Association between Hospital Cardiac Catheter Laboratory Status, use of an Invasive Strategy and Outcomes after NSTEMI

Short running title: Cath lab status and outcomes for NSTEMI

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Word count: 2970

Keywords: Non-ST elevation acute myocardial infarction (NSTEMI), cardiac catheterization facilities, coronary angiography, Percutaneous coronary intervention.

Summary:

Our study shows that use of invasive coronary strategy varies according to availability of cardiac catheterization facilities at the admitting hospital. Patients admitted to hospitals with diagnostic catheter laboratory are less likely to receive invasive coronary strategy. In high-risk NSTEMI patients, admission to diagnostic hospitals was also associated with increased odds of in-hospital mortality. The lower rates of invasive coronary strategy in patients admitted to diagnostic hospitals suggests that in clinical practice, physicians are likely to adopt a risk-averse strategy particularly in high-risk NSTEMI patients. Future efforts are particularly required to develop regional pathway for uniform access to invasive coronary strategy particularly in high-risk NSTEMI patient.

Abstract:

Background:

While previous studies report increased use of invasive coronary strategy in patients admitted to hospitals with onsite cardiac catheter laboratory (CCL) facilities, the utility of invasive coronary strategy according to types of CCL facilities at the first admitting hospital and clinical outcomes is unknown.

Methods: We included 452,216 patients admitted with a diagnosis of NSTEMI in England & Wales between 2007-2015. The admitting hospitals were categorized into; no-laboratory, diagnostic and PCI hospitals according to CCL facilities. Multilevel logistic regression models were used to study association between CCL facilities and in-hospital outcomes.

Results: 97,777 (21.6%) were admitted to `no laboratory` whereas 134,381 (29.7%) and 220,058 (48.7%) patients were admitted to `diagnostic` and PCI hospitals, respectively. Use of coronary angiography was significantly higher in PCI hospital (77.3%) compared to `diagnostic` (63.2%) and `no laboratory` (61.4%) hospitals. The adjusted odds of in-hospital mortality were similar for `diagnostic` (OR 0.93 95%CI 0.83-1.04) and PCI hospitals (OR 1.09 95%CI 0.96-1.24), compared to `no laboratory` hospitals. However, in high-risk NSTEMI (defined as GRACE score>140) subgroup, an admission to `diagnostic` hospitals was associated with significantly increased in-hospital mortality (OR 1.36 95%CI 1.06-1.75) compared to `no laboratory` and PCI hospitals.

Conclusions: Our study highlights important differences in both the utilisation of invasive coronary strategy and subsequent management/outcomes of NSTEMI patients according to admitting hospital CCL facilities. High-risk NSTEMI patients admitted to 'diagnostic'

hospitals had greater in-hospital mortality, possibly because of reduced PCI use, which needs to be addressed.

Introduction:

Invasive coronary angiography (CA) is the gold standard diagnostic modality for the assessment of coronary artery disease in patients admitted with acute coronary syndromes (ACS). Patients who present with ST-elevation acute myocardial infarction (STEMI) are urgently transferred for primary percutaneous coronary intervention (PCI) even when they initially present to hospitals without onsite cardiac catheter laboratory facilities. In contrast, the decision to undertake CA in patients admitted with NSTEMI is based on initial presentation, ECG changes, risk factors, presence of haemodynamic instability and co-existing comorbidities[1-3]. Organisational factors, such as the availability of cardiac catheter laboratory facilities at the presenting hospital, are important determinants of utilisation of CA and further management[4-6].

NSTEMI patients may be admitted to hospitals without PCI capability and in some cases without diagnostic catheter laboratory facilities.[7-10] Previous studies have reported a positive association between the presence of an on-site catheter laboratory and receipt of CA in patients with ACS[5, 6, 11-14] but the association between catheter laboratory facilities at the admitting hospital with clinical outcomes were inconsistent [5, 6, 11-13, 15, 16]. The interpretation of these data is challenging because the majority of previous studies are based on mixed cohorts of ACS patients including STEMI as well as NSTEMI patients and the availability of diagnostic only and PCI capable interventional facilities, in particular, is not considered separately. Currently, guidelines recommend an early invasive coronary strategy within 24 hours in NSTEMI patients presenting with high-risk features such as those with GRACE score >140, however, such time target times are unlikely to be met without the presence of onsite cardiac catheter laboratory facilities[1, 2]. More importantly, there is a paucity of data around the use of invasive coronary strategy and clinical outcomes stratified according to admitting hospital catheter laboratory facilities in high-risk NSTEMI patients such as those with GRACE risk score >140. As such, it remains unclear how the types of cardiac catheter laboratory facilities at the first admitting hospital might influence the utilisation of invasive coronary strategy in the form of CA or PCI and outcomes of patients with NSTEMI.

The main aim of the present study was to describe associations between use of invasive coronary strategy and outcomes in patients with NSTEMI and how these associations are influenced by the catheter laboratory and interventional (PCI) facilities of admitting hospitals. In order to further delineate the association between baseline NSTEMI risk and clinical outcomes, we also undertook a pre-specified subgroup analysis of high-risk patients with a GRACE score >140.

Methods:

Study Design:

The Myocardial Ischemia National Audit Project (MINAP) is a national audit which prospectively collects information around the management of ACS in England and Wales to meet the audit requirements of National Service Framework (NSF) for coronary heart disease[17-19]. Data are collected prospectively at each hospital, electronically encrypted, and transferred online to a central database. MINAP amasses almost 85,000 hospital admissions per year with a diagnosis of ACS admitted to acute National Health Service (NHS) hospitals in England and Wales[20]. Each entry in the MINAP dataset provides comprehensive information about patient's journey encompassing patient demographics, coexisting comorbidities, admission method/route, clinical characteristics and investigations, in-hospital drug treatments, primary reperfusion treatment, interventional treatments, in-hospital outcome, diagnosis on discharge and discharge (secondary prevention) treatment[21-23].

Study population:

The analytic cohort for this study included all patients over the age of 18 years, admitted with a diagnosis of NSTEMI in one of the 235 hospitals in the England and Wales from 1st Jan 2007 and 31st Dec 2015. We only included the first admission of each patient in the dataset which was then matched to the first admitting hospital catheter laboratory facilities at the time of admission to minimize the influence of changing status of cardiac catheter laboratory facilities over time. The discharge diagnosis of NSTEMI was determined by local clinicians according to presenting history, clinical examination, and the results of inpatient investigations in keeping with the consensus document of the Joint European Society of Cardiology and American College of Cardiology[24]. Patients with missing age, gender, and in-hospital mortality information were excluded from the analysis (Supplementary Figure S1). All patients were stratified into three groups; according to the catheter laboratory facilities of the admitting hospital as follows: `no lab` hospitals – hospital without catheter laboratory; `diagnostic`

hospitals – hospitals with diagnostic catheter laboratory only; PCI hospitals – hospital with interventional laboratory facilities. We collected information on the patient's baseline characteristics, details of the presentation, comorbidities, in-hospital and discharge pharmacology, receipt of invasive strategies during admission and GRACE score. GRACE 2.0 score was calculated as previously described[25] and patients were categorised into low (<109), intermediate (109-140) and high-risk (>140) categories as per international guidelines[1, 2]. The outcomes of interest were in-hospital all-cause mortality, cardiac mortality, and major bleeding. The in-hospital major bleeding in MINAP is defined as a composite of intracranial bleeding, retroperitoneal bleeding, any bleed with Hb fall > 50g or any bleed with Hb fall > 30g and < 50g or any bleed with Hb fall <30 g. We also examined the association between the presence of cardiac catheter laboratory facilities and in-hospital clinical outcomes in high-risk NSTEMI patients defined as GRACE>140 as a complete case analysis. In order to further delineate the differences in treatment practices of high-risk NSTEMI patients admitted first in diagnostic hospitals, we performed a sensitivity analysis of patients receiving CA onsite at the diagnostic hospitals compared to those transferred out directly to PCI hospitals from the diagnostic hospitals for CA.

Ethical approval

The MINAP database is collected and used for research purposes without informed patient consent by the National Institute for Cardiovascular Outcomes Research (NICOR) under section 251 of the National Health Service Act 2006. Therefore, ethical approval was not required for this study under current arrangements by the National Health Service research governance.

Statistical analysis

The baseline characteristics across the three groups were described using the number and percentages for categorical variables and median and interquartile ranges for continuous variables. In order to limit the influence of biases related to missing data, we used multiple imputation techniques with chained equations to account for the missing data. Age, gender, hospital catheter laboratory status, ethnicity and in-hospital all-cause and cardiac mortality were registered as regular variables in the imputations model whereas all other variables including body mass index (BMI), GRACE risk score, seen by cardiologists, left ventricular (LV) systolic function, ECG changes defined as ST depression or transient ST elevation or T wave inversion, prior history of PCI, coronary artery bypass graft (CABG), heart failure,

hypercholesterolemia, angina, cerebrovascular disease, peripheral vascular disease, chronic renal failure, diabetes, hypertension, smoking status, asthma/COPD, family history of coronary disease, in-hospital use of low molecular weight heparin, warfarin, loop diuretics, glycoprotein 2b3a inhibitors, discharge medications including aspirin, P2Y12 inhibitors, statin, ACE inhibitor, beta-blocker, in-hospital major bleeding, receipt of coronary angiography and receipt of PCI were imputed. The variable selection in the model was based on the previous studies using MINAP registry and prior clinical knowledge. Using these models, 10 imputed datasets were generated which were used to perform all the analyses. Multivariable logistic regression models were used to study the independent predictors of the receipt of invasive procedures. In order to account for the nested structure of the data, patients within hospital sites, multilevel logistic regression models were fitted. Thus, a random intercept for hospital sites was used. In terms of the information on cardiac catheter lab facilities, this was categorized into "no lab, diagnostic hospitals and PCI hospital" and modelled as a fixed effect in the models. The multilevel logistic regression model captures any unobserved hospital components and hospital factors that were omitted but may influence the outcomes. All models included the same aforementioned variables used in the multiple imputation models as well as the year of admission. Estimates in the form of odds ratios and 95% confidence intervals were reported and statistical significance was considered with an alpha of 0.05 in all the two-sided tests used. Stata college station version 14.1 was used to perform all the analyses.

Results:

Patient characteristics

The analytical cohort consisted of 452,216 patients admitted with a final diagnosis of NSTEMI across 235 acute hospitals in England and Wales between January 1, 2007, and December 31, 2015 (supplementary Figure S1). 97,777 patients (21.6%) were admitted to `no lab` hospitals, 134,381 (29.7%) to `diagnostic` hospitals and 220,058 (48.7%) to PCI capable hospitals. Table 1shows the baseline characteristics of the patients stratified into three groups according to cardiac catheter laboratory facilities. Typically, patients admitted to PCI capable hospitals were younger [median age 72 interquartile range (60.8-81)], had worse baseline cardiovascular profiles with increased prevalence of hypercholesterolemia (39.9%), peripheral vascular disease (5.8%), current smoking (22.4%) and family history of coronary heart disease (32.1%) compared to those patients admitted to `no lab` and `diagnostic` hospitals. Higher proportions of patients admitted to 'no lab' (59.6%) and 'diagnostic' hospitals (58.9%) were

high-risk (defined as GRACE risk score >140) compared to PCI hospitals (53.4%). Rates of CA were higher in PCI capable hospitals (77.3%) compared with `diagnostic` and `no lab` (63.2% and 61.4%) hospitals respectively. Likewise, patients in PCI capable hospitals were almost twice as likely to receive PCI (45.9%) compared to `no lab` (28.3%) and `diagnostic` hospitals (22.4%). Higher proportions of patients (59.6%) admitted to `no lab` hospitals were in high-risk NSTEMI category compared to PCI capable hospitals (53.4%) and diagnostic hospitals (58.9%). Patients admitted to hospitals with `no lab` facilities were less likely to be seen by a cardiologist (87.6%) compared with those admitted to PCI capable hospitals (95.6%) and diagnostic hospitals (90.9%)

Characteristics of patients receiving coronary angiography

Among patients receiving coronary angiography, patients admitted to PCI capable hospitals were more likely to be older, male and have electrographic changes on admission. There were no differences in baseline risk as defined by the GRACE scores across the three groups (Supplementary Table S2). Patients receiving coronary angiography with high-risk features such as those with high GRACE score, out of hospital cardiac arrest or electrographic changes on admission were more likely to be medically managed in if first admitted to `no lab` hospitals compared to `diagnostic` and PCI capable hospitals (Supplementary table S3). Review of high-risk patients receiving CA, by a consultant cardiologist, was also less likely in the 'no lab' hospitals compared with' diagnostic' or 'PCI capable' hospitals

Characteristics of high-risk NSTEMI patients

In the sensitivity analysis looking at the utilisation of invasive coronary strategy and clinical outcomes in 100,898 high-risk NSTEMI patients (defined as GRACE score >140) 21,226 (21.0%) were admitted to `no lab` hospitals, whereas 24,448 (24.3%) and 55,224 (54.7%) to `diagnostic` and PCI capable hospitals respectively (Supplementary table S4). Out of the 24,448 admitted to `diagnostic` hospitals, 5,184 (21.2%) were transferred out to the nearest PCI hospital for an invasive coronary strategy in the form of CA or PCI, whereas 19,264 (78.8%) were managed onsite at the first admitted diagnostic hospital. In this high-risk NSTEMI sub-cohort (GRACE score>140) admitted to diagnostic hospitals only, patients transferred out to a PCI capable hospital displayed a significantly worse baseline cardiovascular profile with increased prevalence of out of hospital cardiac arrest, electrographic changes, history of previous PCI or CABG, hypertension and current smoking status compared to those that remained and were managed in the diagnostic hospital. However,

the high-risk patients who are treated onsite in `diagnostic` hospitals had a higher prevalence of non-cardiac comorbidities such as chronic renal failure, asthma or COPD, previous cerebrovascular accident and peripheral vascular disease compared to those transferred to PCI hospitals for invasive coronary strategy.

Temporal trends

In the whole NSTEMI cohort, overall rates of CA increased from 50.8% to 86.0% during the study period while the number of PCI hospitals increased from 87 to 99 (Supplementary Figures S2, S3). Utilisation of CA also increased in patients admitted across all the hospitals and by 2015 were similar in `no lab`, `diagnostic` and PCI hospitals (86.4%, 86.0% and 85. 6%) (Figure 1a). However, although receipt of PCI also increased in patients across all hospitals during the study period it remained consistently lower (36.2%) in patients admitted to `diagnostic` hospitals compared to patients admitted to PCI hospitals (55.1%) and by 2015, was also lower compared to patients admitted to `no lab` hospitals (45.9%) (Figure 1b). A similar pattern was seen for receipt of any revascularisation (composite of PCI or CABG) procedures in the patients admitted to `diagnostic` hospitals where receipt of any revascularisation procedure was 43.3% in diagnostic hospital patients compared to no lab (53.1%) and PCI hospitals (62.5%) patients (Figure 1c). A similar trend was observed in the use of revascularisation procedures in the form of PCI, CABG or any revascularisation in the overall cohort, in subgroup of patients receiving coronary angiography and high-risk (GARCE score >140) subgroup when stratified according hospital catheter laboratory facilities. For instance, overall receipt of CABG was 5.3% in diagnostic hospitals compared to 5.4% in lab and 7.1% in PCI hospital respectively. (Supplementary Figures S4-S6). Finally, there was a steady decline in the in-hospital mortality and bleeding complications across all hospitals, however PCI hospitals had the lowest mortality and higher bleeding complications (Supplementary Figures S7-S8)

Independent predictors of receipt of CA and PCI

Independent predictors of receipt of CA and PCI in the overall cohort are reported in Table 2. Overall, high-risk NSTEMI patients defined by GRACE score >140 were less likely to receive CA (OR 0.89 95%CI 0.83-0.95) or PCI (OR 0.88 95%CI 0.84-0.94). Compared to patients treated in `no lab` hospitals, the odds of receiving CA were 14% higher in the `diagnostic` hospitals (OR 1.14 95%CI 1.11-1.16) and 64% higher in PCI hospitals (OR 1.64 95%CI 1.60-1.68). Conversely, the odds of receiving PCI were lower in `diagnostic` hospitals

(OR 0.88 95%CI 0.86-0.90) but higher in PCI hospitals (OR 1.69 95%CI 1.66-1.73) compared to `no lab` hospitals.

Clinical outcomes

Supplementary Figure 3 illustrates unadjusted in-hospital outcomes stratified according to admission to the `no lab`, `diagnostic` and PCI hospitals respectively. In-hospital mortality was lowest (10.5%) in PCI hospitals compared with `diagnostic` (12.0%) and `no lab` (12.6%) hospitals. After adjustment for differences in baseline clinical characteristics, no differences in hospital mortality, cardiac mortality or bleeding complications were observed by type of hospitals in the overall cohort.

Among the high-risk NSTEMI patients with a GRACE score > 140, the odds of in-hospital all-cause mortality (OR 1.36 95% 1.06-1.75) and cardiac mortality (OR 1.28 95%CI 0.99-1.65) were higher in `diagnostic` hospitals compared to PCI hospitals and `no lab` hospitals (reference group). (Table 3). In the subgroup analysis of high-risk NSTEMI cohort admitted to diagnostic hospital and then either managed onsite or transferred out to PCI hospital for further invasive management, patients from diagnostic hospitals receiving CA onsite at the admitting hospital had a significant increase in in-hospital mortality (OR 1.45 95%CI 1.13-1.87) and cardiac mortality (1.35 95%CI 1.05-1.75) whereas patients who were admitted to 'diagnostic' hospital and then transferred out to nearest PCI hospital directly had significant reduced odds of all-cause mortality (OR 0.35 95%CI 0.21-0.51) and cardiac mortality (OR 0.40 95%CI 0.24-0.65) compared to patients admitted to PCI hospitals or 'no lab' hospitals (reference group). (Table 4, Figure 2).

Discussion:

In this national analysis of patients admitted with a diagnosis of NSTEMI in England and Wales, patients admitted to hospitals with onsite cardiac catheter laboratory facilities have similar outcomes compared to those admitted at hospitals without such facilities. In high-risk NSTEMI patients (with GRACE score >140), admission to a diagnostic hospital was associated with an increased risk of in-hospital all-cause and cardiac mortality. This mortality hazard was even more pronounced in the high-risk NSTEMI subgroup who were admitted to diagnostic hospital and received coronary angiography locally compared to those transferred to the nearest PCI hospital from diagnostic hospitals. Our analysis suggests that the presence of onsite catheter laboratory facilities was associated with increased utilisation of invasive coronary angiography, although paradoxically patients admitted to diagnostic hospitals were less likely

to receive PCI or CABG compared to hospitals without onsite catheter laboratory facilities or PCI hospitals. These findings have important implications in developing regional treatment pathways for NSTEMI care to allow effective access to invasive coronary strategy.

Several studies have reported the influence of on-site catheter laboratory facilities on invasive coronary strategy in ACS patients[6, 13, 15, 16, 26-29]. Unsurprisingly, the majority of these studies show increased use of invasive coronary strategy in patients admitted to hospitals with onsite cardiac catheter laboratory facilities. There are no data studying the relationship between the type of catheter laboratory facilities of the admitting hospital and receipt of invasive coronary strategy in an exclusively NSTEMI national cohort. The referral patterns and utilisation of invasive coronary strategy are likely to be different in NSTEMI patients, compared to STEMI patients where referral pathways are focussed on transfer to a PCI capable hospital for primary PCI and early reperfusion. In our study, we observed a uniform uptake in the overall use of CA in patients admitted with a diagnosis of NSTEMI in England and Wales independent of catheter laboratory facilities of the admitting hospital, however, patients admitted to diagnostic hospitals were less likely to receive invasive coronary strategy in the form of PCI or CABG. This is likely to be due to selection bias and variation in referral patterns of the admitting hospital, as patients admitted to hospitals without any laboratory facilities are likely to be referred to a nearest tertiary hospitals with onsite PCI facilities[30]. In contrast, patients admitted to diagnostic hospitals receive CA locally before a decision about further revascularisation is made by the treating physician, who may not necessarily be an interventional cardiologist. Consequently, such patients may be potentially denied early access to guideline recommended invasive coronary strategies[1, 2]. The lower rates of PCI and CABG in patients admitted to diagnostic hospitals suggests that in clinical practice, physicians are likely to adopt a risk-averse strategy even after obtaining information from CA particularly in patients admitted first to diagnostic hospitals.

In this prospective observational cohort study of over 450,000 patients, we did not observe any difference in in-hospital all-cause and cardiac mortality or bleeding complications from an NSTEMI and type of catheter laboratory facilities at the first admitting hospital. The effect of onsite site versus off site cardiac catheter laboratory facilities in ACS patients was compared in the GRACE registry showing that patients admitted to hospital with onsite cardiac catheter laboratory facilities had similar outcomes as compared to those admitted to hospital without such facilities[16]. Similar findings were reported by the European Network of Acute Coronary Treatment (ENACT) and National Registry of Myocardial Infarction investigators

showing no benefit of onsite cardiac catheter laboratory facilities in ACS[31, 32]. To the best of our knowledge, this is the first study comparing association with different levels of hospital cardiac catheter laboratory facilities and clinical outcomes in an exclusive NSTEMI cohort. Our findings also highlight important differences in institutional practices and treatment gaps, particularly in high-risk NSTEMI patients. In the high-risk NSTEMI cohort, patients admitted to diagnostic hospitals first were at increased risk of in-hospital all-cause and cardiac mortality, which may be related to a significantly lower use of invasive coronary strategies in the form of PCI or CABG in these hospitals. We observed a similar mortality hazard in high-risk NSTEMI patient receiving CA onsite in diagnostic hospitals compared to those referred for CA to PCI hospitals from the diagnostic hospitals. Previous studies from international registries have shown that the use of invasive coronary strategies is independently associated with improved survival in NSTEMI patients[21, 33]. Ideally, hospitals treating these patients should be able to offer effective care and uniform access to CA and revascularisation as per guidelines recommendations. Therefore, regionalisation of care for NSTEMI patients whereby merging the diagnostic hospitals with PCI hospitals and direct referral of patients to PCI hospitals after appropriate risk stratification may translate into early, uniform access to invasive coronary strategy, better resource allocation and improved patient care[26, 34].

Current guidelines emphasize on an early invasive approach followed by revascularisation either in the form of PCI or CABG in patients with GRACE score ≥140 or other high-risk features[1, 2]. Our results indicate that patients presenting with high-risk features such as those with LV dysfunction, heart failure, history of diabetes and high GRACE score ≥140 were least likely to receive CA or PCI independent of the type of admitting hospitals. This finding is consistent with well-known treatment risk paradox whereby patient who mostly likely to benefit from an intervention are least likely to receive it[35, 36]. A recent individual patients' level meta-analysis of eight RCTs including 5,324 patients found significantly lower mortality in high-risk patients such those with history of diabetes, age above 75 years and GRACE score ≥ 140 when treated with early invasive strategy[37]. Appropriate risk stratification, recognition of this paradox and development of quality improvement programmes are required to offer guidelines recommended treatment to patients presenting with high-risk features.

Our analysis is subject to certain limitations that should be borne in mind whilst interpreting these findings. We do not have follow up data beyond hospital discharge so only in-hospital outcomes were evaluated. However, previous studies have reported similar comparable outcomes at shorter and longer term follow up in patients who were admitted to hospitals with

or without cardiac catheter laboratory facilities in all ACS patients[6, 13]. Although completion of mandatory data fields has improved considerably in MINAP over time, there was a significant amount of missing data in important variables such as GRACE risk score that could have biased the estimates. However, in order to limit the influence of bias from missing data we implemented an imputation strategy as previously described and validated for use in this registry[38]. MINAP registry does not further define the types of different P2Y12 inhibitors (ticagelor, prasugrel) use, rather all antiplatelet information is recorded under variable "P2Y12 inhibitor use". Furthermore, use of anticoagulant agent information is also limited to warfarin in the dataset and the information around use of direct oral anticoagulants (DOACs) is not collected. Therefore, although we adjusted for use pf P2Y12 inhibitors on the outcomes, we were not able to adjust for different types of P2Y12 inhibitors and DOACs. Finally, the observational nature of the study is susceptible to unmeasured confounding and only associations rather than causal relationships can be inferred.

Conclusion:

In this large, contemporary analysis from a national healthcare system, we report significant disparities in utilisation of invasive coronary strategy, which is influenced by the type of cardiac catheter laboratory facilities of the admitting hospital. Our study serves to highlight important differences in institutional practices and treatment gaps whereby high-risk NSTEMI patients admitted to diagnostic hospitals were less likely to receive invasive coronary strategy in the form of PCI or CABG and were at increased risk of in-hospital mortality. These differences in the care of NSTEMI may be improved by developing a stronger network of a regional system of care with transfer algorithms and implementation of guidelines directed invasive strategies for high-risk NSTEMI patients.

Acknowledgements: We gratefully acknowledge the contributions of all hospitals and

health care professions who participate in the MINAP registry

Author Contributions: Dr Rashid had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Rashid, Mamas.

Acquisition, analysis, or interpretation of data: Rashid, Timmis, Mamas.

Drafting of the manuscript: Rashid, Mamas.

Critical revision of the manuscript for important intellectual content: All authors.

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Administrative, technical, or material support: Rashid, Mamas.

Study supervision: Kontopantelis, Mamas.

Conflict of interest:

All authors declare that there is no competing conflict of interest relevant to this study or any content presented in the manuscript.

Funding Source: None

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Table 1: Baseline characteristics of the patients stratified according to `no lab`, `diagnostic` and PCI hospitals.

Variables	No lab 97,777 (21.6%)	Diagnostic hospitals 134,381 (29.7%)	PCI hospitals 220,058 (48.7%)	P value
Age	74 [63-83]	74 [63-83]	72 [60.8-81]	<0.001
Male (%)	60,422(61.8%)	82,210 (61.2%)	144,096 (65.5%)	<0.001
Caucasians (%)	82,809 (84.7)	118,426 (88.2%)	179,008 (81.4%)	<0.001
BMI median [IQR]	27.0 [23.8-30.7]	26.9 [23.9-30.6]	27.2 [24.2-30.7]	0.0001
Presenting Characteristics				
Heart rate, bpm, median (IQR)	80 [67-94]	80 [67-94]	77 [65-91]	<0.001
Systolic blood pressure, median (IQR)	140 [121-158]	139 [121-158]	140 [121-158]	0.001
ECG changes	75,885 (79.6%)	104,960 (80.1%)	169,050 (78.6%)	0.001
Trop positive	88,066 (92.5%)	122,484 (94.1%)	196,414 (91.8%)	0.001
Out of hospital cardiac arrest	1,105 (1.2%)	1,175 (0.9%)	2,285 (1.1%)	<0.001
Creatinine, median (IQR)	93 [77-119]	94 [77-118]	90 [74-114]	<0.001
Seen by cardiologist	79,522 (87.6%)	111,775 (90.9%)	202,235 (95.6%)	<0.001
LV systolic function				<0.001
Good	21,533 (58.2%)	29,450 (59.3%)	56,750 (60.4%)	
Moderate	10,438 (28.2%)	13,975(28.2%)	26,380(28.1%)	
Poor	5,002 (13.6%)	6,202 (12.5%)	10,836 (11.5%)	
GRACE risk score				<0.001
Low <109	6,120(17.2%)	7,178 (17.3%)	20,742 (20.1%)	
Intermediate 109-140	8,251 (23.2%)	9,863 (23.8%)	27,351 (26.5%)	
High >140	21,226 (59.6%)	24,448 (58.9%)	55,224 (53.4%)	
Previous medical history				
Percutaneous coronary intervention	11,527(12.4%)	14,559(11.8%)	35,519 (16.6%)	<0.001
Coronary artery bypass graft	8,149 (8.7%)	11,352 (9.2%)	21,248 (10.2%)	<0.001
Heart failure	8,711 (9.3%)	10,930 (8.8%)	14,659 (7.1%)	0.001
Hypercholesterolemia	30,475 (33.2%)	44,900(36.4%)	82,128 (39.9%)	<0.001
Angina	34,059 (36.5%)	48,243(38.9%)	69,637 (33.5%)	0.001
Cerebrovascular disease	10,594 (11.1%)	13,771 (11.1%)	20,469 (9.8%)	<0.001
Peripheral vascular disease	4,980 (5.4%)	6,714 (5.5%)	11,758 (5.8%)	<0.001
Chronic renal failure	8,013 (8.6%)	10,100 (8.2%)	17,375 (8.4%)	0.04
Diabetes	24,212 (25.3%)	32,395 (24.6%)	56,291 (26.1%)	0.001
Hypertension	51,125 (54.6%)	67,945 (54.3%)	119,921 (57.0%)	0.001
Smoking status				<0.001
Previous smoker	36,946 (39.6%)	48,324 (38.3%)	78,747 (38.0%)	
Current smoker	18,941 (20.9%)	26,136 (20.8%)	46,456 (22.4%)	
Asthma / COPD	16,738 (18.0%)	23,049 (18.8%)	33,638 (16.3%)	0.001
Family history of CHD	20,315 (27.4%)	27,909 (27.6%)	57,252 (32.1%)	<0.001
In-hospital Pharmacology				

Low molecular weight heparin	58,058(64.3%)	77,468 (64.4%)	109,781 (57.2%)	<0.001
Warfarin	6,105 (6.9%)	8,649 (7.3%)	11,215 (6.1%)	<0.001
Loop Diuretic	28,666 (32.0%)	38,048 (32.1%)	52,755 (28.7%)	<0.001
Glycoprotein use	2,098 (2.3%)	2,554 (2.2%)	11,067 (5.9%)	<0.001
Coronary angiography	49,755 (61.4%)	72,277 (63.2%)	153,668 (77.3%)	<0.001
Discharge Medications				
Aspirin	61,470 (89.9%)	83,883 (89.0%)	181,828 (94.7%)	<0.001
P2Y12 inhibitors	82,895 (86.3%)	112,105 (84.9%)	192,776 (90.0%)	<0.001
Statins	61,600 (91.9%)	85,890 (91.8%)	178,985 (94.4%)	<0.001
ACE inhibitors	52,967 (80.8%)	71,151 (77.6%)	154,188 (83.9%)	<0.001
Beta-Blockers	52,108 (77.7%)	72,641 (77.6%)	156,595 (83.5%)	<0.001

Table 2: Independent predictors of receipt of coronary angiography and percutaneous coronary intervention in the overall cohort

	Predictors of receipt of CA	Predictors of receipt of PCI
Variables	OR (95% CI)	OR (95% CI)
Grace risk Score (low risk baseline)		
Intermediate (109-140)	1.17 (1.12-1.23)	1.09 (1.06-1.13)
High (>140)	0.89 (0.83-0.95)	0.88 (0.84-0.94)
Female Gender	0.73 (0.71-0.74)	0.76 (0.75-0.77)
Age	0.94 (0.944-0.946)	0.97 (0.978-0.981)
Previous acute myocardial infarction	0.65 (0.63-0.66)	0.70 (0.69-0.72)
Previous coronary artery bypass grafting	0.92 (0.89-0.95)	0.99 (0.96-1.02)
Previous percutaneous coronary intervention	1.28 (1.24-1.32)	1.36 (1.32-1.40)
History of angina	0.86 (0.84-0.88)	0.86 (0.84-0.88)
Hypertension	1.07 (1.05-1.08)	0.99 (0.97-1.07)
Hypercholesterolemia	1.24 (1.22-1.26)	1.26 (1.23-1.28)
Peripheral vascular disease	0.96 (0.92-0.96)	1.03 (0.99-1.07)
Asthma/ COPD	0.94 (0.92-0.96)	0.99 (0.97-1.01)
Chronic renal failure	0.73 (0.70-0.76)	0.88 (0.85-0.91)
Heart failure	0.70 (0.68-0.73)	0.82 (0.79-0.85)
Cerebrovascular accident	0.67 (0.65-0.68)	0.75 (0.73-0.77)
Diabetes	0.84 (0.83-0.86)	0.86 (0.84-0.88)
Left ventricular dysfunction		
Moderate	0.86 (0.83-0.89)	0.94 (0.92-0.96)
Severe	0.67 (0.64 -0.70)	0.71 (0.68-0.74)
Family history of coronary heart disease	1.33 (1.30-1.36)	1.23 (1.21-1.25)
Seen by cardiologist	6.09 (5.79-6.41)	4.27 (4.01-4.55)
Catheter laboratory facilities (ref=no lab)		
Diagnostic hospitals	1.14 (1.11-1.16)	0.88 (0.86-0.90)
PCI hospitals	1.64 (1.60-1.68)	1.69 (1.66-1.73)

Table 3: Adjusted in-hospital clinical outcomes and different level of cardiac catheter laboratory facilities

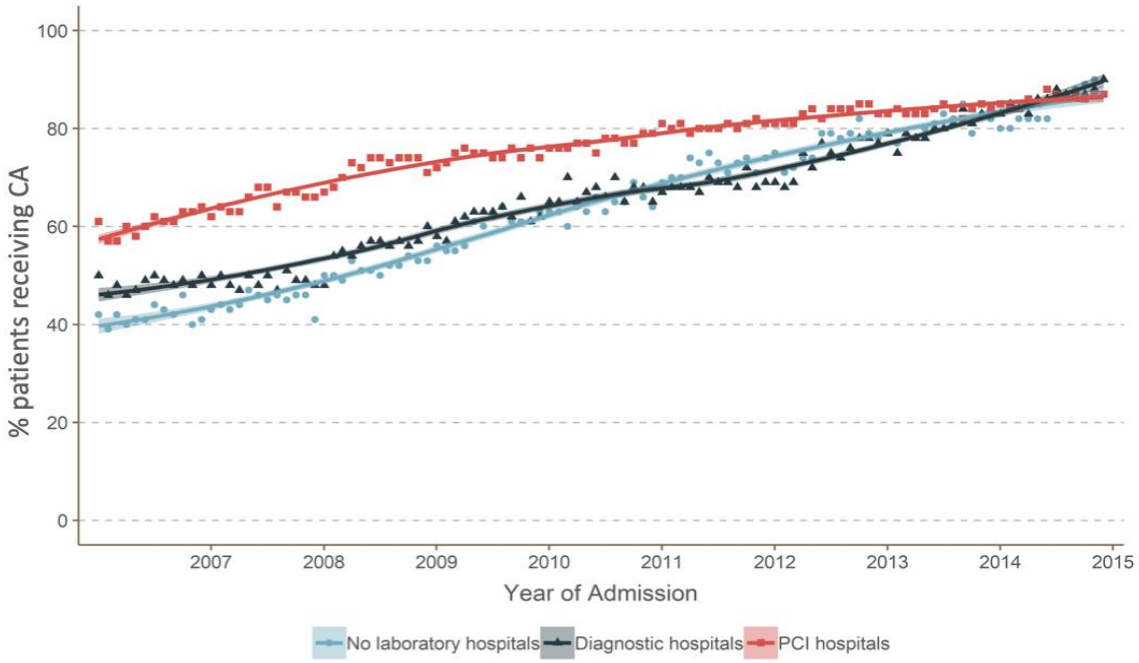
Clinical outcomes Ref (no lab centres)	PCI hospitals	Diagnostic hospitals
In hospital death	1.09 (0.96-1.24)p=0.17	0.93 (0.83-1.04)p=0.22
Cardiac mortality	1.03 (0.90-1.18)p=0.61	0.95 (0.84-1.07)p=0.43
Bleeding	0.95 (0.73-1.23), p=0.70	0.99 (0.77-1.26),p=0.95
Clinical outcomes in patients with GRACE score >140		
In hospital death	1.10 (0.87-1.39)p=0.38	1.36 (1.06-1.75)p=0.01
Cardiac mortality	0.94 (0.75-1.18)p=0.62	1.28 (0.99-1.65)p=0.05
Bleeding	0.62 (0.37-1.03), p=0.06	0.96 (0.65-1.43),p=0.87

Table 4: Clinical outcomes in patients with high GRACE risk score > 140 and in-hospital clinical outcomes.

Clinical outcomes Ref (no lab centres)	Diagnostic hospitals (treated off-site)	Diagnostic hospitals (treated on-site)	PCI centres
In-hospital mortality	0.35 (0.21-0.51)	1.45 (1.13-1.87)	1.06 (0.84-1.33)
Cardiac Mortality	0.40 (0.24-0.65)	1.35 (1.05-1.75)	0.90 (0.72-1.14)
Bleeding	0.24 (0.12-0.47)	0.72 (0.43-1.20)	0.96 (0.65-142)

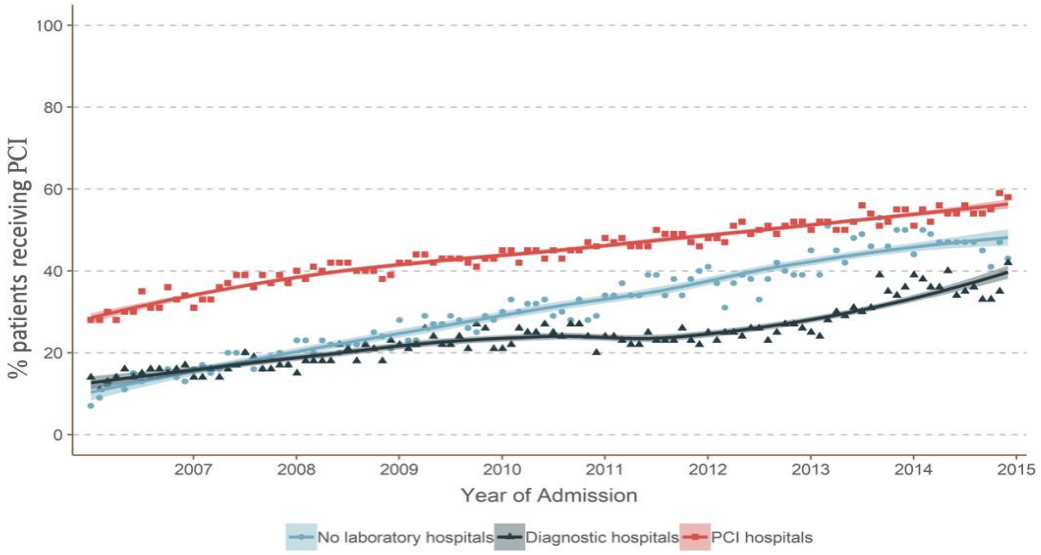
Figures

1A: Receipt of invasive coronary angiography stratified according to hospital cardiac catheter laboratory facilities in England and Wales from January 1,2007 to December 31,2015



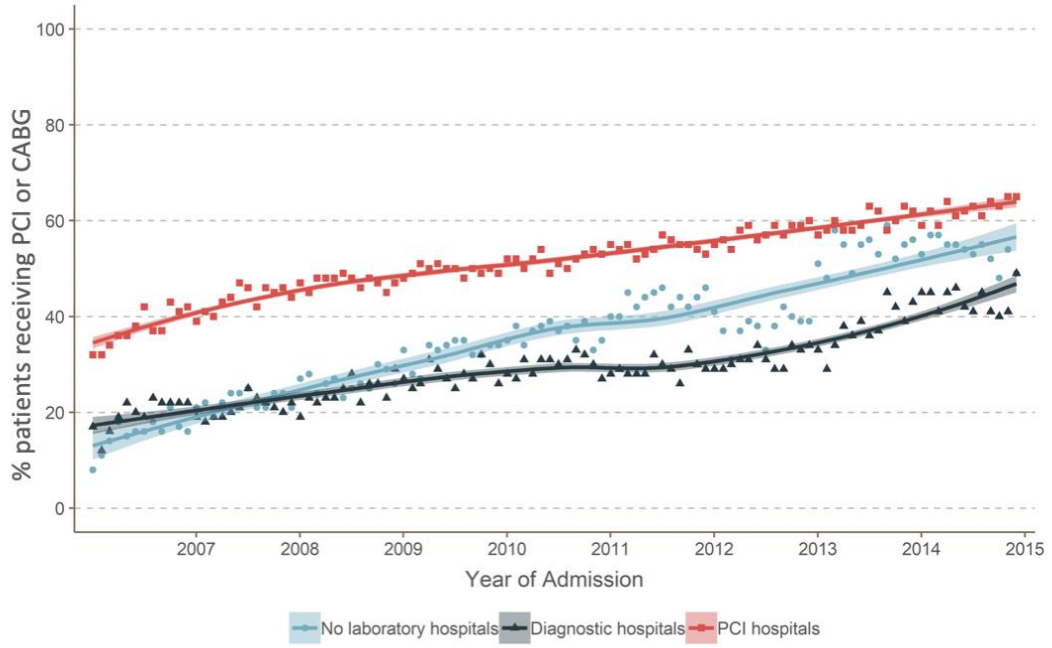
CA= coronary angiography

1B: Receipt of percutaneous coronary intervention stratified according to hospital cardiac catheter laboratory facilities in England and Wales from January 1,2007 to December 31,2015



PCI= percutaneous coronary intervention

1C: Receipt of any revascularisation procedure stratified according to hospital cardiac catheter laboratory facilities in England and Wales from January 1,2007 to December 31,2015



PCI= percutaneous coronary intervention, CABG= coronary artery bypass graft surgery

Figure 2: Association between presence of cardiac catheter laboratory facilities and clinical outcomes