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openheart P2Y₁₂ inhibitor pre-treatment in NSTEMI-ACS: translating trial evidence into UK clinical practice

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ABSTRACT

Background Dual antiplatelet therapy is indicated in the management of non-ST-elevation acute coronary syndrome (NSTEMI-ACS) and can be administered before coronary angiography (pre-treatment) or after coronary anatomy is known. Based on clinical trials with rapid access to inpatient coronary angiography, clinical guidelines recommend invasive assessment prior to commencing a second antiplatelet. We aimed to evaluate the impact of a change in clinical policy from routine P2Y₁₂ inhibitor pre-treatment to no routine pre-treatment on in-hospital outcomes in a UK healthcare context.

Methods A retrospective observational study of hospitalised NSTEMI-ACS patients with a planned invasive strategy at a tertiary cardiac centre in Northeast England was conducted. Two cohorts were identified: *routine pre-treatment* (1 January 2021 to 31 December 2021) and *no routine pre-treatment* (1 July 2022 to 30 June 2023). Primary endpoints were in-hospital ST-elevation myocardial infarction (STEMI) and actionable bleeding events, reported as propensity score-adjusted ORs (ORs) and 95% CIs.

Results Of 2506 NSTEMI-ACS cases, 1219 presented before and 1287 after the policy change, which was adhered to in most cases (84.2%). Median time from admission to angiography was 3.6 days (IQR 1.9, 5.8). In comparison to a *routine pre-treatment* strategy, a *no routine pre-treatment* strategy was associated with greater risk of in-hospital STEMI (1.7% vs 0.4%, adjusted OR 4.40, 95% CI 1.78 to 13.3), but lower risk of actionable bleeding events (0.2% vs 0.9%, adjusted OR 0.18, 95% CI 0.03 to 0.70). There was evidence of pre-treatment effect modification by procedural waiting time on in-hospital STEMI incidence (p for interaction=0.026).

Conclusion We observed a greater risk of in-hospital STEMI but lower rates of bleeding following the change from a *routine pre-treatment* to a *no routine pre-treatment* strategy. UK waiting times for in-patient coronary angiography are typically considerably longer than the trials on which guidance is based, which may impact the risk/benefit balance in clinical practice.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ In non-ST-elevation acute coronary syndrome (NSTEMI-ACS), routine pre-treatment with a P2Y₁₂ inhibitor in addition to aspirin is no longer recommended provided patients proceed to early invasive coronary angiography due to disproportionately increased bleeding risk.

WHAT THIS STUDY ADDS

⇒ When the average waiting time from admission to coronary angiography was 3.6 days, we observed that a change in clinical policy from routine to no routine pre-treatment in NSTEMI-ACS was associated with a greater risk of in-hospital ST-elevation myocardial infarction alongside a comparable reduction in risk of actionable bleeding.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ We described a time-dependent increased ischaemic risk that was not evident in pre-treatment randomised controlled trials, which had significantly shorter waiting times to coronary angiography. Our study emphasises the need to interpret trial data and guidelines within the context of the available healthcare provision, where the risk-benefit balance may be altered.

INTRODUCTION

In the UK, there are over 50 000 admissions for non-ST-elevation acute coronary syndrome (NSTEMI-ACS) annually.^{1 2} Patients presenting with suspected NSTEMI-ACS typically receive dual antiplatelet therapy (DAPT), a combination of aspirin and a P2Y₁₂ receptor inhibitor. DAPT is indicated to mitigate the risk of recurrent myocardial infarction and, where percutaneous coronary intervention (PCI) is performed, to facilitate revascularisation and reduce stent thrombosis risk.¹⁻⁴

Recent guidelines recommend that patients with NSTEMI-ACS receive aspirin monotherapy

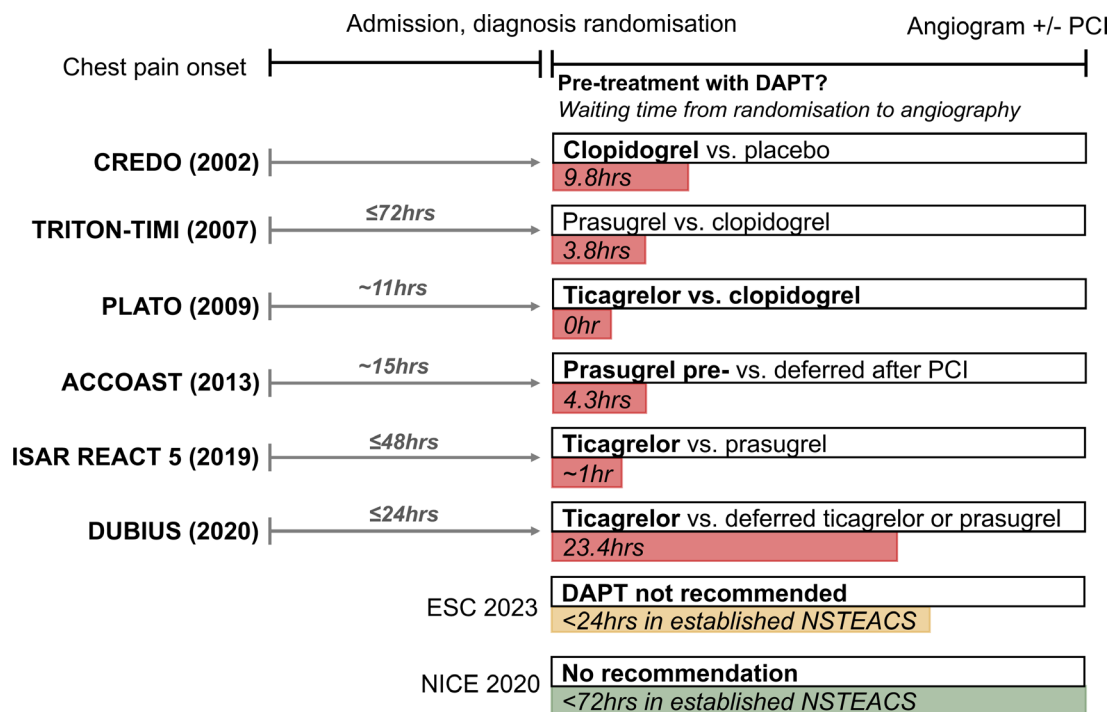


Figure 1 Summary of pre-treatment strategies in trials and guidelines. DAPT, dual antiplatelet therapy; ESC, European Society of Cardiology; NICE, National Institute for Health and Care Excellence; NSTEMI-ACS, non-ST-elevation acute coronary syndrome.

initially, with the addition of a second antiplatelet only after early invasive coronary angiography within 24 hours of presentation.^{1,3} Delayed administration of a second antiplatelet agent is supported by the ACCOAST and ISAR-REACT 5 trials, which demonstrated that pre-coronary angiography treatment with prasugrel and ticagrelor respectively, may increase the risk of life-threatening bleeding without reducing major ischaemic events.^{5,6} Delaying DAPT may also offer practical advantages, including facilitating early coronary artery bypass graft (CABG) surgery and avoiding unnecessary dual antiplatelet exposure in patients with undifferentiated chest pain.⁷

In the UK, only 55% of stable NSTEMI-ACS patients undergo invasive coronary angiography within the nationally recommended 72 hours after diagnosis.^{1,3} The target waiting time is several-fold longer than the average time delays between randomisation and coronary angiography in trials comparing pre-treatment to no pre-treatment with DAPT (figure 1). Guidelines acknowledge the theoretical potentiation of patient ischaemic risk with delayed DAPT, leaving an opportunity for nuanced decision-making.^{1,3} To fill a gap in the evidence, we aimed to assess the impact of a change in clinical policy from routine DAPT pre-treatment to no routine pre-treatment in patients presenting with NSTEMI-ACS on in-hospital rates of ischaemic and bleeding outcomes, and their relationship with time to coronary angiography as seen in UK practice.

METHODS

Study population and design

A retrospective observational study of consecutive patients with NSTEMI-ACS referred for a planned invasive strategy at the James Cook University Hospital, a tertiary cardiac centre serving a population of 1.5 million people in Northeast England.

Patients who were diagnosed with NSTEMI-ACS and proceeded to an invasive management strategy (coronary angiography) were eligible for inclusion. For patients who experienced more than one NSTEMI-ACS episode during the study period, only the first episode was included. Non-ST elevation myocardial infarction was diagnosed in accordance with the fourth Universal Definition of MI.^{3,8} Unstable angina was defined by ischaemic chest pain at rest or on minimal exertion, as ascertained by the admitting cardiology team and without cardiac troponin above the 99th percentile upper reference limit.^{1,3} Exclusion criteria were unequivocal non-acute coronary syndrome diagnoses as determined by the operator following invasive coronary angiography and ST-elevation myocardial infarction (STEMI) on presentation. In the absence of contraindications, patients were routinely prescribed subcutaneous fondaparinux and secondary prevention, including a lipid-lowering agent (preferably, a statin), a beta-blocker and an ACE inhibitor. Based on the patient's angiographic findings, comorbidities, clinical history and current status, the interventional cardiology team recommended medical therapy, PCI or referral for CABG during the same hospital admission as per standard practice.

Two cohorts were defined and compared by 12-month admission periods before and after the change in clinical policy, using an intention-to-treat-style approach to evaluate the policy's effect: *routine pre-treatment* (1 January 2021 to 31 December 2021) and *no routine pre-treatment* (1 July 2022 to 30 June 2023). *Routine pre-treatment* defined the administration of a P2Y₁₂ receptor inhibitor in addition to aspirin prior to coronary angiography; if the patient was referred for CABG surgery, the P2Y₁₂ receptor inhibitor was suspended prior to the operation. *No routine pre-treatment* defined the administration of a single antiplatelet (SAPT), usually aspirin prior to coronary angiography; the patient was loaded with a second antiplatelet, usually a P2Y₁₂ receptor inhibitor, in the catheter lab unless they were referred for CABG surgery. There was a 6-month transition period where patients were not included in the current analysis.

The study was based on routinely collected anonymised data and was registered and conducted as a service evaluation in line with local governance requirements. Formal ethical approval was not required. Patients or the public

were not involved in the design, conduct, reporting or dissemination plans of this research.

Data sources

The patient population was established from the regional referral system for NSTEMI-ACS to identify all cases, with procedural and surgical data sourced from the locally collected British Coronary Intervention Society dataset for PCI and the National Adult Cardiac Surgery Audit, respectively.^{9 10} Additional data for clinical events extracted from the electronic health record included the clinical history, referral information, multi-disciplinary team decisions and patient status updates. Local data were collected by clinicians and verified by a separate clinical audit team for national reporting purposes. Antiplatelet status at the time of coronary angiography was verified by cross-referencing the three data sources. Data validity was additionally assessed by review of randomly selected patient records from 10% of the patient sample.

Demographic and clinical variables included age, sex, cardiovascular risk factors, comorbidities and dates of

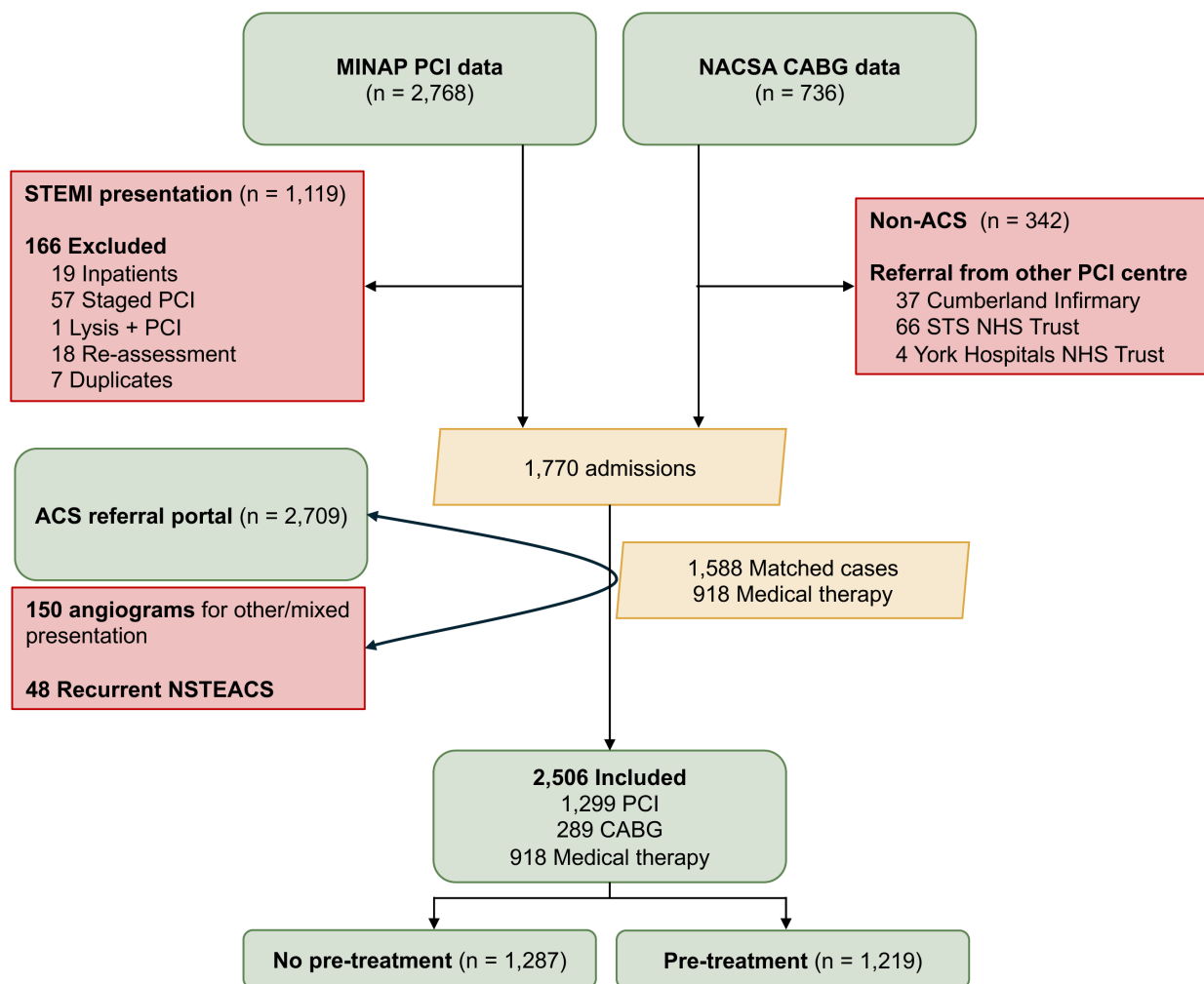


Figure 2 Study flowchart. ACS, acute coronary syndrome; CABG, coronary artery bypass graft surgery; MINAP, Myocardial Ischaemia National Audit Project; NACSA, National Adult Cardiac Surgery Audit; NHS, National Health Service; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction; STS, South Tyneside and Sunderland.

hospital admission, procedure and discharge. Procedural details included arterial access route, coronary vessels treated, intravascular imaging, calcium modification techniques, use of glycoprotein IIb/IIIa inhibitor during PCI and number, type of grafts and duration on cardiopulmonary bypass for CABG surgery.

Outcomes

The primary outcome was in-hospital STEMI incidence, defined by chest pain at rest with new STE on 12-lead ECG leading to primary PCI. Cases of STEMI were

ascertained by review of paper and electronic patient records including 12-lead ECG by two independent clinicians. The safety endpoint was actionable bleeding events prior to discharge, defined as $\geq$ type 2 bleeding by the Bleeding Academic Research Consortium (BARC) classification.¹¹ This ranged from any bleeding episode requiring medical intervention (BARC type 2) to fatal bleeding (BARC type 5).¹¹ Other outcomes were non-actionable bleeding (BARC type 1) and in-hospital death from any cause.

Table 1 Baseline clinical characteristics

	Overall (n=2506)	No routine pre-treatment (n=1287)	Routine pre-treatment (n=1219)	P value
Age (years)	64.8 $\pm$ 11.5	64.8 $\pm$ 11.6	64.7 $\pm$ 11.5	0.84
Male	1746 (69.7)	895 (69.5)	851 (69.8)	0.90
Treatment strategy				0.047
PCI	1299 (51.8)	673 (52.3)	626 (51.4)	
CABG	289 (11.5)	129 (10.0)	160 (13.1)	
Medical therapy	918 (36.6)	485 (37.7)	433 (35.5)	
Admission route				0.050
In-patient	12 (0.5)	5 (0.4)	7 (0.6)	
Direct admission	971 (38.7)	528 (41.0)	443 (36.3)	
Interhospital	1523 (60.8)	754 (58.6)	769 (63.1)	
Admission to angiography time (days)	3.6 (1.9, 5.8)	3.3 (1.9, 5.4)	3.8 (2.0, 6.1)	0.001
People who smoke*	562 (24.0)	296 (25.0)	266 (23.0)	0.27
Hypercholesterolaemia	1383 (55.2)	699 (54.3)	684 (56.1)	0.38
Hypertension	1458 (58.2)	752 (58.4)	706 (57.9)	0.81
Diabetes mellitus	577 (23.0)	296 (23.0)	281 (23.1)	1.0
Known CAD	655 (26.1)	342 (26.6)	313 (25.7)	0.62
LV function†				0.54
LVEF>50%	630 (58.1)	313 (57.9)	317 (58.4)	
35%<LVEF≤50%	327 (30.2)	159 (29.4)	168 (30.9)	
LVEF≤35%	127 (11.7)	69 (12.8)	58 (10.7)	
Haemoglobin (g/L)*	141 $\pm$ 21	141 $\pm$ 21	141 $\pm$ 21	0.84
Platelet ($\times 10^9$ /L)*	251 $\pm$ 80	252 $\pm$ 85	251 $\pm$ 74	0.88
Creatinine (μ mol/L)*	88 $\pm$ 53	88 $\pm$ 50	89 $\pm$ 56	0.37
Total cholesterol (mmol/L)†	4.7 $\pm$ 1.4	4.7 $\pm$ 1.4	4.7 $\pm$ 1.4	0.42
Glucose (mmol/L)†	7.3 $\pm$ 3.9	7.3 $\pm$ 3.8	7.4 $\pm$ 3.9	0.69
DAPT	1281 (51.1)	211 (16.4)	1070 (87.8)	<0.001
Aspirin	2407 (96.0)	1227 (95.3)	1180 (96.8)	0.065
Clopidogrel	319 (12.7)	109 (8.5)	210 (17.2)	<0.001
Ticagrelor	1048 (41.8)	129 (10.0)	919 (75.4)	<0.001
Prasugrel	13 (0.5)	13 (1.0)	0 (0.0)	<0.001
Long-term anti-coagulation therapy	728 (29.1)	375 (29.1)	353 (29.0)	0.93

Data are in mean $\pm$ SD or median (Q1, Q3) for numerical variables and n (%) for categorical variables unless otherwise stated.

*<10% missing data.

†>10% missing data.

CABG, coronary artery bypass graft; CAD, coronary artery disease; DAPT, dual antiplatelet therapy; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention.

Statistical analysis

Continuous variables were summarised as mean±SD or median and IQR, with group comparisons performed using the two-sample Student's t-test or the Mann-Whitney U test, depending on data distribution. Categorical

variables were presented as proportions, with group comparisons performed using Fisher's exact or χ^2 test dependent on expected category counts.

Propensity score (PS)-adjusted binary logistic regression modelled outcomes by treatment group, mitigating

Table 2 Angiographic and procedural characteristics in patients treated by PCI, CABG and medical therapy

	Overall	No routine pre-treatment	Routine pre-treatment	P value
PCI (n)	1299	673	626	
Radial access*	908 (96.2)	612 (96.2)	296 (96.1)	1.0
Single-vessel PCI†	985 (77.9)	503 (78.5)	482 (77.4)	0.68
Vessels treated†				
LMCA	104 (8.2)	60 (9.4)	44 (7.1)	0.15
LAD	614 (48.6)	305 (47.6)	309 (49.6)	0.50
LCx	371 (29.4)	179 (27.9)	192 (30.8)	0.27
RCA	432 (34.2)	225 (35.1)	207 (33.2)	0.51
Graft	26 (2.1)	16 (2.5)	10 (1.6)	0.32
IVUS*†	200 (15.8)	134 (20.9)	66 (10.6)	<0.001
OCT†	110 (8.7)	44 (6.9)	66 (10.6)	0.021
Pressure-wire assessment†	95 (7.5)	43 (6.7)	52 (8.3)	0.29
IVL†	26 (2.1)	16 (2.5)	10 (1.6)	0.32
RA†	33 (2.6)	22 (3.4)	11 (1.8)	0.077
Cutting balloons†	123 (9.7)	67 (10.5)	56 (9.0)	0.39
Thrombectomy catheter delivery†	37 (2.9)	16 (2.5)	21 (3.4)	0.41
DCB delivered†	161 (12.7)	73 (11.4)	88 (14.1)	0.15
DES delivered†	1176 (93.4)	599 (94.0)	577 (92.8)	0.43
Tirofiban†	106 (8.4)	70 (11.0)	36 (5.8)	0.001
TIMI 3 flow in IRA post-PCI*	1140 (98.2)	566 (97.8)	574 (98.6)	0.28
Discharged within 24 hours	1085 (83.6)	561 (83.5)	524 (83.7)	0.94
CABG (n)	289	129	160	
Angiography to CABG time (days)	7.0 (6.0, 9.8)	7.0 (5.0, 11.0)	7.0 (6.0, 9.0)	0.41
3-vessel CABG*	157 (55.5)	66 (53.2)	91 (57.2)	0.55
LIMA graft†	239 (99.2)	96 (99.0)	143 (99.3)	1.0
RIMA graft†	10 (4.1)	2 (2.1)	8 (5.6)	0.32
Radial graft†	13 (5.4)	8 (8.2)	5 (3.5)	0.15
CPB duration (min)	73 (57, 89)	76 (59, 94)	72 (57, 86)	0.18
≤5 day discharge	170 (59.0)	73 (57.0)	97 (60.6)	0.55
Medical therapy (n)	918	485	433	
IVUS	14 (1.5)	6 (1.2)	8 (1.8)	0.79
OCT	21 (2.3)	8 (1.6)	13 (3.0)	0.48
Pressure-wire assessment	80 (8.7)	38 (7.8)	42 (9.7)	0.86
Discharged within 24 hours	888 (97.0)	470 (97.0)	418 (96.5)	0.57

Data are in median (Q1, Q3) for numerical variables and n (%) for categorical variables unless otherwise stated.

*>10% missing data.

†<10% missing data.

CABG, coronary artery bypass graft surgery; CPB, cardiopulmonary bypass; DCB, drug-coated balloon; DES, drug-eluting stent; IRA, infarct-related artery; IVL, intravascular lithotripsy; IVUS, intravascular ultrasound; LAD, left anterior descending artery; LCx, left circumflex artery; LIMA, left internal mammary artery; LMCA, left main coronary artery; OCT, optical coherence tomography; PCI, percutaneous coronary intervention; RA, rotational atherectomy; RCA, right coronary artery; RIMA, right internal mammary artery; TIMI, thrombolysis in myocardial infarction.

potential confounding from unbalanced covariates between the two groups. A generalised linear regression model with a logit link function calculated the PS, defined as the probability of being in the *no routine pre-treatment* and *routine pre-treatment* arms based on clinically important baseline covariates, respectively. We included demographic information (age, sex and smoking status), history of cardiometabolic and cardiovascular disease (hypercholesterolaemia, hypertension, diabetes and known coronary artery disease), admission route and time from admission to angiography. The main analysis population was all patients presenting within each policy period. We pre-specified two sensitivity analysis populations: (1) patients who were prescribed the policy-recommended antiplatelet therapy during each period and excluding those treated with oral anticoagulants and (2) excluding those who had NSTEMI-ACS complicating an inpatient episode with a non-cardiac condition. In an exploratory analysis, we assessed the potential effect modification of *time from admission to angiography* by introducing its cross-product interaction term with treatment

group into the regression model. ORs and their 95% CI were reported.

Statistical significance was considered at the two-sided 5% level ($p < 0.05$). Statistical analysis was performed on R V.4.3.1 (Vienna, Austria: R Core Team). Relevant statistical packages were *tidyverse* and *ggplot2*.

RESULTS

After exclusions, 2506 NSTEMI-ACS patients were identified, including 1287 in the *no routine pre-treatment* and 1219 in the *routine pre-treatment* cohorts (figure 2). The baseline clinical characteristics were similar between cohorts (table 1). The patients were on average 64.8 ± 11.5 years of age with 1746 (69.7%) males. Common comorbidities included hypercholesterolaemia (55.2%), hypertension (58.2%), diabetes mellitus (23.0%) and known coronary artery disease (26.1%). Of the 1084 patients with documented echocardiography, 11.7% had severe left ventricular systolic impairment.

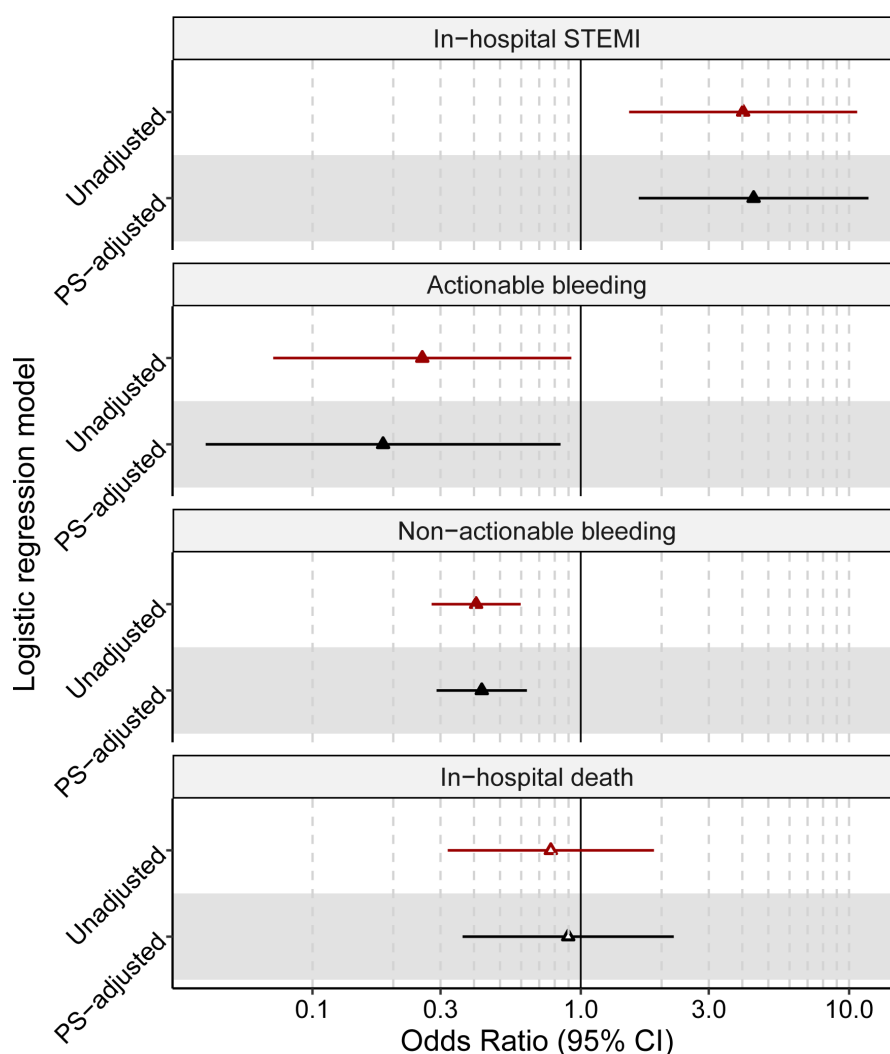


Figure 3 The association between change from routine pre-treatment to no routine pre-treatment and risk of in-hospital outcomes. PS, propensity score; STEMI, ST-elevation myocardial infarction.

Patient pathway and intervention

The majority of patients were referred from neighbouring non-PCI centres (60.8%), with the remainder admitted directly (38.7%); a further 12 patients developed NSTEMI-ACS while hospitalised for another condition (table 1). The median waiting time from admission to invasive coronary angiography was 3.6 (IQR 1.9, 5.4) days. The change in the clinical policy on DAPT coincided with a small reduction in time to procedure (3.3 (1.9, 5.4) vs 3.8 (2.0, 6.1) days, $p=0.001$). Patients who were transferred from a neighbouring hospital had a longer wait than those who were admitted directly to the PCI centre (4.2 (2.8, 6.3) vs 2.2 (1.0, 4.3) days, $p<0.001$).

The two treatment periods had comparable PCI rates. Overall, 1299 (51.8%) patients proceeded to PCI, with 93.4% receiving at least one stent, most commonly by radial access (96.2%), table 2. The change in policy to *no routine pre-treatment* coincided with more frequent tirofiban prescription (11.0% vs 5.8% ($p=0.001$)) and IVUS imaging (20.9% vs 10.6% ($p<0.001$)), but less frequent optical coherence tomography imaging (6.9% vs 10.6% ($p=0.021$)) during PCI. Alongside the policy change, there was a decrease in the rate of CABG surgery from 13.1% to 10.0% and an increase in the rate of medical therapy from 35.5% to 37.7% ($p=0.047$, table 1). Overall, median time from angiography to CABG surgery was unchanged at 7.0 (6.0, 9.8) days ($p=0.41$). By postoperative day 5, 59.0% of patients undergoing CABG surgery were discharged. 97.0% of patients treated with medical

therapy and 83.6% of patients treated by PCI were discharged within 24 hours of their procedure.

Antiplatelet therapy

The most commonly prescribed antiplatelet therapies before proceeding to invasive coronary angiography were aspirin (96.0%) and ticagrelor (41.8%). A long-term oral anticoagulant medication was prescribed in 29.1% of patients. Overall, adherence to local guidelines was high: 1041 (80.9%) were prescribed SAPT in the *no routine pre-treatment* cohort and 1070 (87.8%) were prescribed DAPT in the *routine pre-treatment* cohort. DAPT prescription rates were unchanged after excluding patients who took a regular oral anticoagulant.

Clinical outcomes

PS-adjusted binary logistic regression demonstrated that *no routine pre-treatment* was associated with greater risk of in-hospital STEMI in comparison to *routine pre-treatment* (1.7% vs 0.4%, adjusted OR 4.40, 95% CI 1.78 to 13.3, figure 3 and table 3). Review of patient records confirmed that 25/26 (96.2%) instances of in-hospital STEMI received antiplatelet therapy in accordance with departmental policy at the time; one patient from the *routine pre-treatment* cohort was not loaded with a second antiplatelet before developing ST-elevation on ECG in the emergency department. An important interaction was noted between pre-treatment strategy and time to invasive coronary angiography: a *no routine pre-treatment* strategy increased the odds of in-hospital STEMI by 13%

Table 3 In-hospital outcomes with sensitivity analyses

	No routine pre-treatment	Routine pre-treatment	Unadjusted OR	PS-adjusted OR
All patients	n=1287	n=1219		
NSTEMI-ACS to STEMI transformation	21 (1.7)	5 (0.4)	4.03 (1.64 to 12.1)*	4.40 (1.78 to 13.3)*
Actionable bleeding	3 (0.2)	11 (0.9)	0.26 (0.06 to 0.82)*	0.18 (0.03 to 0.70)*
Non-actionable bleeding	40 (3.1)	89 (7.3)	0.41 (0.28 to 0.59)†	0.43 (0.29 to 0.63)†
Death from any cause	9 (0.7)	11 (0.9)	0.77 (0.31 to 1.87)	0.90 (0.35 to 2.24)
Per policy pre-treatment w/o anticoagulation	n=733	n=757		
NSTEMI-ACS to STEMI transformation	15 (2.0)	3 (0.4)	5.25 (1.72 to 22.7)*	5.84 (1.91 to 25.4)*
Actionable bleeding	3 (0.4)	7 (0.9)	0.44 (0.09 to 1.59)	0.32 (0.05 to 1.42)
Non-actionable bleeding	24 (3.3)	54 (7.1)	0.44 (0.27 to 0.71)*	0.49 (0.29 to 0.80)*
Death from any cause	5 (0.7)	7 (0.9)	0.74 (0.22 to 2.32)	0.80 (0.23 to 2.67)
NSTEMI-ACS hospital presentation	n=1282	n=1212		
NSTEMI-ACS to STEMI transformation	16 (1.2)	4 (0.3)	3.82 (1.40 to 13.4)*	4.12 (1.50 to 14.4)*
Actionable bleeding	3 (0.2)	11 (0.9)	0.26 (0.06 to 0.82)*	0.18 (0.03 to 0.70)*
Non-actionable bleeding	40 (3.1)	87 (7.2)	0.42 (0.28 to 0.61)†	0.44 (0.29 to 0.64)†
Death from any cause	9 (0.7)	11 (0.9)	0.77 (0.31 to 1.87)	0.90 (0.35 to 2.40)

Data are in n (%) unless otherwise stated.

** $p<0.05$.

† $p<0.001$.

NSTEMI-ACS, non-ST-elevation acute coronary syndrome; PS, propensity score; STEMI, ST-elevation myocardial infarction.

for each additional 24-hour delay from admission to angiography (p for interaction=0.026, figure 4).

In comparison to a *routine pre-treatment* strategy, a *no routine pre-treatment* strategy was associated with lower incidences of actionable bleeding events (0.2% vs 0.9%, adjusted OR 0.18, 95% CI 0.03 to 0.70) and non-actionable bleeding events (3.1% vs 7.3%, adjusted OR 0.43, 95% CI 0.29 to 0.63), respectively (figure 3 and table 3). Time to invasive coronary angiography was not a significant modifier of the relationship between pre-treatment strategy and actionable bleeding events ($p=0.10$, figure 4).

Of the 14 actionable bleeding events, 10 (71.4%) were CABG-related, requiring re-operation, including 8 in the *routine pre-treatment* and 2 in the *no routine pre-treatment* cohorts, respectively. There was no difference in time from invasive coronary angiography to CABG between patients with and without actionable bleeding events (8.4 (4.5 to 11.4) vs 7.5 (0.6 to 27.3) days, $p=0.94$). Of the four non-CABG-related actionable bleeding events, two were attributed to tamponade after coronary perforation and two were vascular complications (ie, a false aneurysm and a groin haematoma) that required vascular follow-up without intervention.

There was no significant difference for in-hospital mortality (0.7% vs 0.9%, adjusted OR 0.90, 95% CI 0.35

to 2.24, figure 3 and table 3). Similar outcomes were observed when the analysis was limited to (1) patients who were prescribed the policy-recommended pre-treatment applicable at the time of presentation as well as not prescribed an oral anticoagulant and (2) excluding patients who had NSTEMI-ACS complicating another acute illness, respectively (table 3).

DISCUSSION

We found that the change in policy from *routine* to *no routine* pre-treatment with P2Y₁₂ inhibitor for patients with NSTEMI-ACS was associated with a greater risk of in-hospital STEMI alongside a comparable reduction in risk of actionable bleeding (figure 5). Comorbidity burden was high, as was the adherence to the clinical policy of the time. The average waiting time from admission to invasive coronary angiography was 3.6 days, which is typical of contemporary UK practice, although markedly longer than the time to angiography reported in the clinical trials underpinning the evidence base (figure 1).²

A meta-analysis of seven trials ($n=13\,226$) of patients with NSTEMI-ACS randomised to either pre-treatment or no pre-treatment demonstrated an increased early major bleeding risk with pre-treatment, without any

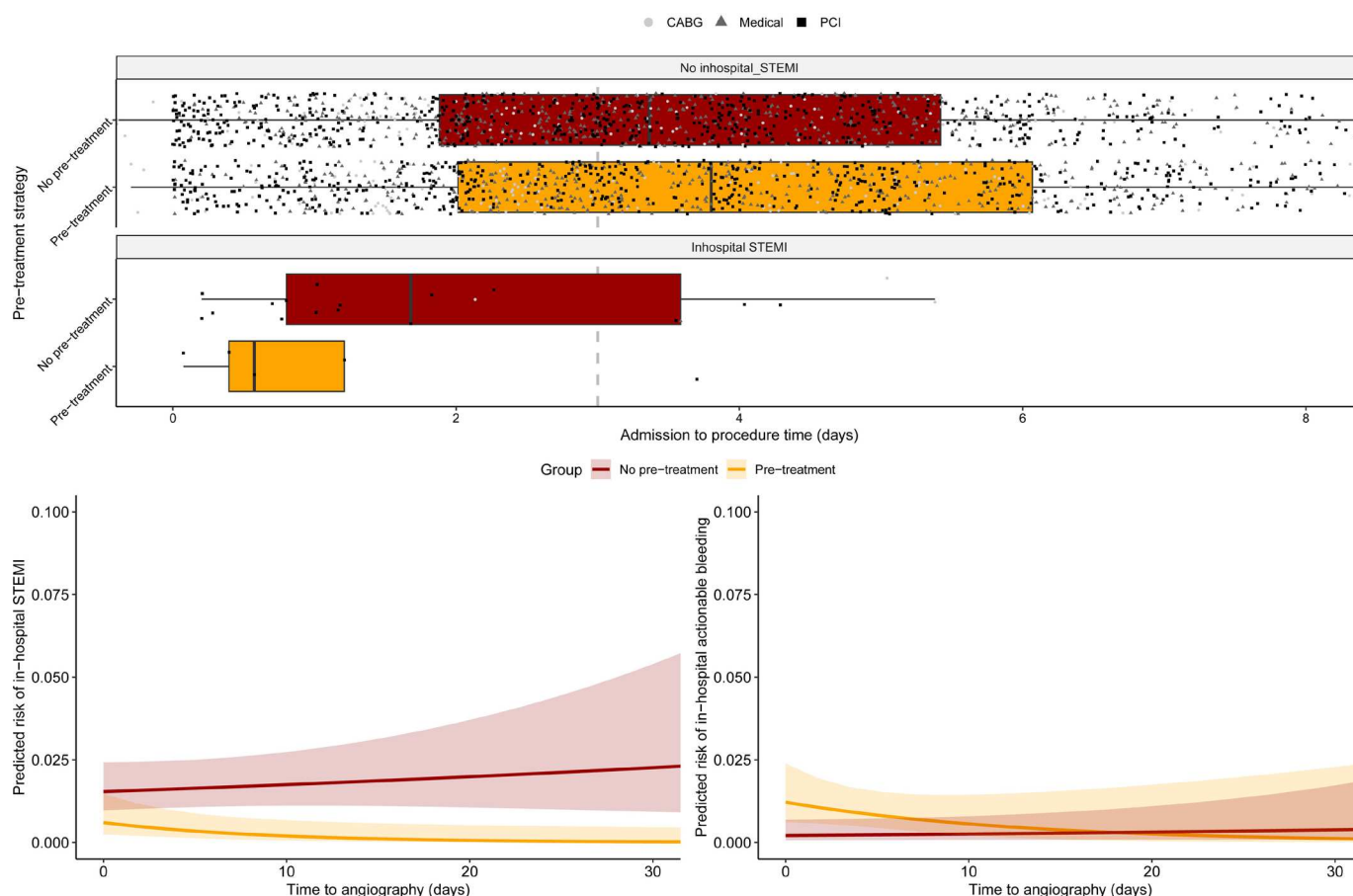


Figure 4 Interaction between pre-treatment strategy, time to invasive coronary angiography and the risk of in-hospital STEMI and actionable bleeding events. CABG, coronary artery bypass graft surgery; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction.

significant reduction in ischaemic risk.¹² The unfavourable risk-benefit profile of pre-treatment was largely related to the ACCOAST trial, which reported a twofold increase in major bleeding with a prasugrel pre-treatment strategy, without any increase in a composite ischaemic endpoint.^{5 12 13} In two earlier trials, the 'Effects of Pretreatment with Clopidogrel and Aspirin followed by Long-Term Therapy in Patients Undergoing Percutaneous Coronary Intervention: the PCI-CURE Study', and the 'Early and Sustained Dual Oral Antiplatelet Therapy Following Percutaneous Coronary Intervention' (CREDO) trial, pre-treatment with clopidogrel at least 6 hours before invasive coronary angiography was associated with reduced risk of death, myocardial infarction and ischaemia-driven revascularisation—without potentiation of bleeding risk.^{14–16} The 'Timing of Oral P2Y₁₂ Inhibitor Administration in Patients with Non-ST-Segment Elevation Acute Coronary Syndrome' (DUBIUS) trial was terminated early after showing no differences in ischaemic or bleeding outcomes between pre-treatment strategies.^{12 17} Two important differences in trial design help to reconcile the contradicting results. First, the time from randomisation to angiography was progressively longer in the CREDO (~10 hours), DUBIUS (~23 hours) and PCI-CURE (~6 days) trials in comparison to the ACCOAST trial (~4 hours) (figure 1).^{5 12 14–17} Second, the two older trials, PCI-CURE and CREDO used clopidogrel, a less potent P2Y₁₂ inhibitor than either prasugrel or ticagrelor.^{14–16}

Clinical practice implications

Our data of routine clinical practice show that delaying administration of a second antiplatelet agent until coronary angiography carried a higher risk of in-hospital STEMI—an ischaemic 'price to pay' that was not evident

in ACCOAST. One reason may be that patients experience significantly greater waiting times to coronary angiography in UK clinical practice, comparable to timelines in DUBIUS and PCI-CURE. We observed a daily cumulative risk of conversion from NSTEMI to STEMI while waiting for coronary angiography on SAPT.

Wary that bleeding risk is typically underestimated in retrospective studies, we observed a reduction in clinically significant bleeding episodes following the change in local clinical policy away from routine P2Y₁₂ receptor inhibitor pre-treatment.¹⁸ Because P2Y₁₂ inhibitors, particularly thienopyridines, can have antiplatelet effects lasting up to 10 days, pre-treatment may have contributed directly to CABG-related bleeding. Overall, our findings support the well-described reductions in bleeding risk observed in the clinical trials.^{19–22}

Major bleeding and ischaemic events are two competing risks that carry a poor prognosis and are associated with high morbidity and mortality in NSTEMI-ACS patients (figure 5).^{23 24} It is therefore reassuring that in-hospital mortality was low regardless of pre-treatment strategy. Nonetheless, our data demonstrate that inpatient waiting for invasive coronary angiography for NSTEMI-ACS is not benign, and UK centres should prioritise the shortening of clinical pathways which have remained persistently above target.²

Our study emphasises the need to interpret clinical trial data and guidelines within the context of the available healthcare provision. In two Swedish and American registry-based observational studies totalling more than 84 000 patients with NSTEMI-ACS, most underwent invasive coronary angiography within 24–48 hours of hospital admission, and pre-treatment conferred greater risk of bleeding without lower risk of ischaemic events.^{7 25} Yet in

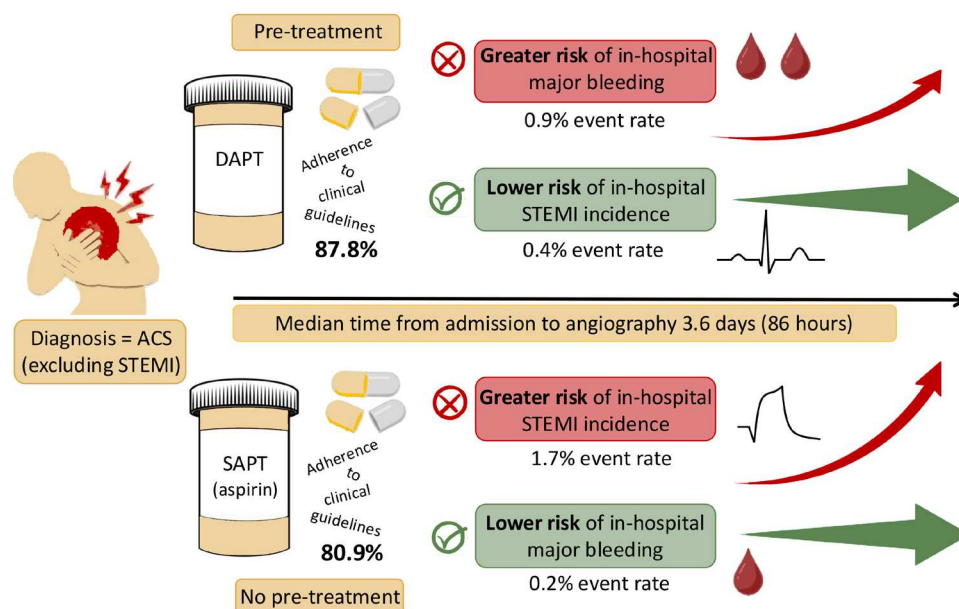


Figure 5 Pre-treatment strategy and its impact on in-hospital outcomes in UK NSTEMI-ACS patients. ACS, acute coronary syndrome; DAPT, dual antiplatelet therapy; NSTEMI-ACS, non-ST-elevation acute coronary syndrome; PCI, percutaneous coronary intervention; SAPT, single antiplatelet therapy; STEMI, ST-elevation myocardial infarction.

the UK and other countries where patients may not reach the catheter laboratory for a planned invasive strategy within 24–48 hours of admission, no pre-treatment may carry a harm that is not captured within the clinical trials.^{2 26 27} We provide compelling real-world evidence supporting the ESC Class IIb recommendation that pre-treatment may be considered in NSTEMI-ACS patients who are not expected to undergo an early invasive strategy within 24 hours of admission.³

Nonetheless, clinically urgent patients who present rapidly to the catheter laboratory and require CABG may well benefit from lower bleeding risks not captured within these aggregated data. Indeed, the most common bleeding events were in pre-treated patients who went on to CABG despite a median delay of 7 days to surgery. Furthermore, a change to a more circumspect antiplatelet policy may have fewer tangible benefits in reducing inappropriate prescribing of DAPT for non-specific cardiac biomarker elevations.

Notably, the no routine pre-treatment policy was associated with increased use of intravenous tirofiban, a fast-acting, potent GPIIb/IIIa inhibitor often reserved for PCI in high thrombotic-risk settings.³ This trend may reflect a real increase in thrombotic concerns, or operator bias regarding antiplatelet status in the absence of a true increase in thrombus burden. The ACCOAST-PCI sub-study found no difference in angiographically identified intracoronary thrombus rates with or without pre-treatment.^{5 28}

Study limitations and strengths

The strength of our analyses is derived from the quality of collected data from a stringently maintained local and national database and the opportunity to evaluate a change in clinical practice.^{9 10} Nevertheless, this is a retrospective observational study, with the inherent limitations therein. Our study evaluated the in-hospital STEMI and bleeding risk in patients with heterogeneous treatments, including choice of antiplatelet combination and invasive treatment following a change in pre-treatment policy. Although adherence to local guidelines was more than 80% with respect to prescription of SAPT in the no routine pre-treatment cohort and DAPT in the routine pre-treatment cohort, the patients were assessed by policy period rather than prescribed treatment, comparable to an intention-to-treat analysis. We suspect that the most common reason for divergence from SAPT pre-treatment in suspected NSTEMI-ACS was the recognition of prolonged delays to planned invasive coronary angiography and therefore P2Y₁₂ inhibitor therapy in patients with low bleeding risk. Finally, we recognise that patients in whom a conservative strategy was pursued from the outset were not represented in these data and that a minority of medically managed patients, who proceeded to cardiovascular magnetic resonance, may have ultimately had a non-coronary aetiology. Overall, our results are likely to be an accurate representation of contemporary UK practice, making them highly relevant.

CONCLUSION

We observed a greater risk of in-hospital STEMI but lower rates of bleeding following the change from a *routine pre-treatment* to a *no routine pre-treatment* strategy. Waiting times in the UK for in-patient coronary angiography are typically much longer than the trials on which guidance is based, which may impact the risk/benefit balance in clinical practice. Clinical trial evidence and guideline recommendations must be interpreted within a local healthcare context.

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