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Pretreatment with $P2Y_{12}$ receptor antagonists in ST-elevation myocardial infarction: a report from the Swedish Coronary Angiography and Angioplasty Registry

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Aims Pretreatment of patients with ST-elevation myocardial infarction (STEMI) with $P2Y_{12}$ receptor antagonists is supported by guidelines and is a common practice despite the lack of definite evidence for its benefit.

Methods and results Using data from the Swedish Coronary Angiography and Angioplasty Registry on procedures between 2005 and 2016, we stratified all patients who underwent primary percutaneous coronary intervention due to STEMI in Sweden by whether or not they were pretreated with $P2Y_{12}$ receptor antagonists. We investigated associations between pretreatment with $P2Y_{12}$ receptor antagonists and the risk of adverse outcomes using propensity score-adjusted mixed-effects logistic regression, which accounted for clustering of patients within hospitals. The primary endpoint was all-cause death within 30 days. Secondary endpoints were infarct-related artery (IRA) occlusion, 30-day stent thrombosis, in-hospital bleeding, neurological complications, and cardiogenic shock. In total, 44 804 patients were included. They were treated with clopidogrel ($N = 26\,136$, 58.3%), ticagrelor ($N = 15\,792$, 35.3%), or prasugrel ($N = 2352$, 5.3%); 37 840 (84.5%) were pretreated, and 30 387 (67.8%) had IRA occlusion. At 30 days, there were 2488 (5.6%) deaths and 267 (0.6%) stent thrombosis. Pretreatment was not associated with better survival at 30 days [odds ratio (OR) 1.08, 95% confidence interval (CI) 0.95–1.24; $P = 0.313$], reduced IRA occlusion (OR 0.98, 95% CI 0.92–1.05; $P = 0.608$), decreased stent thrombosis (OR 0.99, 95% CI 0.69–1.43; $P = 0.932$), higher risk of in-hospital bleeding (OR 1.05, 95% CI 0.89–1.26; $P = 0.526$), or neurological complications (OR 0.66, 0.72, 95% CI 0.43–1.21; $P = 0.210$).

Conclusion Pretreatment of STEMI patients with $P2Y_{12}$ receptor antagonists was not associated with improved clinical outcomes.

Keywords Antiplatelet therapy • ST-elevation myocardial infarction • $P2Y_{12}$ receptor antagonists • Primary PCI • Observational study • Swedish Coronary Angiography and Angioplasty Registry

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Introduction

Early administration of $P2Y_{12}$ receptor antagonists to patients with ST-elevation myocardial infarction (STEMI) is supported by the American College of Cardiology (ACC)/American Heart Association (AHA) and European Society of Cardiology (ECS)/European Association of Cardio-Thoracic Surgery (EACTS) guidelines and is a common practice despite the lack of definite evidence for its benefit.[1–4] Most of the available data in favour of pretreatment with $P2Y_{12}$ receptor antagonists in STEMI are indirect and old.[5–11] No previous trials in which the timing of treatment with $P2Y_{12}$ receptor antagonists was studied had adequate statistical power to evaluate mortality and clinically relevant complications. The only randomized trial in patients with STEMI did not demonstrate that pretreatment with $P2Y_{12}$ receptor antagonists had beneficial effects on reperfusion indices or clinical outcomes.[12]

In this report based on a nationwide, contemporary, large cohort of patients with STEMI undergoing primary percutaneous coronary intervention (PCI), we compared pretreatment with $P2Y_{12}$ receptor antagonists vs. no pretreatment with $P2Y_{12}$ receptor antagonists in relation to mortality, patency of infarct-related artery (IRA), stent thrombosis, cardiogenic shock, bleeding, and neurological complications.

Methods

Databases and patient selection

We used data from the prospective SCAAR (Swedish Coronary Angiography and Angioplasty Registry) database. Established in 1992, SCAAR is a national registry of all coronary angiographies and PCIs performed in Sweden. Each catheterization procedure is described with ~50 angiographic and 200 PCI variables, both demographic and procedure related. The registry is sponsored by the Swedish Health Authorities and does not receive any funding from commercial interests. All consecutive patients who underwent PCI for STEMI in Sweden between 1 January 2005 and 1 November 2016 were included in the study. We did not perform sample size analysis before statistical modelling. Patients who did not receive pre-hospital acetylsalicylic acid or who underwent thrombolysis before PCI were excluded. More detailed information about SCAAR's organization and the database has been reported.[13,14]

Definitions and outcomes

Patients were considered to have diabetes, hypertension, hyperlipidaemia, previous myocardial infarction, or previous stroke if any of those conditions had been diagnosed according to the International Classification of Diseases codes.[14] Information about the previous PCI, previous coronary artery bypass grafting, cardiogenic shock, and procedural details are entered directly into the database by interventional cardiologists. Standardized definitions are utilized across all hospitals for cardiogenic shock and other procedure-related information. Non-Swedish citizens were excluded from the study. Patients were defined as pretreated if they received treatment with clopidogrel, prasugrel, or ticagrelor at the time of first medical contact outside the catheterization laboratory. Patients who received $P2Y_{12}$ antagonists in the catheterization laboratory at the start of primary PCI were defined as not pretreated. The treating PCI operator specifically enters this information into the registry.

Endpoints

The primary endpoint was mortality at 30 days. Vital status and date of death were obtained from the Swedish National Population Registry until 14 December 2016. SCAAR was merged with the Swedish National Population Registry by the Epidemiologic Center of the Swedish National Board of Health and Welfare according to Swedish personal identification numbers. Because the use of personal identification numbers is mandatory, the death registry in Sweden has a high degree of completeness, but it is not reviewed or adjudicated to establish cardiac vs. non-cardiac causes of death. The secondary endpoints were IRA patency at the time of primary PCI, stent thrombosis at 30 days, cardiogenic shock, neurological complication, and bleeding during the index hospitalization. Stent thrombosis was defined as an acute stent occlusion verified by coronary angiography. The neurological complication was defined as a new neurological deficit during PCI or during hospitalization after the index PCI. In-hospital bleeding was defined as any of the following: puncture site haematoma >5 cm or pseudo-aneurysm requiring intervention, cardiac tamponade, drop in haemoglobin >20 g/L, intracranial bleeding, or prolonged compression-treatment (>6 hours), transfusion, or surgical intervention.[15]

Statistics

Continuous variables are presented as a median and interquartile range (IQR) and categorical variables as frequencies. Normal distribution of variables was assessed by inspecting the distribution of values on histograms and by the Shapiro–Wilk test. Intergroup differences in continuous variables were tested by linear regression. Differences in categorical variables were tested by logistic regression.

Imputation protocol

Missing data were imputed with the multiple imputation chain-equation method[16,17] with five data sets. The calendar year, an indicator of missingness and an event indicator were included as regular variables.[18] Continuous variables were imputed by ordinary least-squares multiple regression, binary variables by logistic regression, and categorical variables by multinomial logistic regression. The imputation procedure and subsequent analyses were done according to Rubin's protocol[19] under the assumption that missing data are missing at random.

Statistical models

After multiple imputation of missing data, propensity score models were used to adjust for differences in patient characteristics. Significant predictors of pretreatment with $P2Y_{12}$ receptor antagonists for each patient were identified by fitting a logistic regression model with (i) a binary dependent variable representing pretreatment or no pretreatment with a $P2Y_{12}$ receptor antagonist and (ii) candidate variables consisting of the patient-related predictors of the type of therapy used. All variables in *Table 1*, as well as the calendar year and hospital, were entered into the logistic model. The estimated propensity score was entered as a categorical variable based on quintiles of propensity score together with the treatment status in multilevel mixed-effects logistic regression with hospital as a random effect variable. The risk estimates were marginalized over the random effect distribution across hospitals. We used random intercept-only models based on the assumption that the intercepts arise from a normal distribution. Propensity score-adjusted median odds ratios (MOR) were used to assess the variability in hospital-level patient outcomes. The MOR is a function of the between-variance estimates and reflects the median odds of outcomes of two patients with identical covariates treated in two different, randomly selected, hospitals.[20] We used propensity score matching as a sensitivity analysis. To ensure close matches, we required that the estimated log-odds scores predicting

Table 1 Patient characteristics

	Pretreated (*N* = 37 840)	Missing	Not pretreated (*N* = 6964)	Missing	Standardized difference	Standardized difference after adjustment
Age (years)						
Mean age (years)	67 ± 12	0	68 ± 12	0	0.132	0.037
Age >75 years, *n* (%)	9866 (26.1)	0	2261 (32.5)	0	0.141	0.028
Male sex, *n* (%)	27 079 (71.6)	0	4903 (70.4)	0	0.020	0.021
Diabetes, *n* (%)	5565 (14.7)	0	1228 (17.6)	0	0.080	0.011
Hypertension, *n* (%)	17 053 (45.1)	0	3453 (49.6)	0	0.091	0.007
Smoking—*n*/total *n* (%)		3238 (8.6)		743 (10.7)		
Never smoker	15 084 (39.9)		2818 (40.5)		0.016	0.002
Previous smoker	11 159 (29.5)		2186 (31.4)		0.037	0.008
Current smoker	11 597 (30.7)		1960 (28.14)		0.054	0.005
Hyperlipidaemia, *n* (%)	9144 (24.2)	0	2295 (33.0)	0	0.202	0.008
Previous stroke, *n* (%)	1768 (4.7)	4323 (11.4)	464 (6.6)	1165 (16.7)	0.123	0.030
History of heart failure, *n* (%)	1155 (3.1)	4347 (11.5)	332 (4.8)	1122 (16.1)	0.107	0.027
Previous myocardial infarction, *n* (%)	5996 (15.6)	0	1719 (24.7)	0	0.229	0.001
Previous PCI, *n* (%)	4636 (12.3)	0	1240 (17.8)	0	0.153	0.018
Previous CABG, *n* (%)	1225 (3.2)	0	371 (5.3)	0	0.107	0.014
Cardiogenic shock, *n* (%)	1031 (2.7)	0	366 (5.3)	0	0.100	0.029
Symptom to first contact (min), median (IQR)	114 (51 295)	0	106 (45 283)	0	0.015	0.001
First contact to start of PCI (min), median (IQR)	75 (50 125)	0	68 (42 134)	0	0.075	0.015
Prehospital heparin	15 442 (40.8)	0	2069 (29.7)	0	0.234	0.071
Days in hospital, mean ± SD	4.9 ± 5.7	0	5.4 ± 5.3	0	0.080	0.032
Medications used at the time of presentation, *n* (%)						
Beta-blockers	11 066 (29.2)	623 (1.6)	2726 (39.1)	91 (1.3)	0.211	0.006
ACE inhibitor	6427 (17.0)	607 (1.6)	1393 (20.0)	85 (1.2)	0.077	0.001
ARB receptor antagonist	4665 (12.3)	602 (1.6)	896 (12.9)	88 (1.3)	0.015	0.010
Acetylsalicylic acid	10 789 (28.5)	414 (1.1)	3175 (45.6)	73 (1.1)	0.360	0.009
$P2Y_{12}$ receptor antagonist	1597 (4.2)	3971 (10.5)	219 (3.1)	1036 (14.9)	0.022	0.009
Statin	9384 (24.8)	423 (1.1)	2394 (34.4)	75 (1.1)	0.211	0.001
OAC or NOAC	593 (1.6)	56 (0.2)	236 (3.4)	27 (0.4)	0.117	0.019

ACE, Angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CABG, coronary artery bypass grafting; CPR, Cardiopulmonary resurrection; NOAC, novel oral anticoagulant; OAC, oral anticoagulant; PCI, percutaneous coronary intervention; SD, standard deviation.

treatment group for matched pairs be within 0.25 standard deviation units of each other.

Post-estimation diagnostics

Goodness-of-fit (calibration) for the models was assessed with the Hosmer–Lemeshow test. Multicollinearity between the variables in the model was evaluated by calculating the variance inflation factor. All reported *P*-values are two-sided and are not adjusted for multiple testing. Stata software (version 15.0, StataCorp) was used for all statistical analyses. All tests were two-tailed, and $P < 0.05$ was considered statistically significant. Because of multiple analyses, $P < 0.05$ was expected to occur by chance in 1 of 20 analyses.

Results

Patient characteristics and treatments

We identified 53 146 patients who underwent primary PCI during the study period (*Figure 1*). We excluded patients who did not receive acetylsalicylic acid before PCI (*N* = 6911), patients who were treated with thrombolysis (*N* = 260), and patients with missing data that were not imputed (*N* = 1171). The remaining 44 804 patients (28.6% female) were included in the study; 6964 (29.6% female) were not pretreated with a $P2Y_{12}$ receptor antagonist. These patients were reported from 30 different hospitals, and the range of reported patients per hospital was 102–6471.

The characteristics of the patients are presented in *Table 1* and procedure-related details in *Table 2*. Patients pretreated with a $P2Y_{12}$ receptor antagonist were on average younger, more likely to be active smokers, and less likely to have hypertension, hyperlipidaemia, diabetes mellitus, heart failure, myocardial infarction, stroke, prior PCI, or prior coronary artery bypass grafting. During PCI, pretreated patients were more often treated with ticagrelor, prasugrel, and bivalirudin but less often with a GP2b/3a receptor antagonist. Pretreated patients were also more likely to have a radial access site and less likely to have complex coronary artery disease. They were more likely to have complete revascularization during the index PCI and

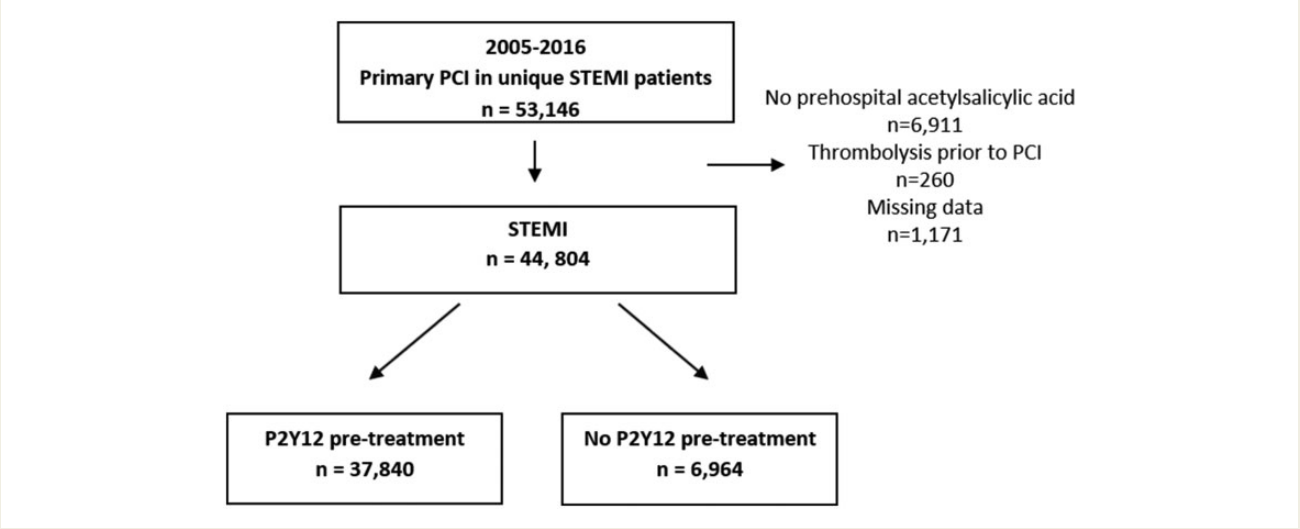


Figure 1 A flowchart for patient selection in SCAAR (Swedish Coronary Angiography and Angioplasty Registry).

thrombus aspiration before stent placement but were less likely to receive a drug-eluting stent. Stents were more often placed without prior balloon dilatation of the lesion in pretreated patients. Pretreated patients were less likely to develop cardiogenic shock. The median time from symptom debut to the first medical contact and from the first medical contact to the start of PCI in the total population was 113 min (IQR 50–293) and 74 min (IQR 48–125), respectively, and these times did not differ significantly between the two groups (*Table 2* and Supplementary material online, *Figure S1*). After adjustment for propensity score, the two groups were well balanced.

Clinical outcomes

Primary endpoint: mortality at 30 days

After adjusting only for age and sex, mortality at 30 days was lower in patients who were pretreated [5.8% vs. 7.6% of those not pretreated; odds ratio (OR) 0.75, 95% confidence interval (CI) 0.67–0.83; $P = 0.023$]. The main analysis (based on the imputed data and propensity score adjusted) showed no difference in 30-day mortality between the groups (OR 1.08, 95% CI 0.95–1.24; $P = 0.313$).

Patency of infarct-related artery

At the time of primary PCI, the IRA was occluded in 67.7% of patients with no difference between patients pretreated or not pretreated with $P2Y_{12}$ receptor antagonists (67.9% vs. 67.5%; adjusted OR 0.98, 95% CI 0.92–1.05; $P = 0.608$). The secondary analysis based on complete cases was consistent with the primary model (Supplementary material online, *Table S1*). Infarct-related artery occlusion was an independent predictor of 30-day mortality (adjusted OR 1.65, 95% CI 1.48–1.85; $P < 0.001$).

Stent thrombosis

The overall incidence of stent thrombosis at 30 days after primary PCI was 0.6% ($N = 267$); unadjusted and adjusted risk were no different in patients with and without $P2Y_{12}$ receptor antagonist pretreatment (0.6% vs. 0.6%, respectively; unadjusted OR 0.93, 95% CI 0.67–1.29; $P = 0.672$; adjusted OR 0.99, 95% CI 0.69–1.43; $P = 0.932$; *Table 3*). The secondary analysis based on the complete cases was consistent with the primary model (Supplementary material online, *Table S1*).

In-hospital events

Data on bleeding was missing in 1278 (2.9%) patients. Bleeding occurred in 2.7% of patients. The incidence of bleeding was lower in patients with $P2Y_{12}$ receptor antagonist pretreatment (2.6% vs. 3.4%, respectively; unadjusted OR 0.73, 95% CI 0.63–0.85; $P < 0.001$) but did not differ between the groups after adjustment (*Table 3*). The secondary analysis based on complete cases was consistent with the primary model (Supplementary material online, *Table S1*).

Data on in-hospital neurological complications was missing in 1002 (2.2%) patients. Neurological complications occurred in 118 (0.3%) patients; the incidence was similar in patients with and without $P2Y_{12}$ receptor antagonist pretreatment (0.2% vs. 0.5%, respectively; unadjusted OR 0.66, 95% CI 0.38–1.30; $P = 0.129$). After adjustment, the risk of neurological complications remained similar in the two groups (*Table 3*). The secondary analysis based on the complete cases was consistent with the primary model (Supplementary material online, *Table S1*).

Cardiogenic shock was reported in 1397 (3.1%) patients; the incidence was higher in patients without $P2Y_{12}$ receptor antagonist pretreatment (5.3% vs. 2.7%; unadjusted OR 0.50, 95% CI 0.45–0.57; $P < 0.001$). However, after adjustment, the estimated risk did not differ between the two groups (*Table 3*).

Subgroup analysis

We found no evidence for effect modification of type of $P2Y_{12}$ receptor antagonist and pretreatment regarding mortality at 30 days (interaction test, $P = 0.124$), occlusion of IRA (interaction test, $P = 0.699$), definite stent thrombosis (interaction test, $P = 0.155$), cardiogenic shock (interaction test, $P = 0.401$), in-hospital bleeding (interaction test, $P = 0.571$), and in-hospital neurological complications

Table 2 Angiography and PCI

	Pretreated (*N* = 37 840)	Missing	Not pretreated (*N* = 6964)	Missing	Standardized difference	Standardized difference after adjustment
Radial artery access, *n* (%)	21 829 (57.7)	0	2470 (35.5)	0	0.457	0.049
Procedure performed off-hours, *n* (%)	24 731 (65.4)	1000 (2.6)	3981 (57.2)	199 (2.9)	0.194	0.046
Infarct-related artery, *n*/total *n* (%)		647 (1.7)		140 (2.0)		
RCA	14 250 (37.7)		2644 (38.0)		0.008	0.002
LAD	16 518 (43.6)		3053 (43.8)		0.008	0.021
LCx	6012 (15.9)		1049 (15.1)		0.022	0.022
LM	413 (1.1)		78 (1.1)		0.003	0.031
Arteries with stenosis, *n*/total *n* (%)		115 (0.3)		46 (0.7)		
0	303 (0.8)		38 (0.6)		0.030	0.003
1	18 584 (49.1)		3153 (45.3)		0.075	0.008
2 or 3 no LM	17 095 (45.1)		3337 (47.9)		0.059	0.012
LM and 1, 2, or 3	1743 (4.6)		390 (5.6)		0.046	0.010
Complete revascularization, *n*/total *n* (%)	21 519 (56.9)	347 (0.9)	3647 (52.4)	93 (1.3)	0.080	0.013
Type of lesion		250 (0.7)		94 (1.3)		
A	2683 (7.1)		521 (7.5)		0.017	0.019
B1	10 657 (28.2)		1969 (28.7)		0.005	0.015
B2	13 234 (35.0)		2449 (35.2)		0.006	0.002
C	7517 (19.9)		1329 (19.1)		0.017	0.032
B1 bifurcation	876 (2.3)		171 (2.5)		0.017	0.005
B2 Bifurcation	1597 (4.2)		295 (4.2)		0.009	0.003
C bifurcation	1026 (2.7)		136 (2.0)		0.049	0.009
Type of stenosis		8 (0.02)		3 (0.04)		
De novo	36 068 (95.3)		6513 (93.6)		0.077	0.012
In-stent	1538 (4.1)		386 (5.5)		0.034	0.008
Other	226 (0.6)		62 (0.9)		0.069	0.010
PCI with stent, *n*/total *n* (%)		1 (0.00)		1 (0.01)		
Drug-eluting stent	18 252 (48.2)		3353 (48.2)		0.061	0.003
Bare metal stent	17 065 (45.1)		2793 (40.1)		0.164	0.025
No stent	2523 (6.7)		818 (11.8)		0.176	0.036
$P2Y_{12}$ receptor antagonist*		0		524 (7.5)		
Clopidogrel	21 642 (57.2)		4494 (64.5)		0.264	0.028
Ticagrelor	14 008 (37.0)		1784 (25.6)		0.200	0.021
Prasugrel	2190 (5.8)		162 (2.3)		0.165	0.016
Thrombus aspiration, *n* (%)	8565 (22.6)	67 (0.2)	1393 (20.0)	44 (0.6)	0.064	0.031
Direct stenting, *n* (%)	6002 (17.7)	0	852 (14.4)	0	0.124	0.096
Bivalirudin, *n* (%)	18 012 (47.6)	492 (1.3)	1677 (24.1)	442 (6.6)	0.504	0.061
GP2b/3a receptor inhibitor, *n* (%)	12 267 (32.4)	0	3045 (43.7)	0	0.316	0.011
Unfractionated heparin, *n* (%)	22 705 (60.0)	11 (0.03)	4895 (70.1)	6 (0.09)	0.226	0.055

*First P2Y12 antagonist administered for each patient. IRA, infarct-related artery; LAD, left anterior descending artery; LCx, left circumflex artery; LM, left main; PCI, percutaneous coronary intervention; RCA, right coronary artery.

(interaction test, $P = 0.603$). We found no evidence for effect-modification of calendar year and pretreatment regarding mortality at 30 days (interaction test, $P = 0.152$), occlusion of IRA (interaction test, $P = 0.376$), definite stent thrombosis (interaction test, $P = 0.825$), cardiogenic shock (interaction test, $P = 0.382$), in-hospital bleeding (interaction test, $P = 0.285$), and in-hospital neurological complications (interaction test, $P = 0.677$). The time from the onset of symptoms to the first medical contact and from the first medical contact to PCI did not significantly interact with pretreatment for any of the endpoints ($P > 0.05$ for all interaction tests).

Data analysis and post-estimation diagnostics

Data were missing for one or several variables in 7437 patients (5774 pretreated and 1663 not pretreated). However, for only four

Table 3 Primary analysis

Clinical outcomes	Pretreated (*N* = 37 840)	Not pretreated (*N* = 6964)	Adjusted OR	95% CI	*P*-value	Missing, *n* (%)
Primary endpoint						
Death at 30 days, *n* (%)	1960 (5.2)	528 (7.6)	1.08	0.95–1.24	0.313	0
Secondary endpoints						
IRA occlusion, *n* (%)	25 686 (67.9)	4701 (67.5)	0.98	0.92–1.05	0.608	0
Definite stent thrombosis at 30 days, *n* (%)	223 (0.6)	44 (0.6)	0.99	0.69–1.43	0.932	0
Cardiogenic shock, *n* (%)	1031 (2.7)	366 (5.3)	1.03	0.88–1.20	0.717	0
In-hospital bleeding	966 (2.6)	238 (3.4)	1.05	0.89–1.26	0.526	1278 (2.9)
In-hospital neurological complications	84 (0.2)	34 (0.5)	0.72	0.43–1.21	0.210	1002 (2.2)

IRA, infarct-related artery.

variables—smoking status, previous stroke, previous heart failure, and treatment with ticagrelor and prasugrel—information was missing for >5% patients (*Table 2*). Post-estimation analysis for the logistic regression models, including propensity score estimation, by the Hosmer–Lemeshow test showed the adequate goodness of fit for the models ($P > 0.05$). Squared covariate terms had no explanatory power in any of the models (link test $P > 0.05$). Balancing properties of the calculated propensity scores were evaluated by multivariate linear and binary and multinomial logistic regressions. After adjustment with the propensity score as a covariate in the regression model, there was no statistical difference in the baseline characteristics between the groups (*Table 2*, Supplementary material online, *Figure S2*). There was an adequate overlap between the groups in quintiles of propensity score (Supplementary material online, *Figure S3*). The average variance inflation factor was below 5.0 for all models, indicating a lack of multicollinearity between the variables. The MOR for the primary endpoint was 1.29 (95% CI 1.21–1.45) across different hospitals. The MOR for the secondary endpoints were 1.28 (95% CI 1.21–1.39) for IRA occlusion, 1.18 (95% CI 1.05–1.68) for definite stent thrombosis at 30 days, 1.78 (95% CI 1.53–2.18) for cardiogenic shock, 1.85 (95% CI 1.05–1.68) for in-hospital bleeding, and 1.84 (95% CI 1.55–2.36) and 1.00 (95% CI 1.00–1.00) for in-hospital neurologic complications.

Discussion

Among 44 804 patients undergoing primary PCI for STEMI in Sweden between January 2005 and November 2016, pretreatment with $P2Y_{12}$ receptor antagonists was not associated with improved survival or with a higher likelihood of patent IRA. Furthermore, we found no difference between pretreatment and no pretreatment with $P2Y_{12}$ receptor antagonists regarding the risks of stent thrombosis at 30 days, cardiogenic shock, neurological complications, or bleeding complications.

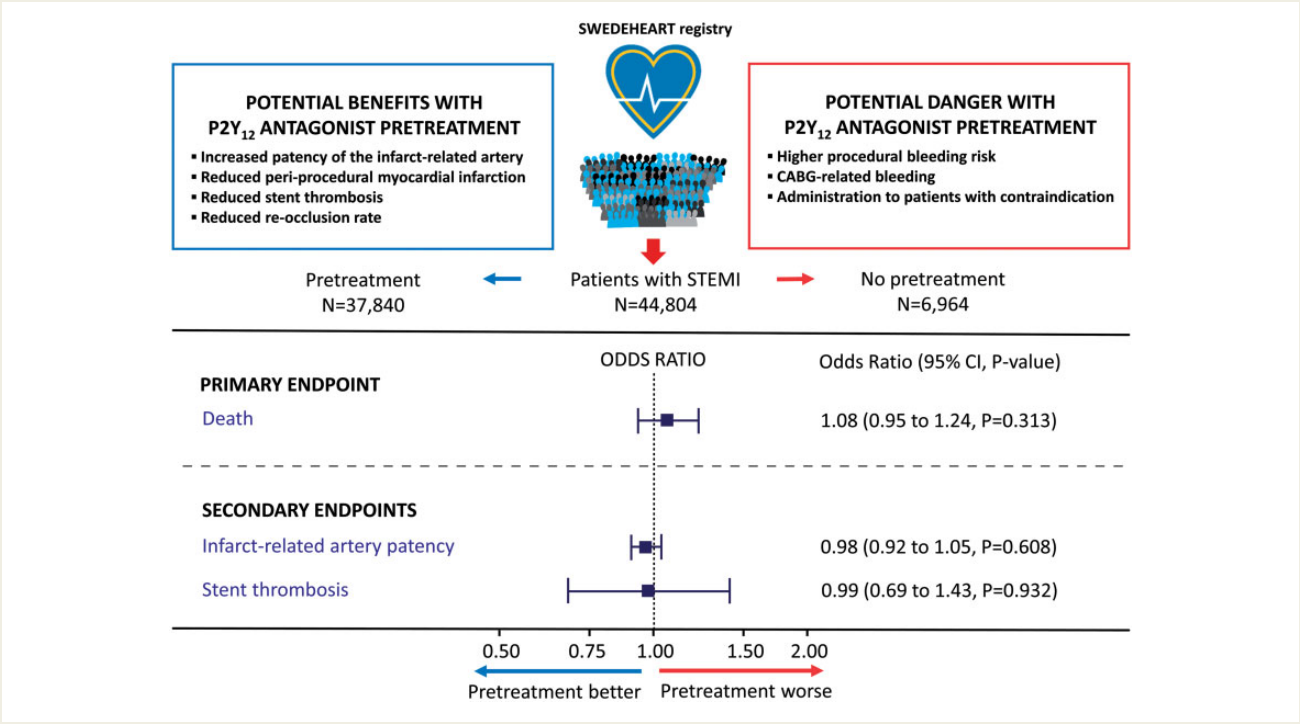
Whereas the ACC/AHA guidelines make no distinction between pre- and in-hospital $P2Y_{12}$ treatment in STEMI,[1] the ESC guidelines during this study period stated a preference for administering $P2Y_{12}$ antagonists before arrival at the treating hospital.[2] This is reflected in the present study by the fact that more than four out of five patients were pretreated with $P2Y_{12}$ receptor antagonists. Of note, the ESC guidelines from 2018 no longer state a preference.

The ATLANTIC study is the only multicentre randomized clinical trial that has directly addressed whether prehospital administration of $P2Y_{12}$ receptor antagonists has benefits over in-hospital administration in patients with STEMI.[12] In the ATLANTIC study, mortality was low and was not significantly different between the groups at 30 days.[12] The rate of probable or definite stent thrombosis was also not statistically significantly different between the groups.[12] Although a lower rate of definite stent thrombosis was observed in the pretreated vs. in-hospital treated group[12] this was contrasted by an excess of deaths within 24 h in the pretreated group.[21] However, only 13 patients in total had definite stent thromboses, and only 16 patients died within 24 h, limiting the reliability of statistical inference concerning these outcomes. In our study, pretreatment with $P2Y_{12}$ receptor antagonists did not affect 30-day mortality or lower the risk of definite stent thrombosis or stroke.

Potential complications of STEMI that are associated with a considerable risk of dying include stent thrombosis, IRA occlusion, and cardiogenic shock. Therefore, the absence of an association between pretreatment with $P2Y_{12}$ receptor antagonists and these events in our study is consistent with the lack of association between pretreatment and 30-day mortality.

An occluded IRA at the time of primary PCI increases the risk of dying after STEMI[22,23] and was an independent predictor of all-cause death in the present study. Recognition of the prognostic importance of IRA patency led to a recommendation that $P2Y_{12}$ antagonists be administered at first medical contact. However, in the ATLANTIC trial, prehospital administration of ticagrelor was not superior to in-hospital administration in regards to either of the two co-primary endpoints: preprocedure resolution of ST-segment elevation and TIMI flow Grade 3 in the IRA. Thus, neither the ATLANTIC trial nor our study—the largest cohort study so far conducted—showed any beneficial effect of pretreatment with $P2Y_{12}$ receptor antagonists on IRA patency.

Although our study provides robust external validation of the results from the much smaller ATLANTIC trial, the reason for lack of effect of pretreatment with $P2Y_{12}$ receptor antagonists remains to be



Take home figure Illustration of potential benefits and danger with pretreatment with P2Y12, and the pretreatment-associated propensity score adjusted risks of the primary and secondary endpoints among the 44 804 patients who underwent acute coronary angiography due to ST-elevation myocardial infarction in Sweden between 1 January 2005 and 1 November 2016.

established. The absorption of oral $P2Y_{12}$ drugs may be delayed in STEMI due to impaired gastrointestinal perfusion secondary to hemodynamic instability, nausea, and vomiting or due to concomitant morphine administration.[24] One of the proposed explanations for the lack of effect of prehospital $P2Y_{12}$ administration in the ATLANTIC study was the relatively short median time from first medical contact to the start of PCI (31 min), which could translate to suboptimal platelet inhibition at the time of PCI, and attenuation of the positive effect of preloading. *Post hoc* analyses from the ATLANTIC trial reported that early administered pre-hospital ticagrelor was associated with lower rates of stent thrombosis[25] and greater pre-procedure ST-resolution among patients with long transfer delays.[26] In contrast, we could not detect a differential effect of pretreatment for patients with longer vs. shorter transfer delays. Although SCAAR does not collect data on the exact time of drug administration $P2Y_{12}$ drugs are given at the time of first medical contact in Sweden, and the median time from the first medical contact to the start of PCI was twice as long in our study as in the ATLANTIC study. Nevertheless, whether early administration of $P2Y_{12}$ antagonists to selected patients with expected long transfer delays can improve pre-PCI coronary flow remains to be fully established. It also remains to be established whether prehospital administration of $P2Y_{12}$ antagonists using approaches to enhance drug absorption, such as crushing oral drugs or whether prehospital administration of the intravenous $P2Y_{12}$ agent cangrelor, can improve outcomes.[24,27–30]

Several limitations of our study should be noted. This is an observational study. As such it provides only the evidence of association, not cause, as we cannot exclude selection bias and residual confounding. Nevertheless, our study provides real-world data from a large cohort of patients. The study is based on the data from a nationwide registry with complete coverage of all STEMI patients who underwent primary PCI in Sweden. During the study period, several large randomized registry clinical trials (TASTE,[14] DETOX,[31] IFR,[32] and VALIDATE[33]) have been conducted in the registry. A recent study from Denmark[34] supports our data. In this smaller, single-centre observational study, upstream treatment with $P2Y_{12}$ was not associated with improved patency of IRA or reductions in adverse cardiovascular events and bleeding. We do not have data on cause-specific mortality. A proportion of patients had missing data. Exclusion of patients from the analysis who had missing data might have biased the results. However, results from the multiple imputation models were congruent with the results of the complete case analysis. We did not have specific data on morphine use or exact TIMI flow in the IRA, as this information is not available in the SCAAR registry. We did not include patients who were mistakenly diagnosed to have STEMI or who were not treated with PCI, as they are not reported in the registry. Previous studies have reported that inadvertent prehospital administration of antiplatelet drugs to patients with contraindications to antithrombotic therapy is common. Therefore, including such patients in the analyses could have influenced the risk estimates towards an increased risk of adverse cardiovascular events with pretreatment. The SCAAR registry does not gather information about the patients who die before hospitalization, and we were unable to provide this data. We did not correct for

multiple testing. We did not adjust for the switch in $P2Y_{12}$ antagonists, which is known to occur among a portion of patients who are treated with PCI.[35] Our analysis is based on the intention-to-treat principle and is grounded on the first $P2Y_{12}$ antagonists that were administered. Some factors related to the patient's characteristics, adjunctive treatment regimens, and logistics in healthcare services changed throughout the study. However, these changes in clinical practice were accounted for by the inclusion of the calendar year as a covariate in the statistical models. Furthermore, the adjusted effects of pretreatment on the primary and secondary outcomes were consistent across different calendar years.

Although information about the exact timing of administration of $P2Y_{12}$ antagonists is not reported in SCAAR, we have information on the time from first medical contact to PCI. As we discuss below, this reported period is likely a close approximation to the time from pretreatment to PCI. The practice in Sweden has been to give $P2Y_{12}$ antagonists at first medical contact (typically by ambulance personnel) in those administrative units that adopted pretreatment with $P2Y_{12}$ antagonists as the default healthcare strategy for patients with STEMI (after diagnosis by 12-lead ECG). In the recent trial VALIDATE-SWEDEHEART (a prospective, randomized trial in an 'all-comers' population in Sweden that compared bilirubin vs. heparin in patients undergoing PCI for STEMI or NSTEMI),[36] we used data from SCAAR (and other registers) but also included trial-specific information—including the time delay from $P2Y_{12}$ antagonist administration to start of primary PCI—that was not normally part of the SWEDEHEART/SCAAR platform. In VALIDATE-SWEDEHEART, we reported that >40% of STEMI patients received $P2Y_{12}$ antagonists >1 h before the start of primary PCI.[36] Because the population with STEMI from VALIDATE-SWEDEHEART is included in the present study, these values corroborate the data reported in our present study in which the median time from first medical contact to PCI was 74 min. Importantly, this time delay in pretreatment is considerably longer than the median of 31 min between the two groups in the ATLANTIC study. We think that these 'real-world data' provide an important complement to the data from the ATLANTIC study.

Conclusions

In conclusion, among patients undergoing primary PCI for STEMI in Sweden between 2005 and 2016, pretreatment with $P2Y_{12}$ receptor antagonists was safe but was not associated with improved IRA patency or better clinical outcome than with in-hospital administration. Our findings independently validate the results of the multicentre randomized ATLANTIC trial.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Conflict of interest: none declared.

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