours' without involving complete replication of weekday hospital services at the weekend.

Strengths and Limitations of the Current Study

Our study is a consecutive but retrospective observational analysis from a single centre's experience. We cannot account for the effects of residual confounding or selection bias. The strength of this study is that it assesses outcome in a large contemporary cohort of consecutive patients undergoing PPCI for STEMI in a regional Heart Attack Centre centre. Therefore, the results are likely to be widely generalisable. The large cohort also ensures that all-cause mortality can be used as the primary end point. This has the advantage of being entirely objective. As this was an observational study the findings may have been subject to confounding factors that we have been unable to control for. However, our dataset includes all major clinical variables known to affect outcome which would support the validity of our results.

Conclusions

A consultant-led protocol for provision of PPCI for treatment of STEMI is not associated with an increase in mortality for patients treated out of hours compared to in hours.

Table 1. Baseline characteristics comparing IHs vs OOHs (*p value < 0.05)

	IHs (n = 1299)	OOHs (n = 2048)	p Value
Gender (Male)	964 (74.2%)	1579 (77.1%)	P=0.051
Age (yrs)	64.02 ± 14.2	63.16 ± 14.3	P=0.126
Hypertension	509 (39.2%)	784 (38.3%)	P=0.344
Diabetes mellitus	225 (17.3%)	362 (17.7%)	P=0.424
Hypercholesterolemia	401 (30.9%)	608 (29.7%)	P=0.253
Smoking History	722 (55.6%)	1188 (58.0%)	P=0.116
Previous MI	171 (13.2%)	242 (11.8%)	P=0.156
Previous CABG	34 (2.6%)	53 (2.6%)	P=0.539
Previous PCI	129 (9.9%)	197 (9.6%)	P=0.449
Cardiogenic Shock	69 (5.3%)	131 (6.4%)	P=0.113
Ethnicity (Caucasian)	865 (66.6%)	1319 (64.4%)	P=0.226
LVEF	43.70 ± 7.5	43.69 ± 7.5	P=0.985
CRF (eGFR <60)	240 (18.5%)	367 (17.9%)	P=0.227

Table 2. Procedural characteristics comparing IHs versus OOHs (P<0.05)

	IHs (n = 1299)	OOHs (n = 2048)	p Value
Femoral Access	779 (60.0%)	1182 (57.7%)	P=0.139
Target Vessel			
Right coronary artery	565 (43.5%)	889 (43.4%)	P=0.490
Left main coronary artery	9 (0.7%)	14 (0.7%)	P=0.585
Left anterior descending (LAD)	643 (49.5%)	969 (47.3%)	P=0.139
Left circumflex coronary artery	123 (9.5%)	168 (8.2%)	P=0.137
Saphenous vein graft	14 (1.1%)	33 (1.6%)	P=0.229
Multi vessel disease	609 (46.9%)	940 (45.9%)	P=0.277
Door to Balloon Time (Median)	30 IQR [18-70]	38 IQR [21-76]	P=0.709
Door to Balloon Time >90	207 (15.9%)	352 (17.2%)	P=0.079
Symptom to Balloon Time (Median)	176 IQR [117-328]	195 IQR [125-330]	P=0.562
Call to Balloon Time (Median)	95 IQR [76-123]	99 IQR [81-141]	P=0.056
Glycoprotein IIb/IIIa inhibitor	1061 (81.7%)	1747 (85.3%)	P=0.007
Thrombectomy	207 (15.9%)	348 (17.0%)	P=0.448
Procedural Success	1095 (84.3%)	886 (84.5%)	P=0.530

Table 3. In-hospital outcomes post PPCI comparing IHs versus OOHs

	IHs (n = 1299)	OOHs (n = 2048)	p Value
Complications			
Bleeding Complications	48 (3.7%)	61 (3.0%)	P=0.165
Haematoma	9 (0.7%)	8 (0.4%)	P=0.274
Blood Transfusion	30 (2.3%)	33 (1.6%)	P=0.140
In Hospital MACE			
Mortality	42 (3.2%)	74 (3.6%)	P=0.321
MI	7 (0.6%)	15 (0.7%)	P=0.415
CVA	2 (0.2%)	6 (0.2%)	P=0.642
Re-intervention PCI	11 (0.9%)	10 (0.5%)	P=0.170
30 day MACE			
Mortality	56 (4.3%)	82 (4.0%)	P=0.336
MI	26 (2.0%)	27 (1.3%)	P=0.207
CVA	3 (0.2%)	6 (0.3%)	P=0.446
Re-intervention PCI	17 (1.3%)	6 (0.3%)	P=0.088

Table 4. Independent predictors of death, and major adverse cardiac events (re-infarction, death and unscheduled revascularisation) at log regression analyses

Event	Variables	HR (95% CI)	P value
Death	Age	1.04 (1.02-1.07)	0.001
	Shock	5.60 (2.96-10.60)	P<0.0001
	eGFR>60	0.32 (0.18-0.58)	P<0.0001
	EF>40	0.18 (0.09-0.36)	P<0.0001
	Procedural Success	0.17 (0.09-0.32)	P<0.0001
	Multi-vessel disease	1.92 (0.99-3.73)	0.053
	Out of Hours	0.74 (0.42-1.29)	0.284
MACE	Age	1.02 (1.01-1.05)	P<0.0001
	Shock	3.94 (2.30-6.74)	P<0.0001
	eGFR>60	0.44 (0.28-0.69)	P<0.0001
	EF>40	0.46 (0.30-0.71)	P<0.0001
	Procedural Success	0.26 (0.15-0.46)	P<0.0001
	Multi-vessel disease	1.57 (1.31-1.90)	0.003
	Out of Hours	0.81 (0.54-1.22)	0.316

Figure 1. Boxplots illustrating door-to-balloon times for PPCI performed IHs and OOHs. The median door-to-balloon time is indicated. The boundaries of the box plots refer to the 25th and 75th percentiles, with the whisker bars representing the 5th and 95th percentiles.

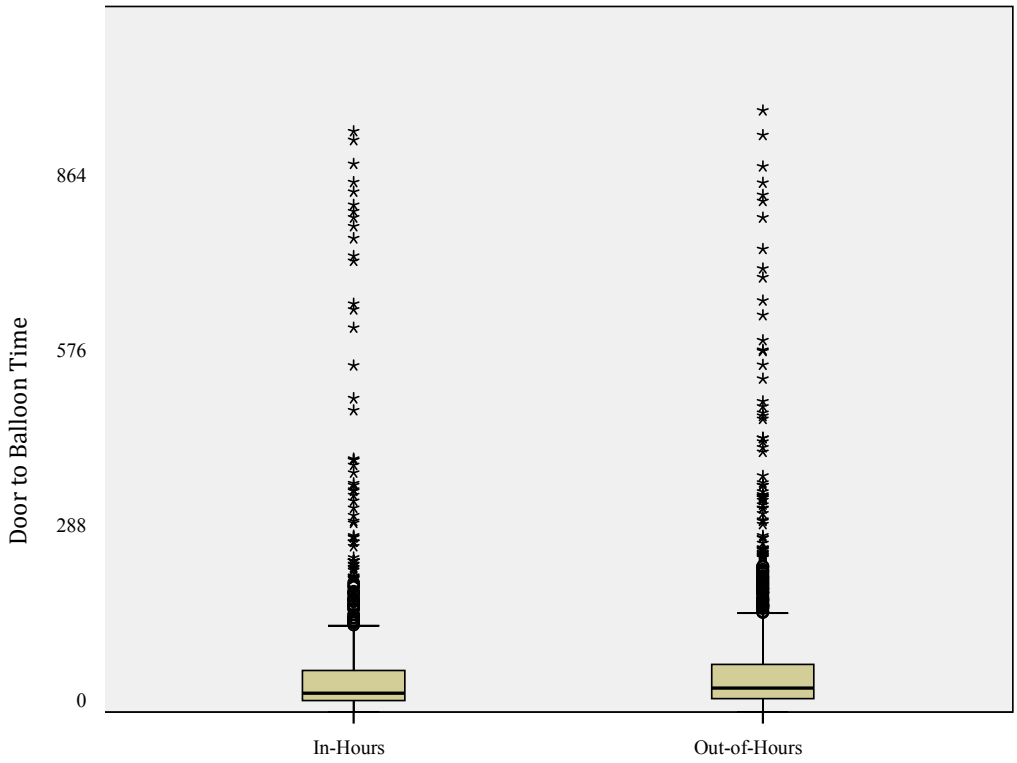
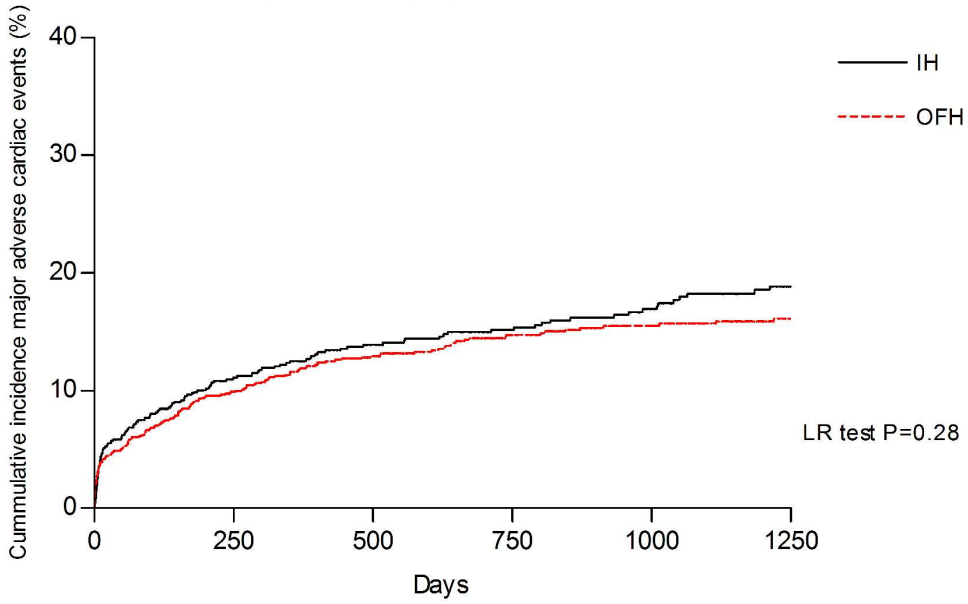


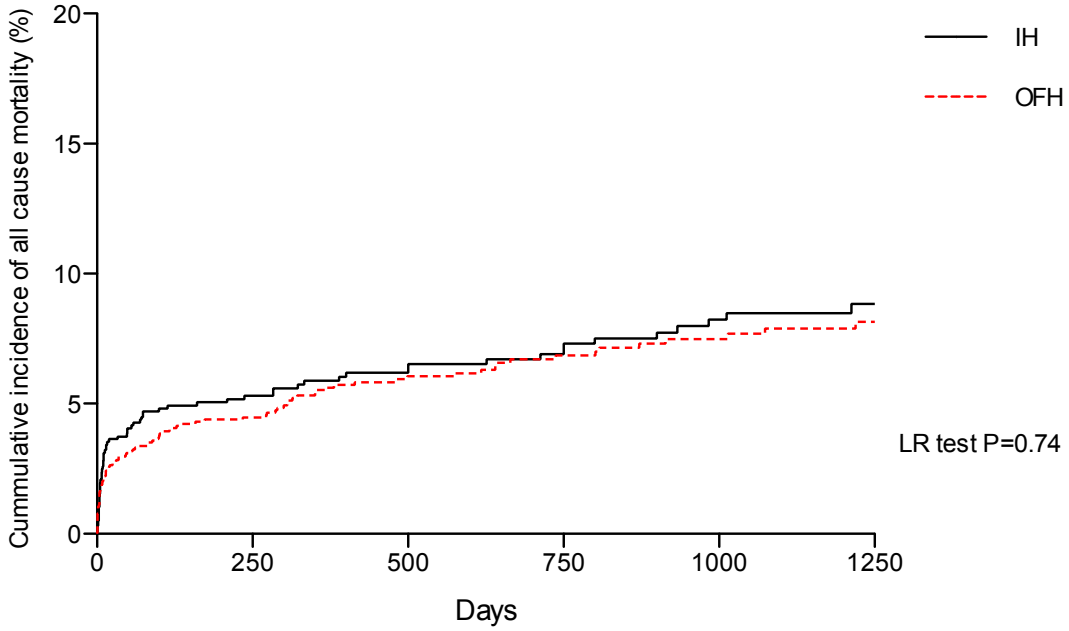
Figure 2 Kaplan Meier curves showing cumulative probability of major adverse cardiac events (MACE) after PCI comparing IHs versus OOHs



Numbers at risk

IH	1299	844	668	545	428	295
OFH	2048	1296	992	784	599	434

Figure 3 Kaplan Meier curves showing cumulative probability of all-cause mortality after PPCI comparing IHs versus OOHs



Numbers at risk

IH	1299	930	748	619	481	339
OFH	2048	1415	1083	861	651	465

Figure 4 Kaplan Meier curves showing cumulative incidence of a). Myocardial infarction and b). Target vessel revascularisation after PPCI comparing IHs versus OOHs

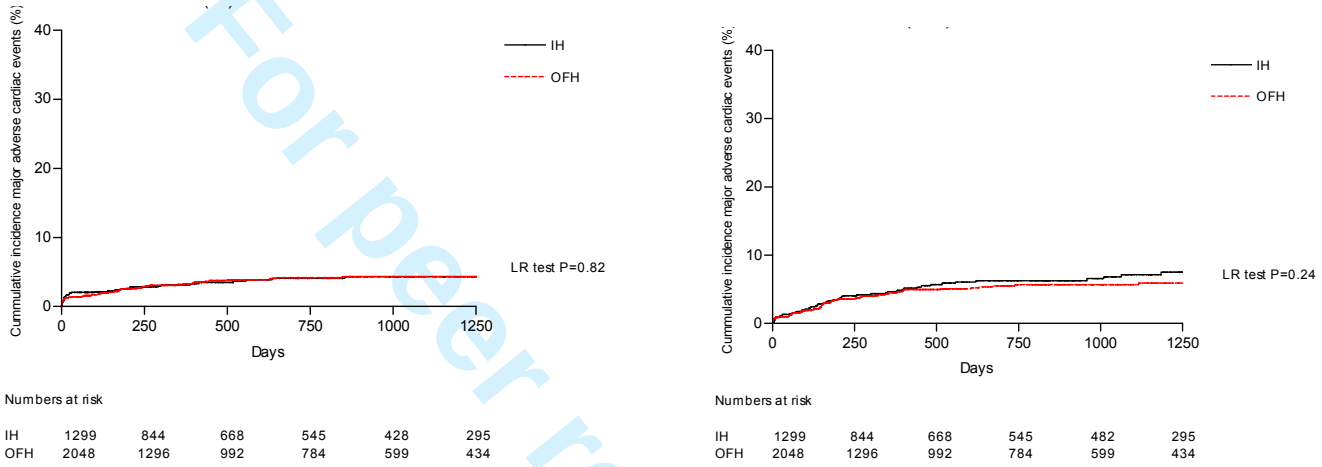


Table 5. Five year mortality rates stratified by propensity score comparing patients treated IHs and OOHs with PPCI

Quintile	OOHs procedures (%)	OOHs mortality rate	IHs mortality rate	Risk ratio (95% CI)
1	68.2	3.8%	0.8%	4.80 (0.61-37.94)
2	64.5	4.8%	5.8%	0.82 (0.33-2.05)
3	61.5	8.4%	6.9%	0.81 (0.38-1.71)
4	57.5	7.7%	7.6%	1.02 (0.49-2.15)
5	57.8	15.7%	13.1%	1.23 (0.70-2.18)
			Overall Mantel Haenszel RR	1.09 (0.77-1.55)

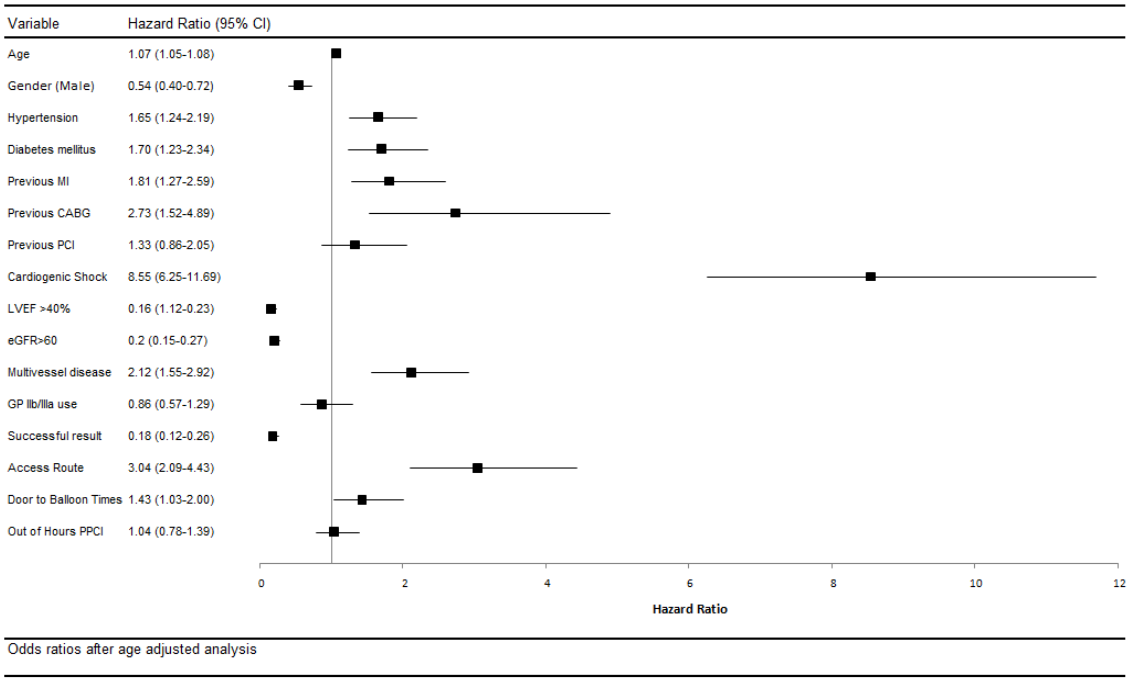


Figure 5 – Forest Plot model of age-adjusted univariate analysis of predictors of mortality

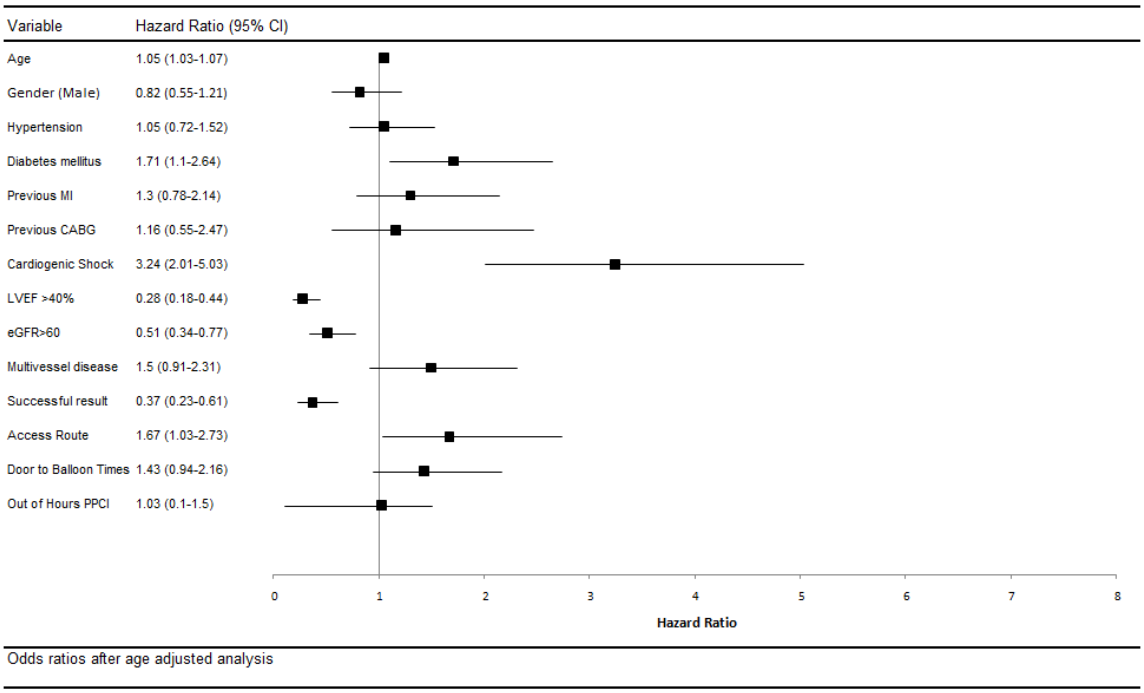


Figure 6 – Forest Plot model of multivariate analysis of predictors of mortality

Contributorship

Krishnaraj S Rathod, Daniel A Jones, Sean M Gallagher, Daniel Bromage, Mark Whitbread, Andrew Archbold, Ajay Jain, Anthony Mathur, Andrew Wragg and Charles Knight

All the above authors of this paper fulfil all three of the ICMJE guidelines for authorship which are

1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data;

2) drafting the article or revising it critically for important intellectual content; and

3) final approval of the version to be published.

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Competing Interests

None

Data sharing

No further additional unpublished data is available

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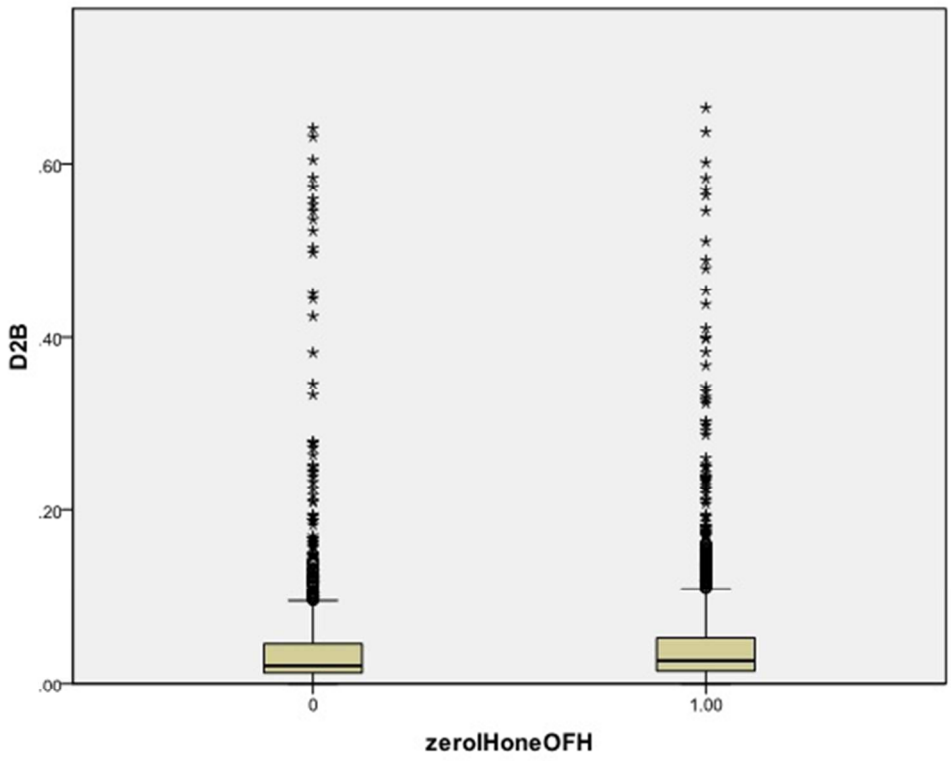

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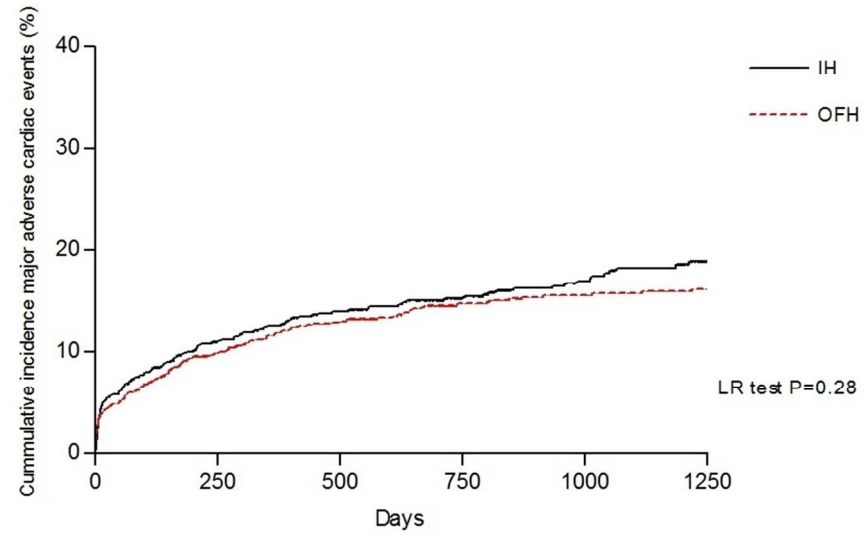

Numbers at risk

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OFH	2048	1296	992	784	599	434

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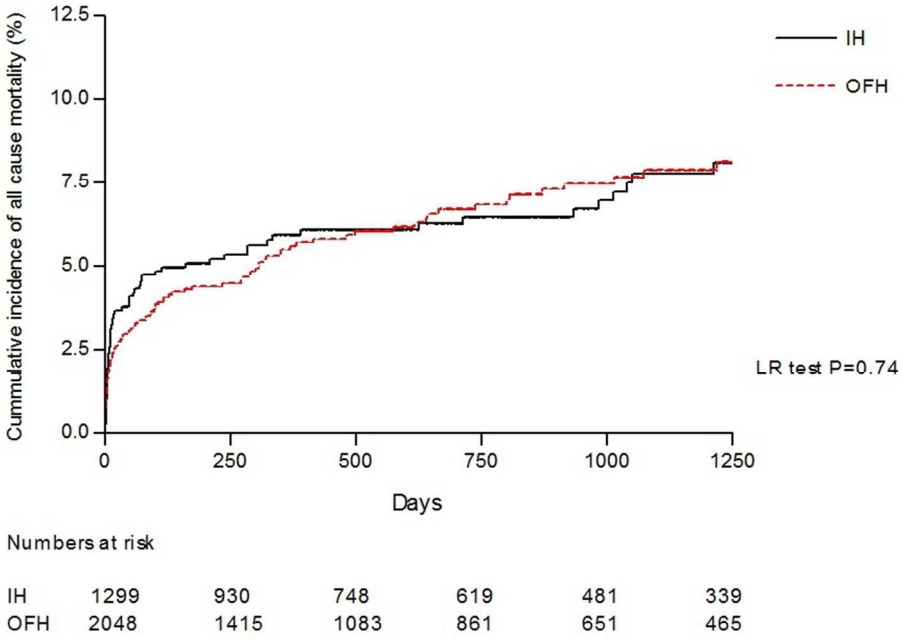

Numbers at risk

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OFH	2048	1415	1083	861	651	465

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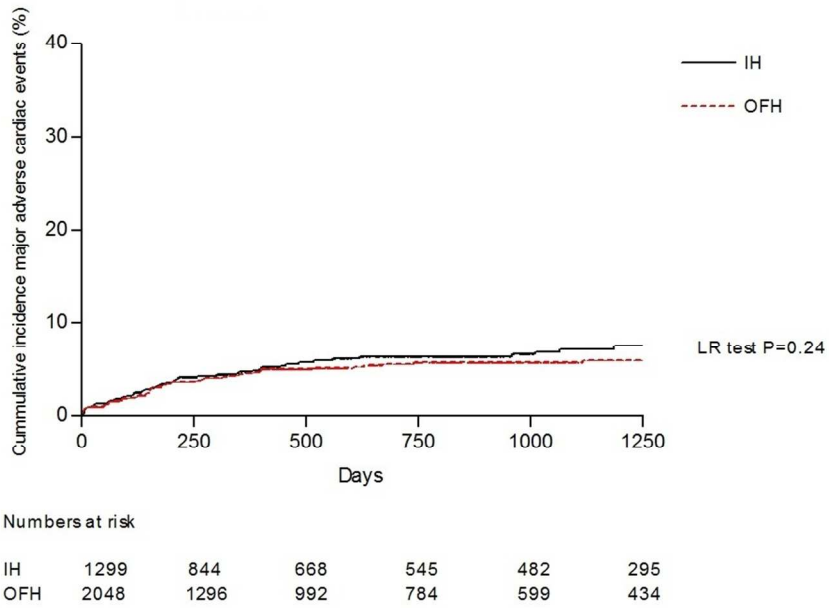

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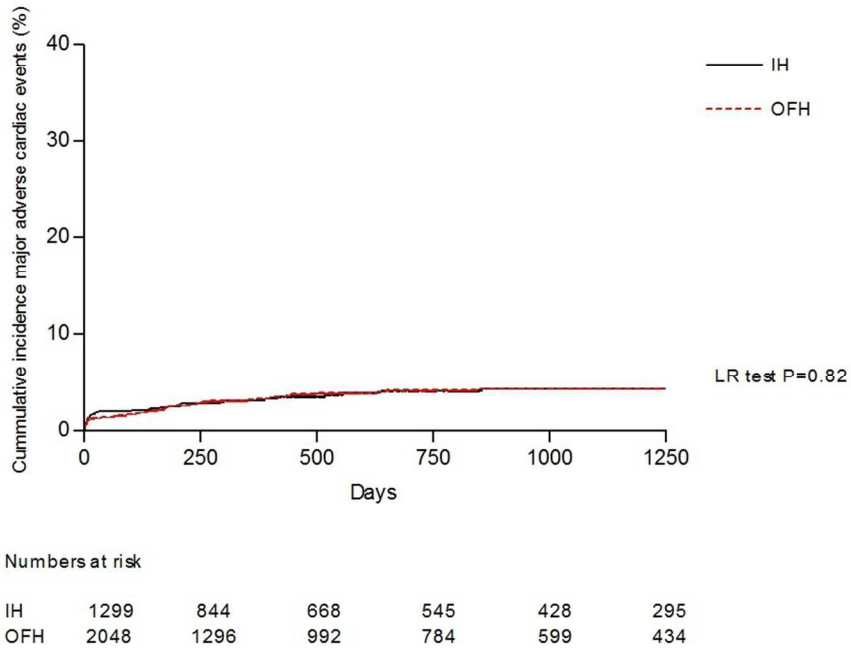

Numbers at risk

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OFH	2048	1296	992	784	599	434

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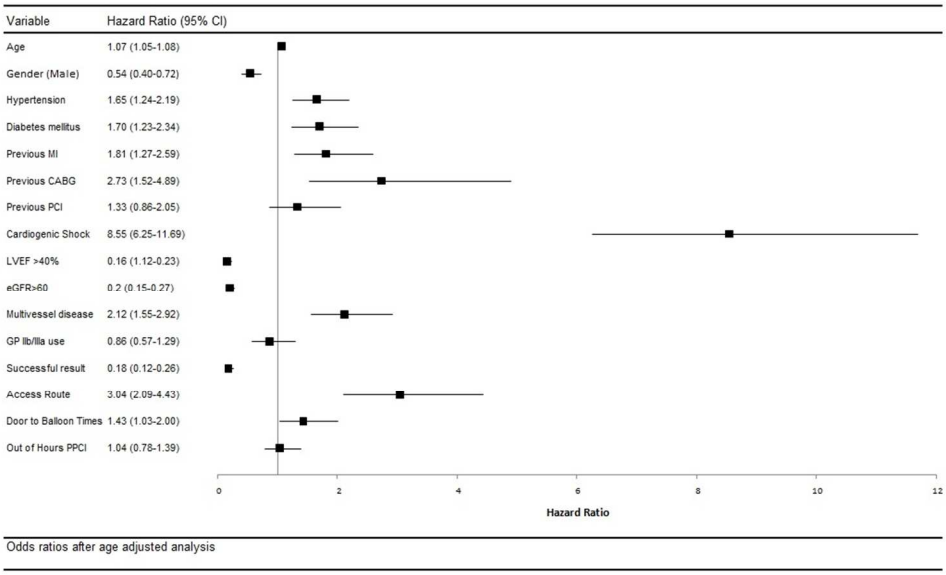

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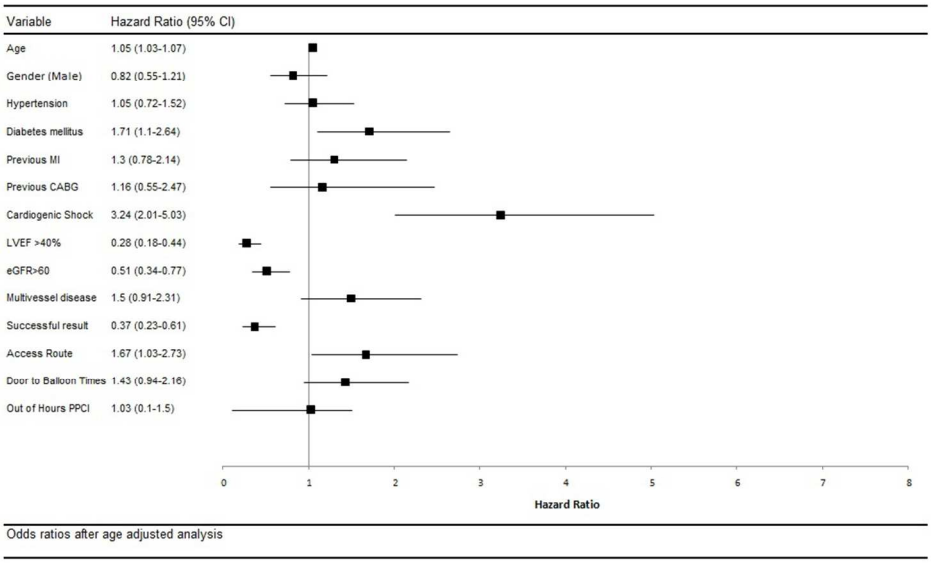

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STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract ✓
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found ✓
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported ✓
Objectives	3	State specific objectives, including any prespecified hypotheses ✓
Methods		
Study design	4	Present key elements of study design early in the paper ✓
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection ✓
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants ✓
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable ✓
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group ✓
Bias	9	Describe any efforts to address potential sources of bias ✓
Study size	10	Explain how the study size was arrived at ✓
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why ✓
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding ✓
		(*b*) Describe any methods used to examine subgroups and interactions ✓
		(*c*) Explain how missing data were addressed ✓
		(*d*) If applicable, describe analytical methods taking account of sampling strategy ✓
		(*e*) Describe any sensitivity analyses ✓
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed ✓
		(b) Give reasons for non-participation at each stage ✓
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders ✓
		(b) Indicate number of participants with missing data for each variable of interest ✓
Outcome data	15*	Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included ✓
		(*b*) Report category boundaries when continuous variables were categorized ✓
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period ✓
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses ✓

Discussion		
Key results	18	Summarise key results with reference to study objectives ✓
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias ✓
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence ✓
Generalisability	21	Discuss the generalisability (external validity) of the study results ✓
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Out of hours Primary Percutaneous Coronary Intervention for ST-elevation myocardial infarction is not associated with excess mortality. A study of 3347 patients treated in an integrated cardiac network

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Out of hours Primary Percutaneous Coronary Intervention for ST-elevation myocardial infarction is not associated with excess mortality. A study of 3347 patients treated in an integrated cardiac network

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Article Summary

Article Focus:

- Recent emerging evidence has suggested that patients admitted during the to hospital out of hours have a higher mortality than those admitted during the normal working day. Whether this is true for patients with ST-Elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PPCI) is unclear.
- The optimum delivery of PPCI requires an integrated network of hospitals, following a multidisciplinary, consultant-led, protocol-driven approach. We investigated whether such a strategy was effective in providing equally effective in-hospital and long-term outcomes for STEMI patients treated by PPCI within normal working hours compared with those treated out of-hours.

Key Messages:

- A consultant-led protocol for provision of PPCI for treatment of STEMI is not associated with an increase in mortality for patients treated out of hours compared to in hours.
- Delivery of primary PCI with a multidisciplinary, consultant-led, protocol-driven approach delivers safe and effective treatment for patients regardless of the time of presentation.
- Similar strategies could be implemented for other acute medical conditions to improve outcomes 'out of hours' without involving complete replication of weekday hospital services at the weekend.

Strengths and Limitations of the Current Study

- The strength of this study is that it assesses outcome in a large contemporary cohort of consecutive patients undergoing PPCI for STEMI in a regional Heart Attack Centre centre, therefore, the results are likely to be widely generalisable. The large cohort also ensures that all-cause mortality can be used as the primary end point, which has the advantage of being entirely objective.
- This study is a consecutive but retrospective observational analysis from a single centre's experience. We cannot account for the effects of residual confounding factors or selection bias that we have been unable to control for.

Abstract

Objectives

Timely delivery of primary percutaneous coronary intervention (PPCI) is the treatment of choice for STEMI. Optimum delivery of PPCI requires an integrated network of hospitals, following a multidisciplinary, consultant-led, protocol-driven approach. We investigated whether such a strategy was effective in providing equally effective in-hospital and long-term outcomes for STEMI patients treated by PPCI within normal working hours compared with those treated out of-hours.

Design: Observational study

Setting: Large PPCI centre in London.

Participants: 3347 STEMI patients were treated with PPCI between 2004 and 2012. The follow-up median was 3.3 years (IQR: 1.2-4.6 years).

Primary and secondary outcome measures: The primary end-point was long-term major adverse cardiac events (MACE) with all cause mortality a secondary endpoint.

Results

Of the 3347 STEMI patients, 1299 patients (38.8%) underwent PPCI during a weekday between 08:00 and 18:00 (routine-hours group) and 2048 (61.2%) underwent PPCI on a weekday between 18:00 and 08:00 or a weekend (out-of-

hours group).

There were no differences in baseline characteristics between the two groups with comparable door to balloon times (IHs 67.8mins vs OOHs 69.6mins, p=0.709), call to balloon times (IHs 116.63 vs OOHs 127.15mins, p=0.60) and procedural success. In hospital mortality rates were comparable between the two groups (IHs 3.6% vs OFHs 3.2%) with timing of presentation not predictive of outcome (HR 1.25 (95%CI 0.74-2.11). Over the follow-up period there were no significant differences in rates of mortality (IHs 7.4% vs. OFHs 7.2%, p=0.442) or MACE (IHs 15.4% vs. OFHs 14.1%, p=0.192) between the two groups. After adjustment for confounding variables using multivariate analysis, timing of presentation was not an independent predictor of mortality (HR 1.04 95%CI: 0.78-1.39).

Conclusion

This large registry study demonstrates that the delivery of PPCI with a multidisciplinary, consultant-led, protocol-driven approach delivers safe and effective treatment for patients regardless of the time of presentation.

Keywords: Primary PCI, In-Hours, Out of Hours, myocardial infarction

Background

There is increasing evidence suggesting that patients admitted during the weekend have a higher mortality than those admitted during the week [1, 2].This excess mortality is thought to be strongly associated with the lack of cover of senior doctors (consultant level), during the weekends [2, 3] and has led to debate around redesigning healthcare provision to eliminate reduced staffing at the weekends.

Primary percutaneous coronary intervention (PPCI) is the accepted gold standard for the treatment of ST-segment elevation myocardial infarction (STEMI) as recognized in all recent guidelines [4-6], and needs to be available at all hours (24/7). The delivery of PPCI services represents a significant logistical challenge, especially as many patients with STEMI present outside of usual hospital working hours (0800 to 1700) and at weekends. Whether patients with STEMI presenting outside of usual hospital working hours have inferior outcomes when compared with patients that present during the working day is still unclear.

Previous studies have demonstrated differing results in outcome after PPCI during 'in-hours' compared to 'out of hours'. Some studies showing no association with adverse outcomes and timing [7-14], whereas other studies suggested higher rates of mortality after PPCI during 'out of hours' compared to 'in hours' [2, 15-18]. It is difficult to compare these studies directly because of

differences in patient characterises and variability in other treatment provided to patients – for example, some of these studies also used fibrinolysis [9, 13, 16, 17, 19].

The aim of this study was therefore to clarify the relative outcomes of patients with STEMI presenting to a UK regional PPCI centre outside of usual hospital working hours with patients presenting during usual working hours.

Methods

This was an observational cohort study of 3347 consecutive patients undergoing PPCI in a high volume centre between January 2004 and July 2012. These patients were divided into two groups based on the timing of PPCI (time taken as hospital arrival time) Those undergoing PPCI during usual hospital working hours, designated 'in-hours' group (IH) (between 0800 and 1700 Monday to Friday) and those undergoing PPCI outside of usual hospital working hours, designated 'out of hours group' (OOH) (i.e. between 1701 and 0759 Monday to Friday and from 1701 Friday to 0759 Monday).

Service arrangement

The London Chest hospital (LCH) is the tertiary heart attack center for the North-East region of London and receives patients with STEMI for primary PCI in an unselected manner. This includes patients with cardiogenic shock and post cardiac arrest, including intubated and ventilated patients. The hospital serves a well developed network of 6 local district general hospitals covering a

population of 1.6 million people and includes close working with the London Ambulance Service. Patients are taken directly to the cardiac catheterization laboratory 24 hours a day with all cases performed by/under supervision of a consultant. Out of hours the catheterization laboratory is covered by an 'on-call team'. The on-call team is composed of an interventional cardiologist, a senior cardiology trainee, two cardiac catheterization laboratory nurses, a cardiac physiologist, and a radiographer. Aside from the senior cardiology trainee who is resident in hospital out of hours, all the on-call team members are non-resident. Out of hours there are also reduced trainees covering the patients care post procedure and other non-cardiac hospital services are also reduced with lower levels of staffing in radiology, pathology and anaesthetics (ITU) (All of these services follow a similar consultant lead service out of hours).

PPCI pathway

During out of hours the on-call team members are contacted immediately upon acceptance of a patient for PPCI. The on-call team members will be in the hospital within 40 minutes of the original call and the catheterization laboratory will be ready to take the patient as soon as they arrive. In the majority of cases, the on-call team will be in the hospital before the arrival of the patient. During routine-working hours, the on-call team is in the hospital and the catheterization laboratories are fully functioning. Upon accepting a patient, the catheterization laboratory coordinators inform the on-call interventional cardiologist and cardiology trainee and the next available free catheterization laboratory is identified. The patient is taken to the catheterization laboratory and PPCI is

performed by the interventional cardiologist who is working in that laboratory. Standard PPCI protocol for our institution includes pre-loading with 300mg aspirin, 300mg or 600mg clopidogrel and GPIIb/IIIA inhibitors unless contraindicated. Aspiration thombectomy was performed at the operator's discretion.

Data was entered prospectively into the clinical database at the time of PPCI including patient characteristics, procedural factors and procedural complications. Successful primary PCI result was defined as final Thrombolysis In Myocardial Infarction flow grade 3 and residual stenosis <30% in the infarct-related artery at the end of the procedure. Post-discharge complications and further revascularisation procedures were entered retrospectively from the electronic patient record and cardiac surgical database. Major Adverse Cardiac Events were defined as death, recurrent myocardial infarction (defined as 'new ischaemic pain with new ST elevation, or ischaemic ECG changes and further elevation of enzymes (increase of creatine kinase-MB to ≥ 2 times the reference value or rise in Troponin T >30ng/l (99th centile <10ng/l)), whether treated with further revascularisation therapy or not') and target vessel revascularisation. MACE events (identified from patient notes and electronic records) were adjudicated by 3 independent physicians who were not involved in the procedure and were unaware of the patient's PPCI timing (in versus out of hours). All-cause mortality was recorded to 11th September 2012 from the UK Office of National Statistics. A retrospective data quality audit of 100 randomly selected medical records established that 94.8% of data fields, including complications, were entered correctly into the database.

Ethics

The data were collected as part of a mandatory national cardiac audit and all patient identifiable fields were removed prior to analysis. The local ethics committee advised us that formal ethical approval was not required.

Statistical analysis

Continuous variables are presented as mean±SD, categorical variables as absolute number and percentages. Normality of distribution of continuous variables was assessed using the Shapiro-Wilkes test. Normally distributed continuous variables were compared with unpaired t-tests, and non-normally distributed variables were compared with the Mann-Whitney test. Categorical variables were compared using the $\chi 2$-test or Fisher's exact test when appropriate. Kaplan Meier curves were used to represent survival and cumulative incidence of events over follow-up, with the log rank test used for evidence of a statistically significant difference between the groups. Time was measured from the first admission for a procedure to outcome (all cause mortality). The association of timing of PPCI (OOH vs IH) with 30-day mortality was assessed using logistic regression analysis, and long-term mortality using Cox regression analyses. The proportional hazard assumption was satisfied for all outcomes evaluated. Finally, a non-parsimonious logistic regression model with procedural timing as the dependent variable was constructed incorporating all baseline clinical and procedural characteristics listed in table 1 and table 2 to generate a propensity score (ie the predicted probability of procedural timing for

each patient), which ranged between 0 and 1, for each patient. We the subdivided our cohort into quintiles based on propensity score so that comparisons could be made between patients with similar baseline probabilities of mortality[20]. The rates of 30-day and 5-year mortality in the IH vs OOH groups in each quintile were compared. Risk ratios (RRs) for mortality were calculated for each quintile, as well as an overall Mantel-Hantzel RR for the stratified analysis.

Results

Within our study population of 3347 patients 1299 (38.8%) PPCIs were performed In-Hours (IHs) and 2048 (61.2%) PPCIs were performed Out-of-Hours (OOHs).

Patient characteristics (Table 1)

Table 1 demonstrates the baseline characteristics between the two groups. There were no differences in baseline characteristics between the IHs group versus the OOHs group.

Procedural Characteristics and Outcomes (Table 2)

There was no difference in access route or target vessel intervention between the two groups. Although the Door to Balloon time were slightly longer in the OOHs group compared to the IHs group, this difference was not statistically significant (Figure 1). In addition, there was no statistically significant difference in the Call to Balloon time between the two groups. There were higher rates of glycoprotein IIb/IIIa inhibitor use in the OOHs group compared to the IHs group. Procedural success rates and use of thrombectomy were similar between the two groups.

Early Outcomes (Table 3)

There were no differences in in-hospital MACE rates (IH 4.5% vs OOH 5.0%; p=0.644). There was no difference in either 30-day MACE rates (IH 6.3% vs OOH 5.8%; p=0.580) or 30 day mortality rates (IH 4.4% vs OOH 4.0%; p=0.613) between the groups.

Predictors of early Outcome (Table 4)

In terms of early (30 day) all-cause mortality and MACE events, Out of hours PPCI was not an independent predictor of mortality (HR 0.74 (95% CI: 0.42-1.29) and MACE events (HR 0.81 (95% CI 0.54-1.22). However, as expected, reduced renal function, shock, low EF and procedural success were independent predictors of early outcome (Table 4).

Long term Outcome (Figures 2-4)

Patients were followed-up for a median of 3.0 years (IQR range: 1.2-4.6 years). MACE event rates were not different between the groups at 1 year (IH 11.8% vs OOH 11.3%; p=0.757) or 3 years (14.2% vs 13.2%; p=0.489). Mortality rates at 1 year (IH 6.3% vs OOH 6.2%; p=0.934) and 3 years (OOH 7.1% vs 7.3%; p=0.938) were not different between the groups.

Predictors of Long term Outcome

Timing of PPCI (out-of-hours vs in-hours) was not a univariate predictor of all cause mortality (unadjusted hazard ratio 1.04 (95% confidence intervals 0.78-1.39) (Figure 5). Incorporation of timing of PPCI into a multivariate cox model did not change this (adjusted hazard ratio 1.03 (95% confidence intervals 0.70-1.50) (Figure 6). In addition, timing of PPCI was also not an independent predictor of MACE (unadjusted hazard ratio 0.93 (95% confidence intervals 0.76-1.14).

Stratification of risk by propensity score (Long term Outcome) (Table 5)

Analysis of patients stratified into quintiles using propensity score showed that higher risk patients were less likely to undergo PPCI out-of-hours (68.2% in Q1 v 57.8% in Q5; table 5). There was no significant difference in long-term mortality between IH and OOH in any of the propensity score quintiles (Overall Mantel Haenszel HR 1.09 (0.77-1.55)).

Discussion

We report both short-term and long-term outcomes after PPCI for STEMI in a large contemporary cohort of patients presenting in and out of usual hospital working hours at a regional UK heart attack centre. We have found that the timing of presentation to hospital does not affect mortality after STEMI. Importantly there was no difference in effective treatment delivery as evidenced by door-to-balloon and call-to-balloon times between patients presenting in-hours and those presenting out-of-hours. That rapid reperfusion can be achieved despite reduced staffing levels is likely to be the key to the equivalent outcomes of our OOH population.

It was first recognised in the 1970s that throughout the Western world mortality is up to 10% higher in patients admitted to acute hospitals at the weekend than during the week [7, 21] with cardiovascular disease one of the main causes of this excess mortality [21]. In particular, there has been focus towards studies that have suggested increased mortality (due to delayed care) in patients with severe medical conditions who are admitted during weekends [7]. Kostis et al also found higher mortality in patients with myocardial infarctions admitted on weekends [16].

Interest in patient management and safety outside normal working hours, has increased recently following a report by Dr Foster Intelligence that showed increased mortality in UK hospitals at the weekend [22], and suggested a clear association between this excess and reduced numbers of senior doctors in

hospitals. Our study clearly shows that the availability of a consultant-led, protocol-driven service at all times of day abolishes the excess out-of hours risk for myocardial infarction - one of the main causes of in-hospital mortality.

Hospital staffing is often reduced out-of-hours compared to normal working hours, which has been linked to increased mortality. In our study despite reduced staffing levels and support services at weekends there was no excess in adverse outcomes suggesting that suitable seniority and experience of the medical care on site is crucial rather than exact replication of weekday service provision. The clear consultant-led protocol that we adopt at our high volume institution is key to providing a standardised management strategy for patients whether it is 'in hours' or 'out of hours'. In our opinion, this system could be adapted to other acute medical emergencies such as upper gastrointestinal bleeds, diabetic ketoacidosis and acute cerebrovascular accidents, although we appreciate the impact of a consultant-led protocol is likely to be different between procedure based and non-procedure based emergency therapies.

Providing a 24/7 service for PPCI is a challenge for both hospitals, medical personnel and the emergency medical services. Recent studies have found that up to two third of STEMI patients are admitted to a PPCI centre outside normal working hours [3] – this was also the case for our series. A finding in the Dr Foster report [22] was that the creation of networks through rationalisation of services in parts of the UK may improve outcomes at weekends, a strategy appropriate for a population such as London. Our study shows that the creation of one such network for Primary PCI in the North East of London is safe and leads to

improved outcomes. Similar strategies could be implemented for other acute medical conditions to improve outcomes 'out of hours' without involving complete replication of weekday hospital services at the weekend.

Strengths and Limitations of the Current Study

Our study is a consecutive but retrospective observational analysis from a single centre's experience. We cannot account for the effects of residual confounding or selection bias. The strength of this study is that it assesses outcome in a large contemporary cohort of consecutive patients undergoing PPCI for STEMI in a regional Heart Attack Centre centre. Therefore, the results are likely to be widely generalisable. The large cohort also ensures that all-cause mortality can be used as the primary end point. This has the advantage of being entirely objective. As this was an observational study the findings may have been subject to confounding factors that we have been unable to control for. However, our dataset includes all major clinical variables known to affect outcome which would support the validity of our results.

Conclusions

A consultant-led protocol for provision of PPCI for treatment of STEMI is not associated with an increase in mortality for patients treated out of hours compared to in hours.

Table 1. Baseline characteristics comparing IHs vs OOHs (*p value < 0.05)

	IHs (n = 1299)	OOHs (n = 2048)	p Value
Gender (Male)	964 (74.2%)	1579 (77.1%)	P=0.051
Age (yrs)	64.02 ± 14.2	63.16 ± 14.3	P=0.126
Hypertension	509 (39.2%)	784 (38.3%)	P=0.344
Diabetes mellitus	225 (17.3%)	362 (17.7%)	P=0.424
Hypercholesterolemia	401 (30.9%)	608 (29.7%)	P=0.253
Smoking History	722 (55.6%)	1188 (58.0%)	P=0.116
Previous MI	171 (13.2%)	242 (11.8%)	P=0.156
Previous CABG	34 (2.6%)	53 (2.6%)	P=0.539
Previous PCI	129 (9.9%)	197 (9.6%)	P=0.449
Cardiogenic Shock	69 (5.3%)	131 (6.4%)	P=0.113
Ethnicity (Caucasian)	865 (66.6%)	1319 (64.4%)	P=0.226
LVEF	43.70 ± 7.5	43.69 ± 7.5	P=0.985
CRF (eGFR <60)	240 (18.5%)	367 (17.9%)	P=0.227

Table 2. Procedural characteristics comparing IHs versus OOHs (P<0.05)

	IHs (n = 1299)	OOHs (n = 2048)	p Value
Femoral Access	779 (60.0%)	1182 (57.7%)	P=0.139
Target Vessel			
Right coronary artery	565 (43.5%)	889 (43.4%)	P=0.490
Left main coronary artery	9 (0.7%)	14 (0.7%)	P=0.585
Left anterior descending (LAD)	643 (49.5%)	969 (47.3%)	P=0.139
Left circumflex coronary artery	123 (9.5%)	168 (8.2%)	P=0.137
Saphenous vein graft	14 (1.1%)	33 (1.6%)	P=0.229
Multi vessel disease	609 (46.9%)	940 (45.9%)	P=0.277
Door to Balloon Time (Median)	30 IQR [18-70]	38 IQR [21-76]	P=0.709
Door to Balloon Time >90	207 (15.9%)	352 (17.2%)	P=0.079
Symptom to Balloon Time (Median)	176 IQR [117-328]	195 IQR [125-330]	P=0.562
Call to Balloon Time (Median)	95 IQR [76-123]	99 IQR [81-141]	P=0.056
Glycoprotein IIb/IIIa inhibitor	1061 (81.7%)	1747 (85.3%)	P=0.007
Thrombectomy	207 (15.9%)	348 (17.0%)	P=0.448
Procedural Success	1095 (84.3%)	886 (84.5%)	P=0.530

Table 3. In-hospital outcomes post PPCI comparing IHs versus OOHs

	IHs (n = 1299)	OOHs (n = 2048)	p Value
Complications			
Bleeding Complications	48 (3.7%)	61 (3.0%)	P=0.165
Haematoma	9 (0.7%)	8 (0.4%)	P=0.274
Blood Transfusion	30 (2.3%)	33 (1.6%)	P=0.140
In Hospital MACE			
Mortality	42 (3.2%)	74 (3.6%)	P=0.321
MI	7 (0.6%)	15 (0.7%)	P=0.415
CVA	2 (0.2%)	6 (0.2%)	P=0.642
Re-intervention PCI	11 (0.9%)	10 (0.5%)	P=0.170
30 day MACE			
Mortality	56 (4.3%)	82 (4.0%)	P=0.336
MI	26 (2.0%)	27 (1.3%)	P=0.207
CVA	3 (0.2%)	6 (0.3%)	P=0.446
Re-intervention PCI	17 (1.3%)	6 (0.3%)	P=0.088

Table 4. Independent predictors of death, and major adverse cardiac events (re-infarction, death and unscheduled revascularisation) at log regression analyses

Event	Variables	HR (95% CI)	P value
Death	Age	1.04 (1.02-1.07)	0.001
	Shock	5.60 (2.96-10.60)	P<0.0001
	eGFR>60	0.32 (0.18-0.58)	P<0.0001
	EF>40	0.18 (0.09-0.36)	P<0.0001
	Procedural Success	0.17 (0.09-0.32)	P<0.0001
	Multi-vessel disease	1.92 (0.99-3.73)	0.053
	Out of Hours	0.74 (0.42-1.29)	0.284
MACE	Age	1.02 (1.01-1.05)	P<0.0001
	Shock	3.94 (2.30-6.74)	P<0.0001
	eGFR>60	0.44 (0.28-0.69)	P<0.0001
	EF>40	0.46 (0.30-0.71)	P<0.0001
	Procedural Success	0.26 (0.15-0.46)	P<0.0001
	Multi-vessel disease	1.57 (1.31-1.90)	0.003
	Out of Hours	0.81 (0.54-1.22)	0.316

Figure legends:

Figure 1. Boxplots illustrating door-to-balloon times for PPCI performed IHs and OOHs. The median door-to-balloon time is indicated. The boundaries of the box plots refer to the 25th and 75th percentiles, with the whisker bars representing the 5th and 95th percentiles.

Figure 2 Kaplan Meier curves showing cumulative probability of major adverse cardiac events (MACE) after PCI comparing IHs versus OOHs

Figure 3 Kaplan Meier curves showing cumulative probability of all-cause mortality after PPCI comparing IHs versus OOHs

Figure 4 Kaplan Meier curves showing cumulative incidence of a). Myocardial infarction and b). Target vessel revascularisation after PPCI comparing IHs versus OOHs

Figure 5 – Forest Plot model of age-adjusted univariate analysis of predictors of mortality

Figure 6 – Forest Plot model of multivariate analysis of predictors of mortality

Table 5. Five year mortality rates stratified by propensity score comparing patients treated IHs and OOHs with PPCI

Quintile	OOHs procedures (%)	OOHs mortality rate	IHs mortality rate	Risk ratio (95% CI)
1	68.2	3.8%	0.8%	4.80 (0.61-37.94)
2	64.5	4.8%	5.8%	0.82 (0.33-2.05)
3	61.5	8.4%	6.9%	0.81 (0.38-1.71)
4	57.5	7.7%	7.6%	1.02 (0.49-2.15)
5	57.8	15.7%	13.1%	1.23 (0.70-2.18)
			Overall Mantel Haenszel RR	1.09 (0.77-1.55)

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Out of hours Primary Percutaneous Coronary Intervention for ST-elevation myocardial infarction is not associated with excess mortality. A study of 3347 patients treated in an integrated cardiac network

~~Primary Percutaneous Coronary Intervention for ST-elevation myocardial infarction (STEMI): consultant-led protocols for treatment are not associated with excess out of hours mortality~~

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Article Summary

Article Focus:

- Recent emerging evidence has suggested that patients admitted during the to hospital out of hours have a higher mortality than those admitted during the normal working day. Whether this is true for patients with ST-Elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PPCI) is unclear.
- The optimum delivery of PPCI requires an integrated network of hospitals, following a multidisciplinary, consultant-led, protocol-driven approach. We investigated whether such a strategy was effective in providing equally effective in-hospital and long-term outcomes for STEMI patients treated by PPCI within normal working hours compared with those treated out of-hours.

Key Messages:

- A consultant-led protocol for provision of PPCI for treatment of STEMI is not associated with an increase in mortality for patients treated out of hours compared to in hours.
- Delivery of primary PCI with a multidisciplinary, consultant-led, protocol-driven approach delivers safe and effective treatment for patients regardless of the time of presentation.
- Similar strategies could be implemented for other acute medical conditions to improve outcomes 'out of hours' without involving complete replication of weekday hospital services at the weekend.

Strengths and Limitations of the Current Study

- The strength of this study is that it assesses outcome in a large contemporary cohort of consecutive patients undergoing PPCI for STEMI in a regional Heart Attack Centre centre, therefore, the results are likely to be widely generalisable. The large cohort also ensures that all-cause mortality can be used as the primary end point, which has the advantage of being entirely objective.
- This study is a consecutive but retrospective observational analysis from a single centre's experience. We cannot account for the effects of residual confounding factors or selection bias that we have been unable to control for.

Abstract

Objectives

Timely delivery of primary percutaneous coronary intervention (PPCI) is the treatment of choice for STEMI. Optimum delivery of PPCI requires an integrated network of hospitals, following a multidisciplinary, consultant-led, protocol-driven approach. We investigated whether such a strategy was effective in providing equally effective in-hospital and long-term outcomes for STEMI patients treated by PPCI within normal working hours compared with those treated out of-hours.

Design: Observational study

Setting: Large PPCI centre in London.

Participants: 3347 STEMI patients were treated with PPCI between 2004 and 2012. The follow-up median was 3.3 years (IQR: 1.2-4.6 years).

Primary and secondary outcome measures: The primary end-point was long-term major adverse cardiac events (MACE) with all cause mortality a secondary endpoint.

Results

Of the 3347 STEMI patients, 1299 patients (38.8%) underwent PPCI during a weekday between 08:00 and 18:00 (routine-hours group) and 2048 (61.2%) underwent PPCI on a weekday between 18:00 and 08:00 or a weekend (out-of-

hours group).

There were no differences in baseline characteristics between the two groups with comparable door to balloon times (IHs 67.8mins vs OOHs 69.6mins, p=0.709), call to balloon times (IHs 116.63 vs OOHs 127.15mins, p=0.60) and procedural success. In hospital mortality rates were comparable between the two groups (IHs 3.6% vs OFHs 3.2%) with timing of presentation not predictive of outcome (HR 1.25 (95%CI 0.74-2.11). Over the follow-up period there were no significant differences in rates of mortality (IHs 7.4% vs. OFHs 7.2%, p=0.442) or MACE (IHs 15.4% vs. OFHs 14.1%, p=0.192) between the two groups. After adjustment for confounding variables using multivariate analysis, timing of presentation was not an independent predictor of mortality (HR 1.04 95%CI: 0.78-1.39).

Conclusion

This large registry study demonstrates that the delivery of PPCI with a multidisciplinary, consultant-led, protocol-driven approach delivers safe and effective treatment for patients regardless of the time of presentation.

Keywords: Primary PCI, In-Hours, Out of Hours, myocardial infarction

Background

There is increasing evidence suggesting that patients admitted during the weekend have a higher mortality than those admitted during the week [1, 2]. This excess mortality is thought to be strongly associated with the lack of cover of senior doctors (consultant level), during the weekends [2, 3] and has led to debate around redesigning healthcare provision to eliminate reduced staffing at the weekends.

Primary percutaneous coronary intervention (PPCI) is the accepted gold standard for the treatment of ST-segment elevation myocardial infarction (STEMI) as recognized in all recent guidelines [4-6], and needs to be available at all hours (24/7). The delivery of PPCI services represents a significant logistical challenge, especially as many patients with STEMI present outside of usual hospital working hours (0800 to 1700) and at weekends. Whether patients with STEMI presenting outside of usual hospital working hours have inferior outcomes when compared with patients that present during the working day is still unclear.

Previous studies have demonstrated differing results in outcome after PPCI during 'in-hours' compared to 'out of hours'. Some studies showing no association with adverse outcomes and timing [7-14], whereas other studies suggested higher rates of mortality after PPCI during 'out of hours' compared to 'in hours' [2, 15-18]. It is difficult to compare these studies directly because of

Comment [G1]: Reference added Cubeddu RJ et al. J Invasive Cardiol 2009;21:518-

Comment [G2]: Reference added Cubeddu RJ et al. J Invasive Cardiol 2009;21:518-

Comment [G3]: Reference added Cubeddu RJ et al. Am J Cardiol 2013;111:946-954

Comment [G4]: Reference added Cubeddu RJ et al. J Invasive Cardiol 2009;21:518-

differences in patient characterises and variability in other treatment provided to patients – for example, some of these studies also used fibrinolysis [9, 13, 16, 17, 19].

The aim of this study was therefore to clarify the relative outcomes of patients with STEMI presenting to a UK regional PPCI centre outside of usual hospital working hours with patients presenting during usual working hours.

Methods

This was an observational cohort study of 3347 consecutive patients undergoing PPCI in a high volume centre between January 2004 and July 2012. These patients were divided into two groups based on the timing of PPCI (time ~~time~~ taken as hospital arrival time) Those undergoing PPCI during usual hospital working hours, designated 'in-hours' group (IH) (between 0800 and 1700 Monday to Friday) and those undergoing PPCI outside of usual hospital working hours, designated 'out of hours group' (OOH) (i.e. between 1701 and 0759 Monday to Friday and from 1701 Friday to 0759 Monday).

Service arrangement

The London Chest hospital (LCH) is the tertiary heart attack center for the North-East region of London and receives patients with STEMI for primary PCI in an unselected manner. This includes patients with cardiogenic shock and post cardiac arrest, including intubated and ventilated patients. The hospital serves a well developed network of 6 local district general hospitals covering a

population of 1.6 million people and includes close working with the London Ambulance Service. Patients are taken directly to the cardiac catheterization laboratory 24 hours a day with all cases performed by/under supervision of a consultant. Out of hours the catheterization laboratory is covered by an 'on-call team'. The on-call team is composed of an interventional cardiologist, a senior cardiology trainee, two cardiac catheterization laboratory nurses, a cardiac physiologist, and a radiographer. Aside from the senior cardiology trainee who is resident in hospital out of hours, all the on-call team members are non-resident. Out of hours there are also reduced trainees covering the patients care post procedure and other non-cardiac hospital services are also reduced with lower levels of staffing in radiology, pathology and anaesthetics (ITU) (All of these services follow a similar consultant lead service out of hours).

PPCI pathway

During out of hours the on-call team members are contacted immediately upon acceptance of a patient for PPCI. The on-call team members will be in the hospital within ~~15-40~~40~~40~~ minutes of the original call and the catheterization laboratory will be ready to take the patient as soon as they arrive. In the majority of cases, the on-call team will be in the hospital before the arrival of the patient. During routine-working hours, the on-call team is in the hospital and the catheterization laboratories are fully functioning. Upon accepting a patient, the catheterization laboratory coordinators inform the on-call interventional cardiologist and cardiology trainee and the next available free catheterization laboratory is identified. The patient is taken to the catheterization laboratory

and PPCI is performed by the interventional cardiologist who is working in that laboratory. Standard PPCI protocol for our institution includes pre-loading with 300mg aspirin, 300mg or 600mg clopidogrel and GPIIb/IIIA inhibitors unless contraindicated. Aspiration thombectomy was performed at the operator's discretion.

Data was entered prospectively into the clinical database at the time of PPCI including patient characteristics, procedural factors and procedural complications. Successful primary PCI result was defined as final Thrombolysis In Myocardial Infarction flow grade 3 and residual stenosis <30% in the infarct-related artery at the end of the procedure. Post-discharge complications and further revascularisation procedures were entered retrospectively from the electronic patient record and cardiac surgical database. Major Adverse Cardiac Events were defined as death, recurrent myocardial infarction (defined as 'new ischaemic pain with new ST elevation, or ischaemic ECG changes and further elevation of enzymes (increase of creatine kinase-MB to ≥ 2 times the reference value or rise in Troponin T >30ng/l (99th centile <10ng/l)), whether treated with further revascularisation therapy or not') and target vessel revascularisation. MACE events (identified from patient notes and electronic records) were adjudicated by 3 independent physicians who were not involved in the procedure and were unaware of the patient's PPCI timing (in versus out of hours). All-cause mortality was recorded to 11th September 2012 from the UK Office of National Statistics. A retrospective data quality audit of 100 randomly selected medical records established that 94.8% of data fields, including complications, were entered correctly into the database.

Ethics

The data were collected as part of a mandatory national cardiac audit and all patient identifiable fields were removed prior to analysis. The local ethics committee advised us that formal ethical approval was not required.

Statistical analysis

Continuous variables are presented as mean±SD, categorical variables as absolute number and percentages. Normality of distribution of continuous variables was assessed using the Shapiro-Wilkes test. Normally distributed continuous variables were compared with unpaired t-tests, and non-normally distributed variables were compared with the Mann-Whitney test. Categorical variables were compared using the $\chi 2$-test or Fisher's exact test when appropriate. Kaplan Meier curves were used to represent survival and cumulative incidence of events over follow-up, with the log rank test used for evidence of a statistically significant difference between the groups. Time was measured from the first admission for a procedure to outcome (all cause mortality). The association of timing of PPCI (OOH vs IH) with 30-day mortality was assessed using logistic regression analysis, and long-term mortality using Cox regression analyses. The proportional hazard assumption was satisfied for all outcomes evaluated. Finally, a non-parsimonious logistic regression model with procedural timing as the dependent variable was constructed incorporating all baseline clinical and procedural characteristics listed in table 1 and table 2 to generate a propensity score (ie the predicted probability of procedural timing for

each patient), which ranged between 0 and 1, for each patient. We the subdivided our cohort into quintiles based on propensity score so that comparisons could be made between patients with similar baseline probabilities of mortality[20]. The rates of 30-day and 5-year mortality in the IH vs OOH groups in each quintile were compared. Risk ratios (RRs) for mortality were calculated for each quintile, as well as an overall Mantel-Hantzel RR for the stratified analysis.

Results

Within our study population of 3347 patients 1299 (38.8%) PPCIs were performed In-Hours (IHs) and 2048 (61.2%) PPCIs were performed Out-of-Hours (OOHs).

Patient characteristics (Table 1)

Table 1 demonstrates the baseline characteristics between the two groups. There were no differences in baseline characteristics between the IHs group versus the OOHs group.

Procedural Characteristics and Outcomes (Table 2)

There was no difference in access route or target vessel intervention between the two groups. Although the Door to Balloon time were slightly longer in the OOHs group compared to the IHs group, this difference was not statistically significant (Figure 1). In addition, there was no statistically significant difference in the Call to Balloon time between the two groups. There were higher rates of glycoprotein IIb/IIIa inhibitor use in the OOHs group compared to the IHs group. Procedural success rates and use of thrombectomy were similar between the two groups.

Early Outcomes (Table 3)

There were no differences in in-hospital MACE rates (IH 4.5% vs OOH 5.0%; p=0.644). There was no difference in either 30-day MACE rates (IH 6.3% vs OOH 5.8%; p=0.580) or 30 day mortality rates (IH 4.4% vs OOH 4.0%; p=0.613) between the groups.

Predictors of early Outcome (Table 4)

In terms of early (30 day) all-cause mortality and MACE events, Out of hours PPCI was not an independent predictor of mortality (HR 0.74 (95% CI: 0.42-1.29) and MACE events (HR 0.81 (95% CI 0.54-1.22). However, as expected, reduced renal function, shock, low EF and procedural success were independent predictors of early outcome (Table 4).

Long term Outcome (Figures 2-4)

Patients were followed-up for a median of 3.0 years (IQR range: 1.2-4.6 years). MACE event rates were not different between the groups at 1 year (IH 11.8% vs OOH 11.3%; p=0.757) or 3 years (14.2% vs 13.2%; p=0.489). Mortality rates at 1 year (IH 6.3% vs OOH 6.2%; p=0.934) and 3 years (OOH 7.1% vs 7.3%; p=0.938) were not different between the groups.

Predictors of Long term Outcome

Timing of PPCI (out-of-hours vs in-hours) was not a univariate predictor of all cause mortality (unadjusted hazard ratio 1.04 (95% confidence intervals 0.78-1.39) (Figure 5). Incorporation of timing of PPCI into a multivariate cox model did not change this (adjusted hazard ratio 1.03 (95% confidence intervals 0.70-1.50) (Figure 6). In addition, timing of PPCI was also not an independent predictor of MACE (unadjusted hazard ratio 0.93 (95% confidence intervals 0.76-1.14).

Stratification of risk by propensity score (Long term Outcome) (Table 5)

Analysis of patients stratified into quintiles using propensity score showed that higher risk patients were less likely to undergo PPCI out-of-hours (68.2% in Q1 v 57.8% in Q5; table 5). There was no significant difference in long-term mortality between IH and OOH in any of the propensity score quintiles (Overall Mantel Haenszel HR 1.09 (0.77-1.55)).

Discussion

We report both short-term and long-term outcomes after PPCI for STEMI in a large contemporary cohort of patients presenting in and out of usual hospital working hours at a regional UK heart attack centre. We have found that the timing of presentation to hospital does not affect mortality after STEMI. Importantly there was no difference in effective treatment delivery as evidenced by door-to-balloon and call-to-balloon times between patients presenting in-hours and those presenting out-of-hours. That rapid reperfusion can be achieved despite reduced staffing levels is likely to be the key to the equivalent outcomes of our OOH population.

It was first recognised in the 1970s that throughout the Western world mortality is up to 10% higher in patients admitted to acute hospitals at the weekend than during the week [7, 21] with cardiovascular disease one of the main causes of this excess mortality [21]. In particular, there has been focus towards studies that have suggested increased mortality (due to delayed care) in patients with severe medical conditions who are admitted during weekends [7]. Kostis et al also found higher mortality in patients with myocardial infarctions admitted on weekends [16].

Interest in patient management and safety outside normal working hours, has increased recently following a report by Dr Foster Intelligence that showed increased mortality in UK hospitals at the weekend [22], and suggested a clear association between this excess and reduced numbers of senior doctors in

hospitals. Our study clearly shows that the availability of a consultant-led, protocol-driven service at all times of day abolishes the excess out-of hours risk for myocardial infarction - one of the main causes of in-hospital mortality.

Hospital staffing is often reduced out-of-hours compared to normal working hours, which has been linked to increased mortality. In our study despite reduced staffing levels and support services at weekends there was no excess in adverse outcomes suggesting that suitable seniority and experience of the medical care on site is crucial rather than exact replication of weekday service provision. The clear consultant-led protocol that we adopt at our high volume institution is key to providing a standardised management strategy for patients whether it is 'in hours' or 'out of hours'. In our opinion, ~~We propose that~~ this system could be adapted to other acute medical emergencies such as upper gastrointestinal bleeds, diabetic ketoacidosis and acute cerebrovascular accidents, although we appreciate the impact of a consultant-led protocol is likely to be different between procedure based and non-procedure based emergency therapies.~~.~~

Providing a 24/7 service for PPCI is a challenge for both hospitals, medical personnel and the emergency medical services. Recent studies have found that up to two third of STEMI patients are admitted to a PPCI centre outside normal working hours [3] – this was also the case for our series. A finding in the Dr Foster report [22] was that the creation of networks through rationalisation of services in parts of the UK may improve outcomes at weekends, a strategy appropriate for a population such as London. Our study shows that the creation of one such

network for Primary PCI in the North East of London is safe and leads to improved outcomes. Similar strategies could be implemented for other acute medical conditions to improve outcomes 'out of hours' without involving complete replication of weekday hospital services at the weekend.

Strengths and Limitations of the Current Study

Our study is a consecutive but retrospective observational analysis from a single centre's experience. We cannot account for the effects of residual confounding or selection bias. The strength of this study is that it assesses outcome in a large contemporary cohort of consecutive patients undergoing PPCI for STEMI in a regional Heart Attack Centre centre. Therefore, the results are likely to be widely generalisable. The large cohort also ensures that all-cause mortality can be used as the primary end point. This has the advantage of being entirely objective. As this was an observational study the findings may have been subject to confounding factors that we have been unable to control for. However, our dataset includes all major clinical variables known to affect outcome which would support the validity of our results.

Conclusions

A consultant-led protocol for provision of PPCI for treatment of STEMI is not associated with an increase in mortality for patients treated out of hours compared to in hours.

Table 1. Baseline characteristics comparing IHs vs OOHs (*p value < 0.05)

	IHs (n = 1299)	OOHs (n = 2048)	p Value
Gender (Male)	964 (74.2%)	1579 (77.1%)	P=0.051
Age (yrs)	64.02 ± 14.2	63.16 ± 14.3	P=0.126
Hypertension	509 (39.2%)	784 (38.3%)	P=0.344
Diabetes mellitus	225 (17.3%)	362 (17.7%)	P=0.424
Hypercholesterolemia	401 (30.9%)	608 (29.7%)	P=0.253
Smoking History	722 (55.6%)	1188 (58.0%)	P=0.116
Previous MI	171 (13.2%)	242 (11.8%)	P=0.156
Previous CABG	34 (2.6%)	53 (2.6%)	P=0.539
Previous PCI	129 (9.9%)	197 (9.6%)	P=0.449
Cardiogenic Shock	69 (5.3%)	131 (6.4%)	P=0.113
Ethnicity (Caucasian)	865 (66.6%)	1319 (64.4%)	P=0.226
LVEF	43.70 ± 7.5	43.69 ± 7.5	P=0.985
CRF (eGFR <60)	240 (18.5%)	367 (17.9%)	P=0.227

Table 2. Procedural characteristics comparing IHs versus OOHs (P<0.05)

	IHs (n = 1299)	OOHs (n = 2048)	p Value
Femoral Access	779 (60.0%)	1182 (57.7%)	P=0.139
Target Vessel			
Right coronary artery	565 (43.5%)	889 (43.4%)	P=0.490
Left main coronary artery	9 (0.7%)	14 (0.7%)	P=0.585
Left anterior descending (LAD)	643 (49.5%)	969 (47.3%)	P=0.139
Left circumflex coronary artery	123 (9.5%)	168 (8.2%)	P=0.137
Saphenous vein graft	14 (1.1%)	33 (1.6%)	P=0.229
Multi vessel disease	609 (46.9%)	940 (45.9%)	P=0.277
Door to Balloon Time (Median)	30 IQR [18-70]	38 IQR [21-76]	P=0.709
Door to Balloon Time >90	207 (15.9%)	352 (17.2%)	P=0.079
Symptom to Balloon Time (Median)	176 IQR [117-328]	195 IQR [125-330]	P=0.562
Call to Balloon Time (Median)	95 IQR [76-123]	99 IQR [81-141]	P=0.056
Glycoprotein IIb/IIIa inhibitor	1061 (81.7%)	1747 (85.3%)	P=0.007
Thrombectomy	207 (15.9%)	348 (17.0%)	P=0.448
Procedural Success	1095 (84.3%)	886 (84.5%)	P=0.530

Table 3. In-hospital outcomes post PPCI comparing IHs versus OOHs

	IHs (n = 1299)	OOHs (n = 2048)	p Value
Complications			
Bleeding Complications	48 (3.7%)	61 (3.0%)	P=0.165
Haematoma	9 (0.7%)	8 (0.4%)	P=0.274
Blood Transfusion	30 (2.3%)	33 (1.6%)	P=0.140
In Hospital MACE			
Mortality	42 (3.2%)	74 (3.6%)	P=0.321
MI	7 (0.6%)	15 (0.7%)	P=0.415
CVA	2 (0.2%)	6 (0.2%)	P=0.642
Re-intervention PCI	11 (0.9%)	10 (0.5%)	P=0.170
30 day MACE			
Mortality	56 (4.3%)	82 (4.0%)	P=0.336
MI	26 (2.0%)	27 (1.3%)	P=0.207
CVA	3 (0.2%)	6 (0.3%)	P=0.446
Re-intervention PCI	17 (1.3%)	6 (0.3%)	P=0.088

Table 4. Independent predictors of death, and major adverse cardiac events (re-infarction, death and unscheduled revascularisation) at log regression analyses

Event	Variables	HR (95% CI)	P value
Death	Age	1.04 (1.02-1.07)	0.001
	Shock	5.60 (2.96-10.60)	P<0.0001
	eGFR>60	0.32 (0.18-0.58)	P<0.0001
	EF>40	0.18 (0.09-0.36)	P<0.0001
	Procedural Success	0.17 (0.09-0.32)	P<0.0001
	Multi-vessel disease	1.92 (0.99-3.73)	0.053
	Out of Hours	0.74 (0.42-1.29)	0.284
MACE	Age	1.02 (1.01-1.05)	P<0.0001
	Shock	3.94 (2.30-6.74)	P<0.0001
	eGFR>60	0.44 (0.28-0.69)	P<0.0001
	EF>40	0.46 (0.30-0.71)	P<0.0001
	Procedural Success	0.26 (0.15-0.46)	P<0.0001
	Multi-vessel disease	1.57 (1.31-1.90)	0.003
	Out of Hours	0.81 (0.54-1.22)	0.316

Figure 1. Boxplots illustrating door-to-balloon times for PPCI performed IHs and OOHs. The median door-to-balloon time is indicated. The boundaries of the box plots refer to the 25th and 75th percentiles, with the whisker bars representing the 5th and 95th percentiles.

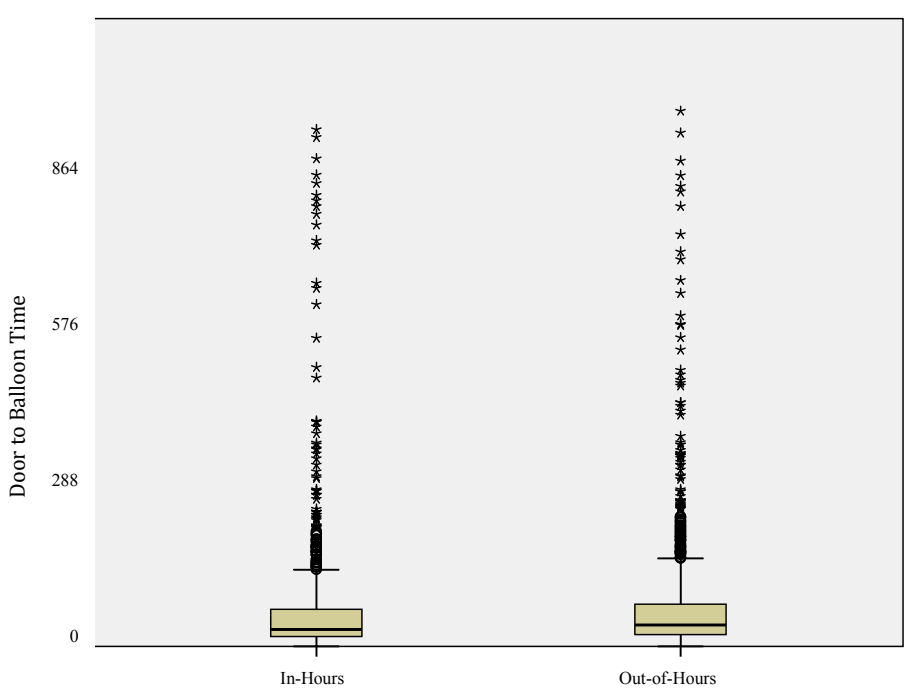
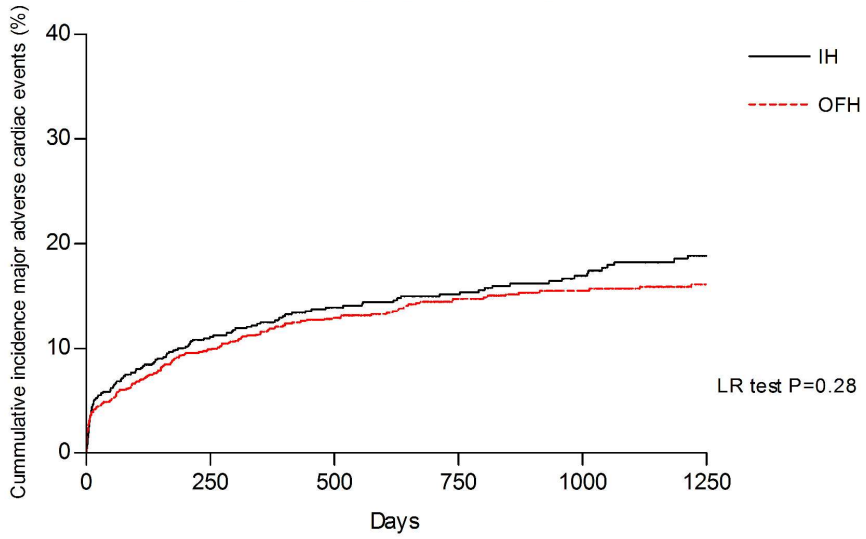


Figure 2 Kaplan Meier curves showing cumulative probability of major adverse cardiac events (MACE) after PCI comparing IHs versus OOHs



Numbers at risk

IH	1299	844	668	545	428	295
OFH	2048	1296	992	784	599	434

Figure 3 Kaplan Meier curves showing cumulative probability of all-cause mortality after PPCI comparing IHs versus OOHs

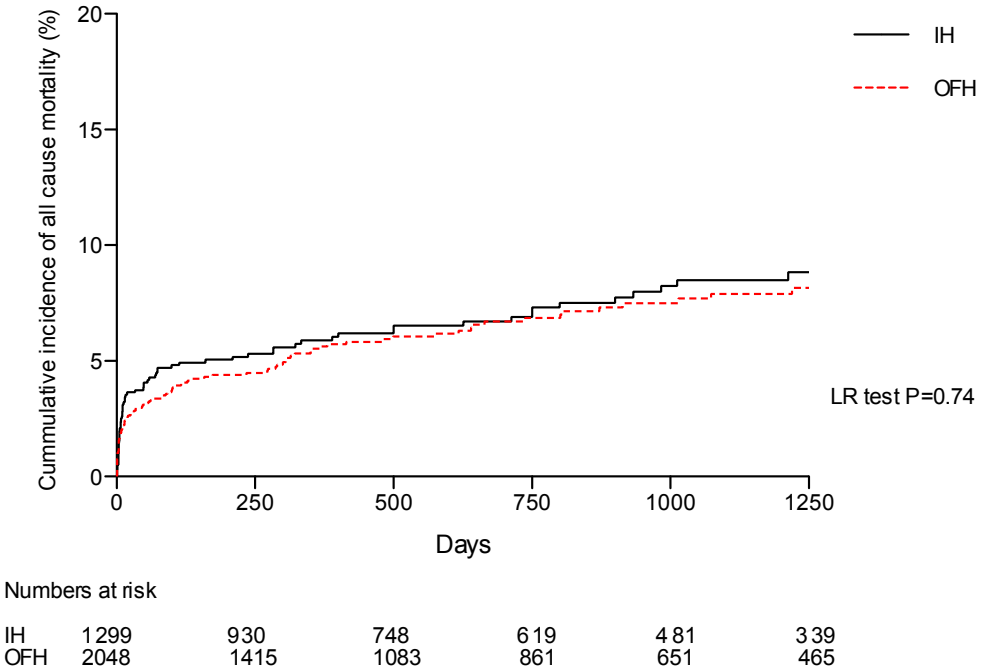


Figure 4 Kaplan Meier curves showing cumulative incidence of a). Myocardial infarction and b). Target vessel revascularisation after PPCI comparing IHs versus OOHs

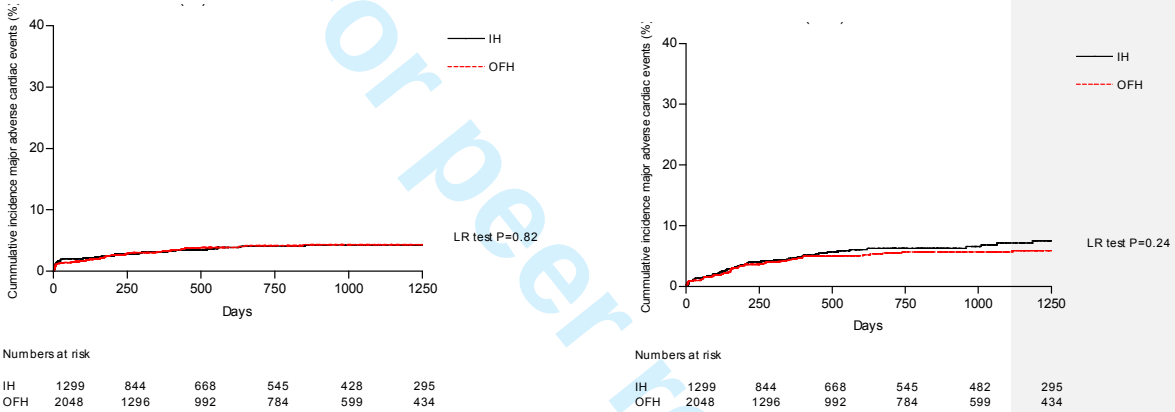


Table 5. Five year mortality rates stratified by propensity score comparing patients treated IHs and OOHs with PPCI

Quintile	OOHs procedures (%)	OOHs mortality rate	IHs mortality rate	Risk ratio (95% CI)
1	68.2	3.8%	0.8%	4.80 (0.61-37.94)
2	64.5	4.8%	5.8%	0.82 (0.33-2.05)
3	61.5	8.4%	6.9%	0.81 (0.38-1.71)
4	57.5	7.7%	7.6%	1.02 (0.49-2.15)
5	57.8	15.7%	13.1%	1.23 (0.70-2.18)
			Overall Mantel Haenszel RR	1.09 (0.77-1.55)

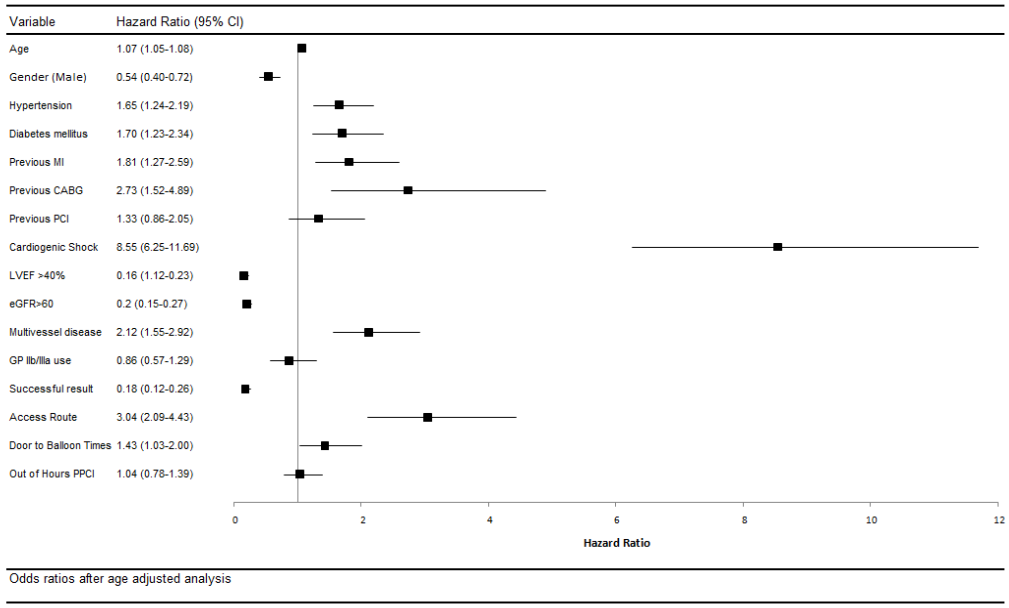


Figure 5 – Forest Plot model of age-adjusted univariate analysis of predictors of mortality

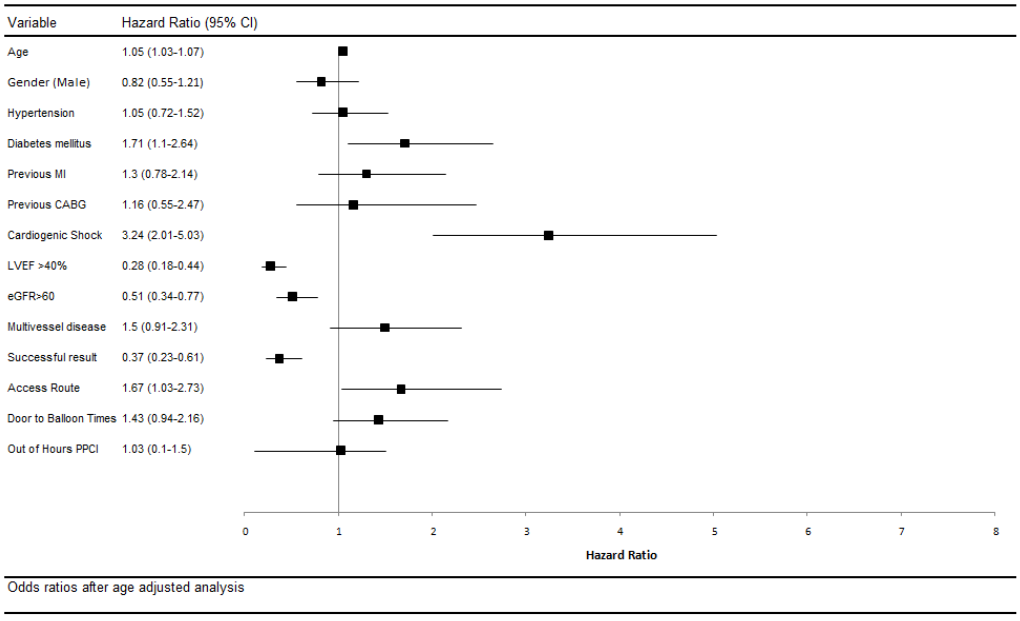


Figure 6 – Forest Plot model of multivariate analysis of predictors of mortality

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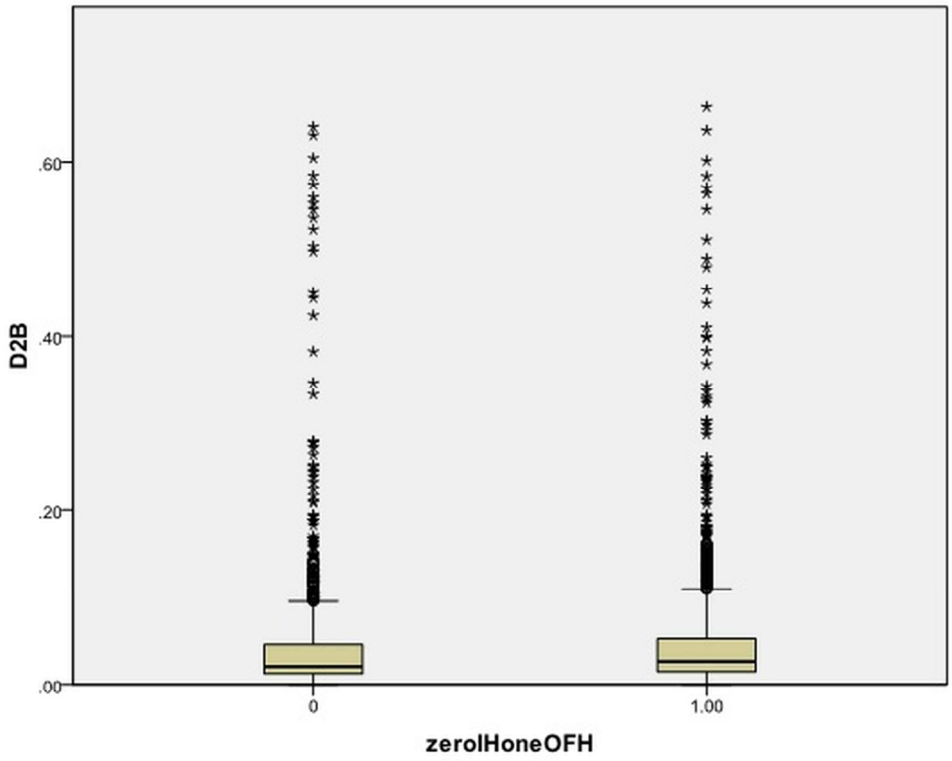

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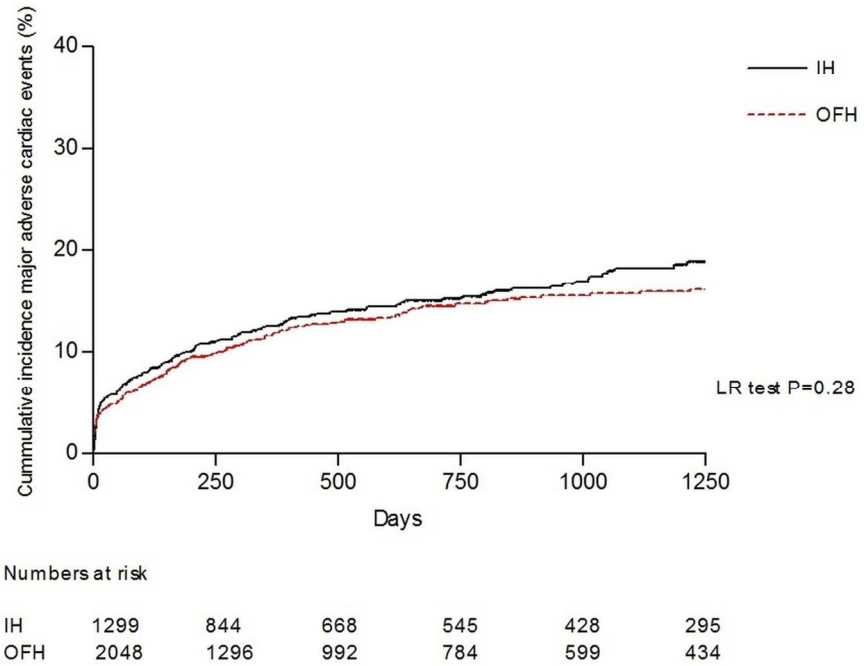

Numbers at risk

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OFH	2048	1296	992	784	599	434

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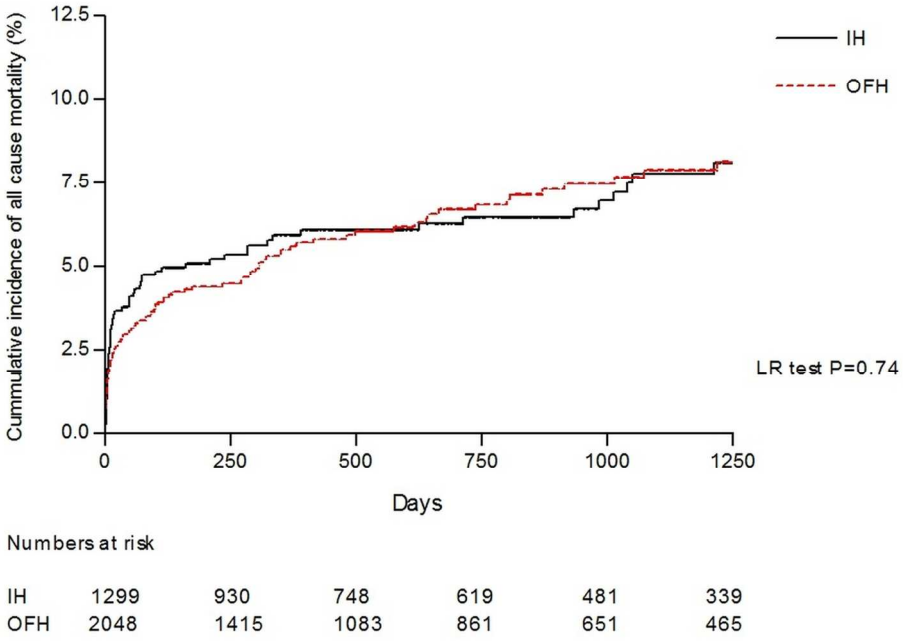

Numbers at risk

IH	1299	930	748	619	481	339
OFH	2048	1415	1083	861	651	465

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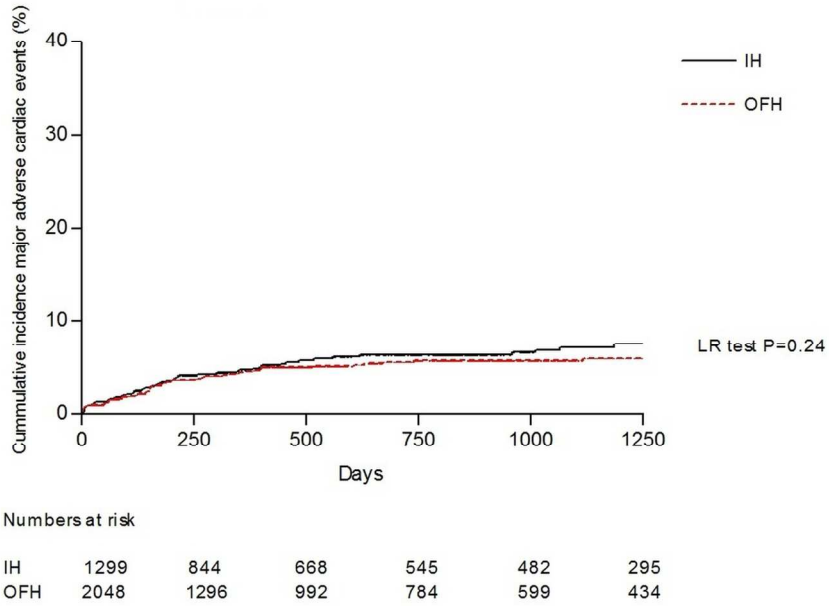

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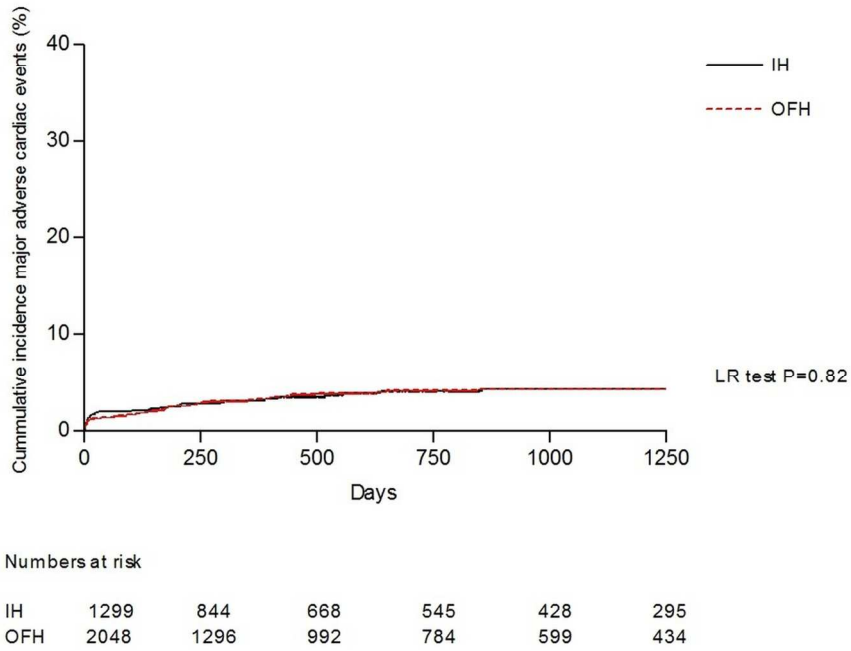

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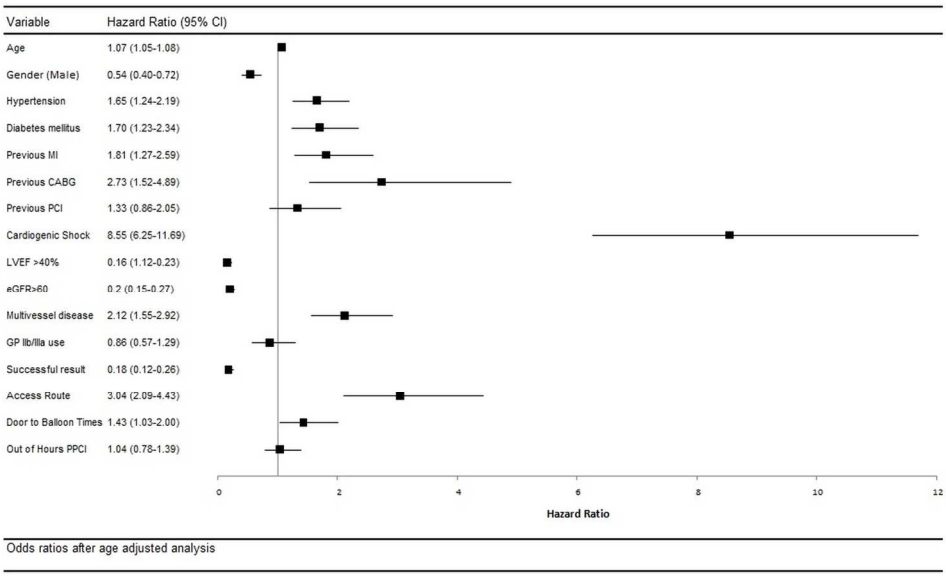

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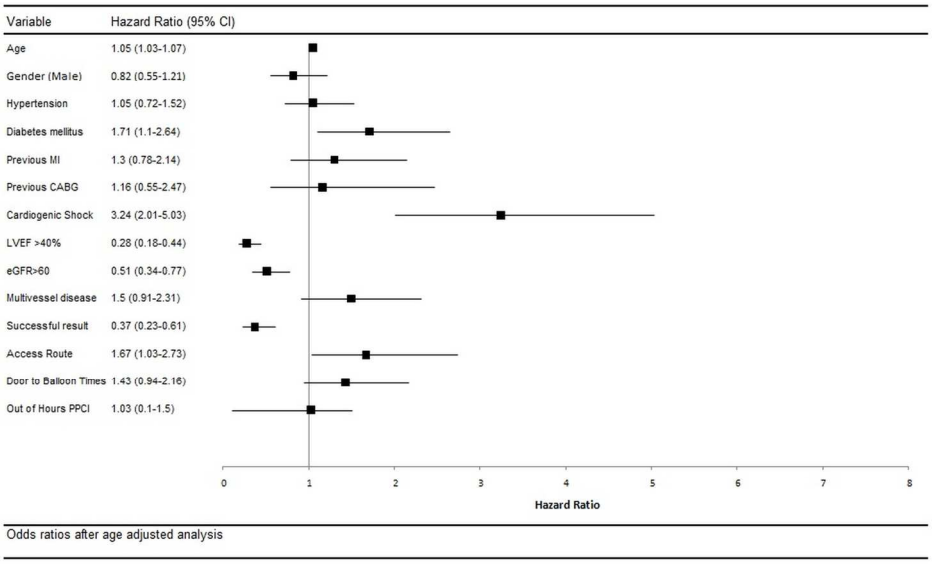

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STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract ✓
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found ✓
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported ✓
Objectives	3	State specific objectives, including any prespecified hypotheses ✓
Methods		
Study design	4	Present key elements of study design early in the paper ✓
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection ✓
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants ✓
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable ✓
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group ✓
Bias	9	Describe any efforts to address potential sources of bias ✓
Study size	10	Explain how the study size was arrived at ✓
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why ✓
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding ✓
		(*b*) Describe any methods used to examine subgroups and interactions ✓
		(*c*) Explain how missing data were addressed ✓
		(*d*) If applicable, describe analytical methods taking account of sampling strategy ✓
		(*e*) Describe any sensitivity analyses ✓
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed ✓
		(b) Give reasons for non-participation at each stage ✓
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders ✓
		(b) Indicate number of participants with missing data for each variable of interest ✓
Outcome data	15*	Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included ✓
		(*b*) Report category boundaries when continuous variables were categorized ✓
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period ✓
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses ✓

Discussion		
Key results	18	Summarise key results with reference to study objectives ✓
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias ✓
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence ✓
Generalisability	21	Discuss the generalisability (external validity) of the study results ✓
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.