Pretreatment with P2Y12 Receptor Antagonists Is Not Associated with Improved Clinical Outcomes in ST-Elevation Myocardial Infarction:

A Report from the Swedish Coronary Angiography and Angioplasty Registry

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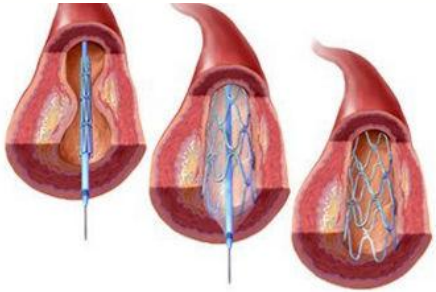
Declaration of interest

- I have nothing to declare

Background

Benefits and danger of pretreatment with antithrombotic agents in ACS



- Reduce periprocedural myocardial infarction
- Reduce early stent thrombosis
- Reduce IRA reocclusion
- Reduce risk when waiting for revascularization

Potential benefits

PRETREATMENT → PCI

- Higher risk for periprocedural bleeding
- Higher risk for CABG-related bleeding
- Prolongation of hospitalization
- Bleeding in patients who were treated inappropriately

Potential danger

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Background

- Data in support of pretreatment with a $P2Y_{12}$ antagonists in patients with STEMI undergoing primary PCI **is indirect and weak**.
- This is reflected in the current guidelines in Europe and USA.

Study	Study drug	Cohort	n	Design	Pre-treatment approach	Key results
CREDO	Clopidogrel	ACS and non-ACS	2116	Randomized	300 mg upstream vs. placebo	No significant benefit for the primary ischaemic endpoint, benefit observed with longer pre-treatment durations (>6 h)
PCI-CURE	Clopidogrel	NSTEMI	2658	Pre-specified analysis of randomized trial	300 mg upstream vs. placebo	Clopidogrel pre-treatment followed by long-term therapy was beneficial in reducing major cardiovascular events
PCI-CLARITY	Clopidogrel	STEMI	1863	Pre-specified analysis of randomized trial	300 mg upstream vs. placebo	Significant reduction of ischaemic events without a significant

No unequivocal evidence of benefit!!!

Bonello et al.	Prasugrel/ Ticagrelor	NSTEMI	213	Randomized	180 mg ticagrelor after admission and before PCI vs. 60 mg prasugrel given at the time of PCI	Less periprocedural myonecrosis in ticagrelor arm, simialar rates of MACE and bleeding in both arms
De Backer et al.	Prasugrel/ Ticagrelor/ Clopidogrel	STEMI	3497	Non-randomized, observational	Pre-treatment with prasugrel vs. ticagrelor vs. clopidogrel	No differences between the three groups for TIMI flow or ischaemic events
ATLANTIC	Ticagrelor	STEMI	1862	Randomized	180 mg pre-hospital vs. 180 mg in hospital	No benefit on TIMI flow or ST segment resolution, no benefit on MACE, no increase in bleeding risk

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Background
what say guidelines?

Europe—STEMI			
2014 ESC/EACTS guidelines for myocardial revaascularization	It is recommended to give P2Y12 inhibitors at the time of first medical contact	I	B
2012 ESC Guidelines for the management of STEMI	Patients undergoing primary PCI should receive a combination of DAPT with aspirin and an ADP receptor blocker, as early as possible before angiography		
USA—STEMI			
2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction:	A loading dose of a P2Y12 receptor inhibitor should be given as early as possible or at time of primary PCI to patients with STEMI. Options include clopidogrel 600 mg, prasugrel 60, ticagrelor 180 mg	I	B

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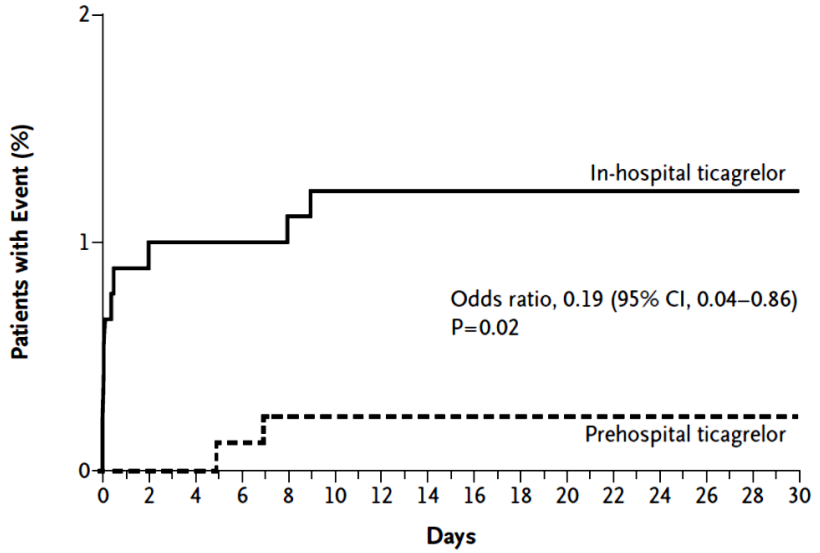
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Prehospital Ticagrelor in ST-Segment Elevation Myocardial Infarction

Table 2. Coprimary Efficacy End Points and Related Secondary End Points in the Modified Intention-to-Treat Population.*

End Point	Prehospital Ticagrelor (N=906)	In-Hospital Ticagrelor (N=952)	Odds Ratio (95% CI)†	P Value†	Difference (95% CI)‡
	no./no. of patients who could be evaluated (%)				
Coprimary end points					
Absence of ST-segment elevation resolution ≥70% before PCI	672/774 (86.8)	722/824 (87.6)	0.93 (0.69 to 1.25)	0.63	–0.008 (–0.041 to 0.025)
Absence of TIMI flow grade 3 in infarct-related artery at initial angiography	681/824 (82.6)	711/856 (83.1)	0.97 (0.75 to 1.25)	0.82	–0.004 (–0.040 to 0.032)



	Patients with Event no. (%)	Total No. of Patients
Prehospital ticagrelor	2 (0.2)	906
In-hospital ticagrelor	11 (1.2)	952

Figure 2. Definite Stent Thrombosis up to 30 Days after Ticagrelor Administration in the Modified Intention-to-Treat Population.

BUT!

Prehospital treatment was associated with a trend for increased mortality at 30 days with an OR of 1.68 (95% CI 0.94–3.01, p =0.08). and

Prehospital treatment was associated with statistically significant higher risk of death within 24 h (OR 3.18, 95% CI 1.02–9.90, p = 0.046).

How common is inappropriate initiation of P2Y12 on in real world in patients with suspected ACS?

~11% in ATLANTIC trial?

Table 1. Demographic Characteristics and Treatment of the Patients at Baseline.*

Characteristic	Prehospital Ticagrelor (N=909)	In-Hospital Ticagrelor (N=953)
Age		
Mean age — yr	60.6±12.4	61.0±12.5
≥75 yr — no. (%)	144 (15.8)	160 (16.8)
Female sex — no. (%)	173 (19.0)	196 (20.6)
Body weight — kg	80.4±15.9	79.7±15.6
BMI ≥30 — no. (%)†	177 (19.5)	178 (18.7)
Diabetes mellitus — no. (%)	115 (12.7)	138 (14.5)
TIMI risk score — no. (%)‡		
0–2	552 (60.7)	573 (60.1)
3–6	337 (37.1)	365 (38.3)
>6	20 (2.2)	15 (1.6)
Killip class I — no. (%)	819 (90.1)	862 (90.5)
First medical contact — no. (%)§		
In ambulance	689 (75.8)	723 (75.9)
In emergency department before ambulance transfer	220 (24.2)	229 (24.0)
Procedures for index event		
Coronary angiography — no. (%)	890 (97.9)	937 (98.3)
Femoral access — no./total no. (%)	280/890 (31.5)	309/937 (33.0)
Radial access — no./total no. (%)	604/890 (67.9)	625/937 (66.7)
Missing data — no./total no. (%)	6/890 (0.7)	3/937 (0.3)
Thromboaspiration — no. (%)	471 (51.8)	470 (49.3)
PCI — no. (%)	800 (88.0)	830 (87.1)
With stent¶	760 (83.6)	776 (81.4)
Drug-eluting stent	467 (51.4)	479 (50.3)
Bare-metal stent	305 (33.6)	312 (32.7)
Without stent	40 (4.4)	54 (5.7)
CABG — no. (%)	10 (1.1)	15 (1.6)
No PCI or CABG — no. (%)	99 (10.9)	108 (11.3)
Study medication — no. (%)		
First loading dose	905 (99.6)	952 (99.9)
Second loading dose	864 (95.0)	908 (95.3)
Maintenance dose	784 (86.2)	809 (84.9)

Aim

- To investigated the effect of $P2Y_{12}$ pretreatment on mortality in a large cohort of consecutive patient treated with primary PCI.
- To provide ”real world evidence”.

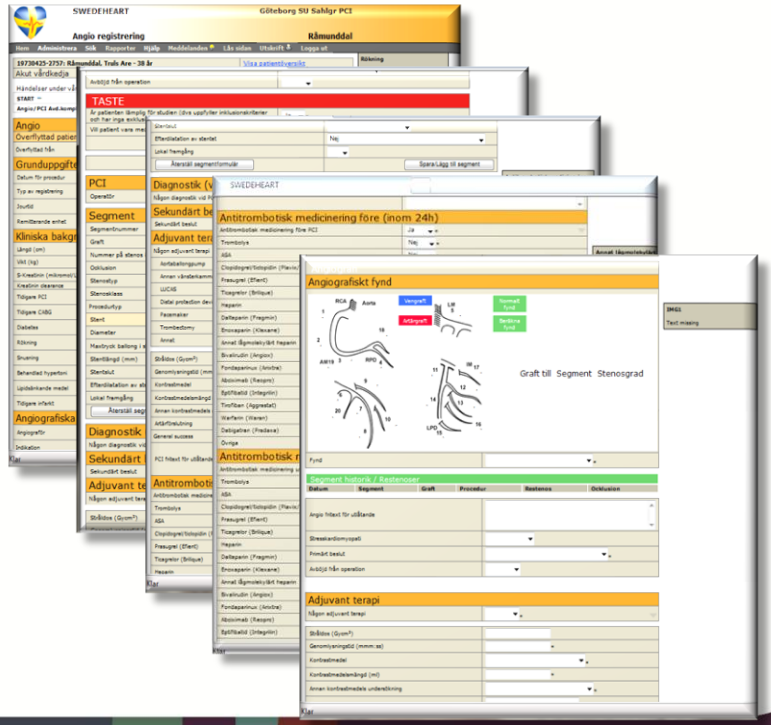
Methods

- Data from the SCAAR registry.
- All consecutive patients who underwent primary PCI between January 1, 2005, and November 1, 2016 in Sweden.
- We excluded patients:
  - who did not receive prehospital acetylsalicylic acid,
  - who underwent thrombolysis before PCI
  - and who had missing data that were not imputed

SCAAR

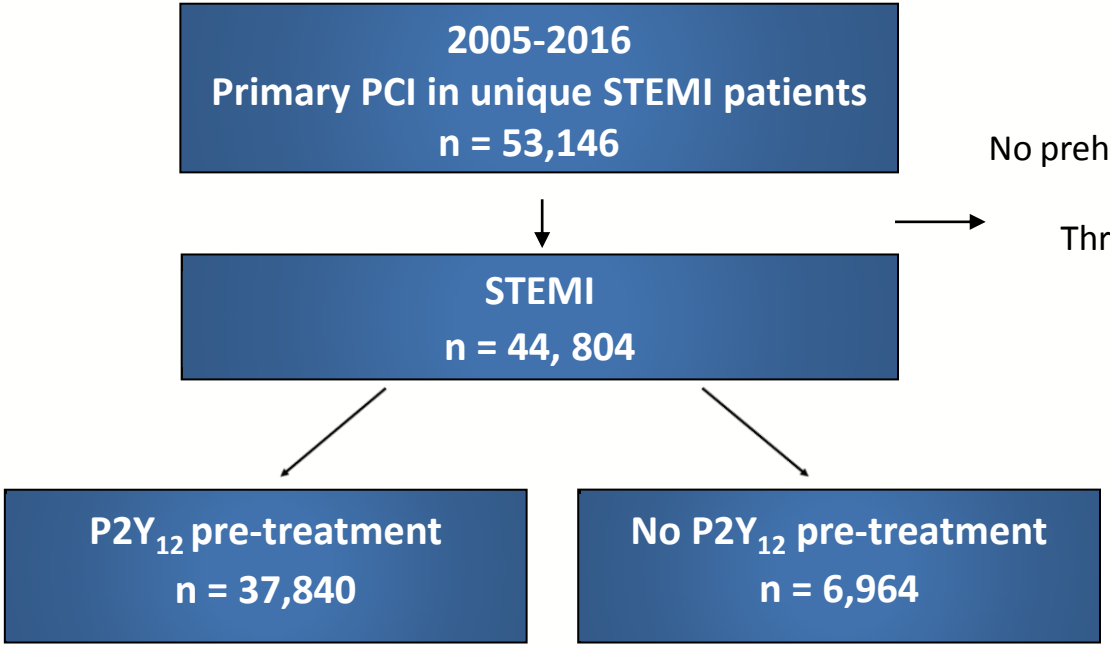
Swedish Coronary Angiography and Angioplasty Registry

- Online national database
- All angiographies and PCI since 1989
- 31 hospitals
- ~ 100% coverage
- Funding by Swedish health authorities only



Methods

- Propensity score adjusted multilevel mixed effects logistic regression with the hospital as a random effect variable
- To adjust for differences in patient's characteristics the following variables were used to estimate propensity score:
  - **age, gender, diabetes, hypertension, hyperlipidemia, year of intervention, hospital, previous PCI, previous CABG, previous myocardial infarction, treated vessel, arterial access site, cardiogenic shock, indicator of missing data, smoking status, previous stroke, history of heart failure, medication at admission, procedure performed off-hours, infarct-related artery, severity of coronary artery disease, complete revascularization, type of lesion, type of stenosis, PCI with stent, $P2Y_{12}$ antagonist at admission, thrombus aspiration, bivalirudin, unfractionated heparin, symptom to first medical contact, first medical contact to start of PCI**


2005-2016
Primary PCI in unique STEMI patients
n = 53,146
No prehospital acetylsalicylic acid
n=6,911
Thrombolysis prior to PCI
n=260
Missing data
n=1,171
STEMI
n = 44, 804
P2Y12 pre-treatment
n = 37,840
No P2Y12 pre-treatment
n = 6,964
Primary endpoint:
death at 30 days
Secondary end points:
IRA patency, stent thrombosis at 30 days
in-hospital bleeding, in-hospital nerologic
complications, cardiogeni shock

Results

patients characteristics

	Pretreated (N= 37,840)	Missing	Not pretreated (N= 6,964)	Missing	P-Value	Adjusted P-Value
Age — year						
Mean age — year	67±12	0	68±12	0	<0.001	0.784
***Age > 75* — no. (%)**	9,866 (26.1)	0	2,261 (32.5)	0	<0.001	0.737
Male sex — no. (%)	27,079 (71.6)	0	4,903 (70.4)	0	0.074	0.990
Diabetes — no. (%)	5,565 (14.7)	0	1,228 (17.6)	0	0.001	0.979
Hypertension — no. (%)	16,509 (44.3)	0	5,362 (43.2)	0	0.026	0.984
Smoking — no./total no. (%)		3238 (8.6)		743 (10.7)		
Never smoker	15,084 (39.9)		2,818 (40.5)		reference	reference
Previous smoker	11,159 (29.5)		2,186 (31.4)		0.210	0.994
Current smoker	11,597 (30.7)		1,960 (28.14)		0.005	0.984
Hyperlipidemia — no. (%)	9,144 (24.2)	0	2,295 (33.0)	0	<0.001	0.982
Previous stroke — no. (%)	1,768 (4.7)	4,323 (11.4)	464 (6.6)	1,165 (16.7)	0.003	1.000
History of heart failure — no. (%)	1,155 (3.1)	4,347 (11.5)	332 (4.8)	1,122 (16.1)	<0.001	0.114
Previous myocardial infarction — no. (%)	5,996 (15.6)	0	1,719 (24.7)	0	<0.001	0.989
Previous PCI — no. (%)	4,636 (12.3)	0	1,240 (17.8)	0	0.002	0.995
Previous CABG — no. (%)	1,225 (3.2)	0	371 (5.3)	0	0.001	0.989
Cardiogenic shock — no. (%)	1,031 (2.7)	0	366 (5.3)	0	<0.001	0.985

Results

patients characteristics

	Pretreated (N= 37,840)	Missing	Not pretreated (N= 6,964)	Missing	P-Value	Adjusted P-Value
Medication at admission — no. (%)						
Beta blockers	11,066 (29.2)	623 (1.6)	2,726 (39.1)	91 (1.3)	<0.001	0.972
ACE inhibitor	6,427 (17.0)	607 (1.6)	1,393 (20.0)	85 (1.2)	0.024	0.989
ARB receptor antagonist	4,665 (12.3)	602 (1.6)	896 (12.9)	88 (1.3)	0.702	1.000
Acetylsalicylic acid	10,789 (28.5)	414 (1.1)	3,175 (45.6)	73 (1.1)	<0.001	0.152
P2Y12 receptor antagonist	1,597 (4.2)	3,971 (10.5)	219 (3.1)	1,036 (14.9)	0.084	0.958
Statin	9,384 (24.8)	423 (1.1)	2,394 (34.4)	75 (1.1)	0.002	0.981
OAC or NOAC	593 (1.6)	56 (0.2)	236 (3.4)	27 (0.4)	<0.001	0.962

Results

patients characteristics

	Pretreated (N= 37,840)	Missing	Not pretreated (N= 6,964)	Missing	P-Value	Adjusted P-Value
Radial artery access — no. (%)	21,829 (57.7)	0	2,470 (35.5)	0	<0.001	0.201
Procedure performed off-hours — no. (%)	24,731 (65.4)	1,000 (2.6)	3,981 (57.2)	199 (2.9)	<0.001	0.745
Infarct related artery — no./total no. (%)		647 (1.7)		140 (2.0)		
RCA	14,250 (37.7)		2,644 (38.0)		reference	reference
LAD	16,518 (43.6)		3,053 (43.8)		0.894	0.874
LCx	6,012 (15.9)		1,049 (15.1)		0.121	0.084
LM	413 (1.1)		78 (1.1)		0.887	0.708
Arteries with stenosis — no./total no. (%)		115 (0.3)		46 (0.7)	0.001	0.900
0	303 (0.8)		38 (0.6)		reference	reference
1	18,584 (49.1)		3,153 (45.3)		0.081	0.943
2 or 3 no LM	17,095 (45.1)		3,337 (47.9)		0.011	0.934
LM & 1,2 or 3	1,743 (4.6)		390 (5.6)		0.001	0.938
Complete revascularization — no./total no. (%)	21,519 (56.9)	347 (0.9)	3,647 (52.4)	93 (1.3)	<0.001	0.907
Type of lesion		250 (0.7)		94 (1.3)		
A	2,683 (7.1)		521 (7.5)		reference	reference
B1	10,657 (28.2)		1,969 (28.7)		0.345	0.920
B2	13,234 (35.0)		2,449 (35.2)		0.338	0.974
C	7,517 (19.9)		1,329 (19.1)		0.097	0.934

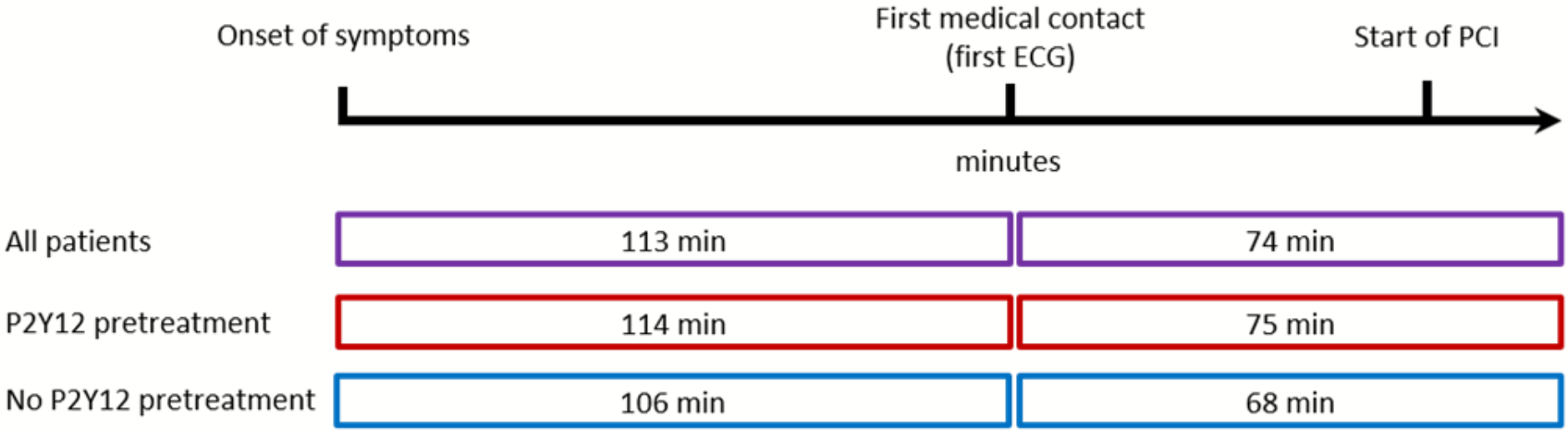
Results

patients characteristics cont.

	B1 bifurcation	876 (2.3)		171 (2.5)		0.596	0.884
	B2 Bifurcation	1,597 (4.2)		295 (4.2)		0.807	0.953
	C bifurcation	1,026 (2.7)		136 (2.0)		<0.001	0.805
Type of stenosis			8 (0.02)		3 (0.04)	0.138	
	De novo	36,068 (95.3)		6,513 (93.5)		reference	reference
	In-stent	1,538 (4.1)		386 (5.5)		0.004	0.992
	Other	226 (0.6)		62 (0.9)		<0.001	0.987
PCI with stent— no./total no. (%)			1 (0.00)		1 (0.01)	<0.001	0.481
	Drug-eluting stent	18,252 (48.2)		3,353 (48.2)		reference	reference
	Bare metal stent	17,065 (45.1)		2,793 (40.1)		<0.001	0.449
	No stent	2,523 (6.7)		818 (11.8)		<0.001	0.415
P2Y12 receptor antagonist*			0		524 (7.5)		
	Clopidogrel	21,642 (57.2)		4,494 (64.5)		reference	reference
	Ticagrelor	14,008 (37.0)		1,784 (25.6)		0.023	0.950
	Prasugrel	2,190 (5.8)		162 (2.3)		0.021	0.836
Thrombus aspiration — no. (%)		8,565 (22.6)	67 (0.2)	1,393 (20.0)	44 (0.6)	<0.001	0.312
Direct stenting — no. (%)		6,002 (17.7)	0	852 (14.4)	0	<0.001	0.990
Bivalirudin — no. (%)		18,012 (47.6)	492 (1.3)	1,677 (24.1)	442 (6.6)	<0.001	0.092
GP2b/3a receptor inhibitor — no. (%)		12,267 (32.4)	0	3,045 (43.7)	0	<0.001	0.839
Unfractionated heparin — no. (%)		22,705 (60.0)	11 (0.03)	4,895 (70.1)	6 (0.09)	<0.001	0.703

Results

reperfusion times



Results

primary outcome

Clinical outcome	P2Y12 Pretreated (N= 37,840)	P2Y12 Not pretreated (N= 6,964)	Adjusted OR	95% CI	P-Value	Missing n (%)
Death at 30-days — no. (%)	1,960 (5.2)	528 (7.6)	1.07	0.94-1.22	0.313	0

Results

secondary outcomes

Clinical outcome	P2Y12 Pretreated (N= 37,840)	P2Y12 Not pretreated (N= 6,964)	Adjusted OR	95% CI	P-Value	Missing n (%)
IRA occlusion — no. (%)	25,686 (67.9)	4,701 (67.5)	1.01	0.95-1.08	0.635	0
Definite stent thrombosis at 30 days — no. (%)	223 (0.6)	44 (0.6)	0.99	0.69-1.41	0.941	0
Cardiogenic shock — no. (%)	1,031 (2.7)	366 (5.3)	0.87	0.74-1.03	0.105	0
In-hospital bleeding	966 (2.6)	238 (3.4)	1.04	0.89-1.23	0.604	1,278 (2.9)
In-hospital neurologic complications	84 (0.2)	34 (0.5)	0.66	0.38-1.30	0.129	1,002 (2.2)

Results

sensitivity analysis – propensity score matching

Clinical outcome	P2Y12 Pretreated (N= 4,967)	P2Y12 not pretreated (N= 4,967)	Adjusted OR	95% CI	P-Value	Missing n (%)
Primary endpoint						
Death at 30-days — no. (%)	312 (6.3)	283 (5.7)	1.11	0.94-1.131	0.220	0
Secondary endpoints						
IRA occlusion — no. (%)	3,390 (68.6)	3,375 (68.0)	1.01	0.93-1.10	0.747	0
Definite stent thrombosis at 30 days — no. (%)	30 (0.6)	31 (0.7)	0.97	0.58-1.6	0.898	0
Cardiogenic shock — no. (%)	190 (3.8)	194 (3.9)	0.91	0.76-1.08	0.290	0
In-hospital bleeding	173 (3.6)	141 (3.0)	1.23	0.98-1.54	0.071	402 (4.1)
In-hospital neurologic complications	16 (0.32)	25 (0.5)	0.64	0.34-1.20	0.158	289 (2.9)

Limitations

- This observational study provides only evidence of association, not cause, as we cannot exclude selection bias and residual confounding.
- No data on cause-specific mortality.
- A proportion of patients had missing data.
- No specific data on TIMI flow in the IRA.
- Patients mistakenly diagnosed with STEMI not treated with PCI were not included.
- No information about the patients who died before hospitalization.

Conclusions

- In this large cohort of STEMI patients undergoing primary PCI, pretreatment with $P2Y_{12}$ antagonists **was not** associated with improved:
  - 30 days survival
  - patency of IRA
  - stent thrombosis at 30 days
- Pretreatment of STEMI patients with $P2Y_{12}$ antagonists **was not** associated with:
  - increased risk for bleeding or neurological complications

Conclusions

- “Routine pre-hospital pre-treatment cannot be recommended for patients with STEMI over the in-lab administration of the drug since the two strategies had similar outcomes. Especially in cases of uncertainty for the diagnosis and whenever surgical aetiologies have not been excluded pre-hospital pre-treatment cannot be recommended.”

  Dirk Sibbing, Adnan Kastrati, Peter B. Berger

- PRIMUM NIL NOCERE!