Interval From Initiation of Prasugrel to Coronary Angiography in Patients With Non–ST-Segment Elevation Myocardial Infarction

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Abstract

Background: In the ACCOAST trial, the prasugrel pretreatment strategy versus placebo was associated with excess bleeding complications and no improved ischemic outcome in non-ST segment elevation myocardial infarction (NSTEMI). Whether patients with the longest pretreatment duration had an ischemic benefit is unknown.

Objectives: This prespecified analysis of the ACCOAST trial aimed to assess the impact of pretreatment duration with prasugrel (time from randomization to angiography) on outcomes.

Methods: Within the 4033 patients randomized in the ACCOAST trial, pretreatment duration was available in 4001 patients (99.2%). The population of the trial was divided into quartiles of pretreatment duration (0.1-2.5 hours, 2.5-3.9 hours, 3.9-13.6 hours, >13.6 hours) with an evaluation of the primary efficacy endpoint of cardiovascular death, MI, stroke, urgent revascularization or GPIIb/IIIa bailout use. Secondary efficacy outcomes including cardiovascular death, MI, or stroke; all-cause death; stent thrombosis and safety outcomes (all CABG or non-CABG TIMI major bleeding) were also evaluated at 7 days.

Results: The primary efficacy outcome of cardiovascular death, MI, stroke, urgent revascularization or GPIIb/IIIa bailout use did not differ between the quartiles of pretreatment duration in the trial population (p= 0.17 for interaction). None of the secondary efficacy outcomes were found to be dependent of pretreatment duration. The safety outcome of all CABG or non-CABG TIMI major bleedings did not differ between the quartiles of pretreatment duration (p= 0.37 for interaction).

Conclusions: In NSTEMI patients, the excess risk of bleeding and the absence of ischemic benefit were consistent across the quartiles of increasing duration of prasugrel pretreatment.

Clinical Trial Registration #: NCT01015287.

Condensed Abstract: In the ACCOAST trial, the prasugrel pretreatment strategy versus placebo was not associated with improved ischemic outcome in non-ST segment elevation myocardial infarction. We evaluated whether this was related to a too short duration of pretreatment and assessed the impact of pretreatment duration with prasugrel on ischemic and bleeding outcomes. We found that neither the primary efficacy outcome of cardiovascular death, MI, stroke, urgent revascularization or GPIIb/IIIa bailout use nor the safety outcome of all CABG or non-CABG TIMI major bleeding differed between the quartiles of pretreatment duration (p= 0.17 and p= 0.37 for interaction respectively).

Abbreviations (in order of appearance)
CABG : coronary artery bypass grafting
PCI: percutaneous coronary intervention
NSTEMI : non-ST elevation myocardial infarction
NSTE-ACS : non-ST elevation acute coronary syndrome
STEMI : ST-segment elevation myocardial infarction
LD : first loading dose
BMI : body mass index

MI : myocardial infarction
HR : Hazard-ratio
SD: standard deviation
CI : confidence intervals

Introduction

Pre-treatment by P2Y$_{12}$ inhibitors can delay coronary artery bypass grafting (CABG) or increase unnecessarily the risk of bleeding in patients managed medically after undergoing an invasive strategy. Indeed, observational and randomized studies as well as meta-analyses have challenged the benefit of routine pre-treatment with clopidogrel in elective percutaneous coronary intervention (PCI) or non-ST elevation acute coronary syndrome (NSTE-ACS) showing no significant effect on mortality and a trend towards a decrease of ischemic endpoints but at the cost of an increase of major bleeding (1-8). The ACCOAST trial evaluated a strategy of pretreatment with prasugrel (versus placebo) in patients with non-ST elevation myocardial infarction (NSTEMI) (9) which did not provide an ischemic benefit but increased bleeding whatever the revascularization strategy chosen (10-12). In the protocol, the randomization was to take place as soon as possible, and the coronary angiography was to be performed within the first 48 hours of randomization, to reflect contemporary practice (13-16). The average delay between the first loading dose (LD) and the coronary angiography was 4.3 hours. One critiscim of the trial results was that this short delay may not have allowed pretreatment to be sufficiently active or protective although fast pharmacodynamics of the loading dose was reported both in ACCOAST and in previously published studies (17-21). The present analysis focuses on the duration of pretreatment within the 48 hours time frame to access the catheterization laboratory and see whether resuts differ in particular with longer duration of prasugrel pre-treatment.

Methods

Study patients

The ACCOAST trial randomized 4033 patients at a 1:1 ratio of active pretreatment with prasugrel or placebo in addition to aspirin and standard of care. The inclusion and exclusion criteria for the ACCOAST trial have been described previously (9,10). Briefly, patients were

eligible for inclusion if they had a diagnosis of a NSTEMI. Randomization was to take place as soon as possible after diagnosis and before the patients received a LD of any $P2Y_{12}$ antagonist. Patients had to be scheduled to undergo coronary angiography within 2 to 48 h from randomization. The ACCOAST study protocol pre-specified the present analysis of the impact of pretreatment duration on outcomes (9,10). The ACCOAST population was therefore divided in quartiles according to the time from the first LD of treatment to the beginning of the coronary angiography. A similar analysis was performed in the PCI population, a subgroup of the ACCOAST trial limited to the patients who underwent PCI and presented in the appendix section.

Study procedures

Patients were randomly assigned to receive either prasugrel or a matching placebo once the patient was admitted with the diagnosis of NSTEMI to the study site. In the pre-treatment arm (patients that received a 30 mg LD of prasugrel), an additional 30 mg of prasugrel was given at the time of PCI once angiography confirmed the indication for PCI. In the no pretreatment arm the approved 60 mg prasugrel LD was given after angiography only in patients undergoing PCI. If angiography revealed anatomy more appropriate for CABG or medical management, patients did not receive the second LD (30 mg) in the pretreatment arm or the LD (60mg) in the no pretreatment arm. Thienopyridine use for patients medically managed or who needed CABG surgery was left to investigators' discretion. The first open-label maintenance dose of prasugrel was administered 18 to 24 h after PCI. Patients received a 10 mg daily maintenance dose of prasugrel in combination with aspirin through the follow-up visit at 30 days. In patients who were 75 years of age or older and/or had body weight <60 kg, a 5 mg daily maintenance dose of prasugrel was administered.

Study outcomes

The primary composite endpoint was time to first occurrence of cardiovascular death, myocardial infarction (MI), stroke, urgent revascularization, or GP IIb/IIIa inhibitor bailout through 7 days from randomization. Secondary efficacy measures included cardiovascular death, MI, or stroke; all-cause death; stent thrombosis. Safety endpoints of TIMI major and minor bleeding were evaluated in terms of CABG surgery–related, or non-CABG surgery–related, and all bleeding.

Statistical analysis

The ACCOAST population was divided in quartiles according to the time from the first LD of treatment to the start of the coronary angiography (since missing data were very rare i.e. less than 1%, no missing data replacement procedure was used). Patients characteristics were compared among the different quartiles by ANOVA for quantitative variables and Chi-square or Fisher's exact test for the qualitative parameters.

Hypothesis that the drug effect on Primary Efficacy or Safety Endpoints may be different according to the time from the first LD of treatment to the start of the coronary angiography has been tested by the interaction between factor treatment and time categorized by quartiles in a Cox model of survival analysis. In addition, difference between treatments for each quartile has been tested by log-rank test. Complementary analyses on efficacy and safety primary endpoints have been made using multivariate Cox model that included risk factors for the studied events (age >75, gender, body mass index (BMI) >30, diabetes, hypertension, previous PCI, previous MI, baseline troponin and region of enrolment). All analyses have been made using SAS version 9.4 (from SAS Institute North Carolina USA)

Results

Study patients

Within the 4033 patients randomized in the ACCOAST trial, pretreatment duration was available in 4001 patients (99.2%) of the global population. The quartiles of duration of pretreatment were 0.1-2.5 hours, 2.5-3.9 hours, 3.9-13.6 hours, >13.6 hours for the global population. The baseline characteristics of the four groups of patients are presented in **Table 1.** The main discrepancy between quartiles of pretreatment duration was the region of enrolment, with shorter pretreatment duration in Eastern Europe centers including Israel, and longer pretreatment duration for Western Europe and Canada. Differences of management strategy and antithrombotic therapy were also found and are displayed in **Table 2**. In comparison with the latest quartile of pretreatment (average time from the first dose to angiography of 23 hours), patients within the earliest quartile (average time from the first dose to angiography of 2.1 hours) had less medical management, less CABG and more PCI at 7 days. They were also mostly treated with unfractionated heparin (77.4%) rather than with low molecular weight heparin (19%) as compared with the latest quartile with a predominant use of low molecular weight heparin (48.1%). For the PCI subgroup of 2770 patients, pretreatment duration was available in 2769 patients (99.96%) and the quartiles of duration of pretreatment were quite similar to the global population (0.1-2.45 hours, 2.45-3.68 hours, 3.68-12.25 hours; $\geq$ 12.25 hours). Procedural characteristics are described in **Table 3**. The main differences between the four groups were the higher rate of femoral approach (63.3%) and bare metal stent implantation (38.1%) found in the first quartile of pretreatment duration. Many of these variables were interrelated, reflecting in particular differences of practice across countries. Finally, we compared the patient's characteristics, medical management and procedural characteristics stratified by randomized arm within the four quartiles which were well balanced between the randomized arms.

Clinical outcomes

The primary efficacy endpoint through 7 days from randomization is presented for each quartile of pretreatment in the **Central Illustration** for the global population (n = 4,001 patients) and for the PCI population (n=2769 patients) in Online Figure 1. There was no interaction between prasugrel pretreatment and pretreatment duration for the primary efficacy endpoint in the global population (p=0.17). This finding was consistent across the secondary efficacy endpoints: MI (p=0.37 for interaction), stroke (p=0.46 for interaction) urgent revascularization (p=0.29 for interaction), GP IIb/IIIa in bail out (p=0.28 for interaction). Cardiovascular mortality could not be interpreted due to a very low rate of events. Full results are displayed in the appendix section table S1. The results concerning the PCI population showed a borderline significant interaction for the primary endpoint (Online Table 2), which must be interpreted with caution considering that pretreatment duration and PCI are two post-randomization variables. Few patients (n=40) were censored as event-free prior to 7 days and the reasons why is described in Online Table 3.

The effect of prasugrel pretreatment on the safety outcomes of TIMI major bleeding through 7 days is reported by quartiles of pretreatment duration in **Figure 1**. There was a consitent increase in the rate of bleeding in all the quartiles for both the global and the PCI population. No interaction between groups was observed with consistent harm associated with pretreatment whatever the duration of pretreatment. The results were similar after multivariate analysis and no significant interaction was found between prasugrel pretreatment and pretreatment duration on the primary efficacy outcome at day 7 (p=0.13).

Discussion

The appropriate timing of $P2Y_{12}$ receptor inhibition in patients with non-ST segment elevation acute coronary syndrome (NSTE-ACS) remains debated, mostlly because of the lack of adequately sized randomized trial addressing this issue. Pretreatment in NSTE-ACS is defined by the administration of a $P2Y_{12}$ antagonist when an invasive strategy has been decided. It implies that the $P2Y_{12}$ antagonist is given before coronary visualization, expecting an ischemic benefit while waiting for catheterization or during and after PCI when such revascularization is decided. Obviously, benefit is not expected from a treatment started before the angiography in patients needing rapid CABG surgery or if the final diagnosis is not a NSTE-ACS (e.g., pericarditis, aortic dissection, pulmonary embolism, hypertension, gastric ulcer, prancreatitis.). The PCI-CURE substudy (22) set the scene for pre-treament although it was performed with clopidogrel and did not fulfill the above definition since an invasive strategy was not required in CURE (23) and catheterization occurred only in 43% of patients. PCI-CURE was then a retrospective analysis of the highly selected 20% of patients who underwent PCI after a 10-day waiting period on average. There is no other study of pretreatment in NSTE-ACS, and both CREDO (8) and PRAGUE-8 (6) were negative studies of pretreatment using clopidogrel and that included only elective PCI. In contrast, ACCOAST prospectively studied patients with an invasive strategy who could be pretreated before knowing their coronary status which was obtained within 48 hours. The benefit and the downsides of the pretreatment strategy can be fairly evaluated with this design, especially with the use of a more potent $P2Y_{12}$ antagonist such as prasugrel. The surprising negative results of ACCOAST were heavily debated. One recurrent critisicm of the results was that the pretreatment duration, altought peformed with prasugrel, was insufficient to allow $P2Y_{12}$ inhibition to be effective since the waiting period was considered by many to be too short (on average 4 hours). However, the 48-hour time window likely reflects

current practice and accepting these critics we should expect an ischemic benefit in patients wih the longest pretreatment duration (1-2 days).

The present results do not support a duration–related benefit of prasugrel pretreatment. The results can be summarized as follows (**Central Illustration**): 1/ The hypothesis that longer pretreatment duration would have modified the results of the ACCOAST trial is not suggested by our analysis not even for the PCI population 2/ The safety issue with pretreatment was consistent across all four quartiles and confirms the drug was effective in all four groups. Of interest, patients within the shortest quartile of pretreatment duration which were given prasugrel 30mg within an average time of 2 hours before the angiography still had a significant increase in major bleeding events as compared with patients who received the loading dose after the angiography, indicating that there was sufficient platelet inhibition to increase bleeding. 3/ Patients of the first quartile with very rapid intervention may have been at higher risk and did not benefit from pre-treatment. They actually had worse ischemic outcomes with pretreatment, with a borderline significant interaction in the PCI subgroup. However, this finding may be due to differences in baseline characteristics and the management used, or to the utilization of post-randomization variables (PCI and pretreatment duration) and we therefore cannot rule out the play of chance despite the multivariate analysis we performed.

In the 2015 ESC Guidelines for the management of NSTE-ACS (24), experts stated that as the optimal timing of ticagrelor or clopidogrel administration in NSTE-ACS patients scheduled for an invasive strategy had not been investigated, no recommendation for or against pretreatment with these agents could be formulated. In the recent 2018 ESC/EACTS guidelines on myocardial revascularization (25) , although no additional trial on pretreatment was performed in the interval, expert recommended to pretreat NSTE-ACS patients undergoing

invasive management with ticagrelor or clopidogrel (if ticagrelor is not an option) as soon as the

diagnosis is established (Class IIa) on the basis that pretreatment was authorized in the PLATO

trial (26) , which is true given the fact that all patients were pretreated. However, it has to be

specified that it was not a trial of pretreatment versus non-pretreatment, and as they cannot

provide any data for this statement the level of evidence C was given. In fact, because of the

design of the PLATO trial a dedicated study, albeit only pharmacodynamic, was conducted to

support the use of ticagrelor after defining coronary anatomy (27). The available randomized

data regrouped in a meta-analysis only support the utilization of pretreatment in STEMI patients,

where pretreatment appears to improve coronary reperfusion before PCI, and reduce major

cardiac adverse events, MI and bail-out GPI use without increase of major bleeding (28),

whereas no benefit was found in the clinical setting of NSTE-ACS with a significant excess of

major bleeding whether an invasive strategy was performed or not (4-5). We believe that such

recommendations are more based on international experts' opinions and local practice than

evidence-based medicine. The current North American guidelines are more cautious and do not

recommend $P2Y_{12}$ inhibitor pre-treatment in NTE-ACS; they simply refer to how the trials were

actually performed (1).

This study has limitations. First this is pre-specified analysis has the inherent limitations

of multiple testing. Second dividing the population in quartiles translated into a loss of power to

show significant differences. However, we believe that the nature of the source data generated

from a double-blind randomized trial and the large sample population would have been sufficient

to show a significant difference or at least a clear trend if the tested hypothesis was true. Finally,

we cannot exclude the play of chance for the borderline significant interaction found in PCI

patients considering this type of subgroup analysis. In conclusion, in NSTEMI patients managed

invasively, a longer duration of prasugrel pre-treament over a period of 48 hours before catheterization has no impact on ischemic outcomes. Thus, the present work refutes the hypothesis that insufficient time was given to prasugrel to provide an ischemic benefit and it confirms the main results of the ACCOAST trial including the bleeding excess that occurred whatever the duration of pretreatment.

Clinical Perspectives

Competency in Patient Care and Procedural Skills: In patients with non-ST segment elevation acute coronary syndrome (NSTE-ACS), addition of the P2Y12 inhibitor, prasugrel, to aspirin and anticoagulation increases major bleeding without ameliorating ischemic risk irrespective of the interval between administration and coronary angiography. One explanation for this lack of benefit may be the heterogeneous mechanisms responsible for the acute syndrome and multiplicity of treatment strategies employed in this population.

Translational Outlook: Additional studies are needed to compare the safety and efficacy of fixed pretreatment regimens with administration of a rapidly acting P2Y12 inhibitor after determination of coronary pathoanatomy in patients with NSTE-ACS.

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Figure Legends:

Central Illustration: Pretreatment Duration in Non-ST Elevation Myocardial Infarction Patients. Primary Efficacy Endpoint (a composite of cardiovascular death, myocardial infarction, stroke, urgent revascularization or GPIIb/IIIa bailout) through 7 days in the global population of the ACCOAST trial. [a]HR is a 95% Cox hazards model with treatment. [b]Within subgroup p-value is from a 2-sided log-rank test. [c]Interaction p-value is from a Cox propotional hazards model with treatment, subgroup, and treatment-by-subgroup interaction as fixed effects.

Figure 1. The safety outcome of all CABG or non-CABG TIMI major bleeding through 7 days in the global population (upper figure) and (lower figure) with non-CABG TIMI major bleeding only.

Table 1. Baseline characteristics of the global population, n=4001 patients.

Pre Treatment Time	Quartile 1 (0.1 - 2.5 hr) (n=1008)	Quartile 2 (2.5 - 3.9 hr) (n=997)	Quartile 3 (3.9 - 13.6 hr) (n= 996)	Quartile 4 (> 13.6 hr) (n=1000)	p value

Demographics (Mean ± SD; n (%))					
Age	63.4 ± 11	63.8 ± 11.3	63.7 ± 11.2	63.7 ± 11	0.91
Elderly patients ≥ 75 yr	165 (16.4%)	177 (17.8%)	176 (17.7%)	188 (18.8%)	0.56
Male	729 (72.3%)	721 (72.3%)	714 (71.7%)	737 (73.7%)	0.78
Weight in Kg	82.4 ± 15.9	81.8 ± 14.9	80.9 ± 14.5	81.3 ± 15.5	0.17
Low body weight < 60 kg	48 (4.8%)	47 (4.7%)	53 (5.3%)	57 (5.7%)	0.71
Body Mass Index	28.1 ± 4.7	28.1 ± 4.5	27.9 ± 4.4	28.0 ± 4.6	0.69
Region of enrolment					
Eastern Europe/Israel	530 (52.6%)	486 (48.7%)	456 (45.8%)	210 (21.0%)	< 0.001*
Western Europe/Canada	478 (47.4%)	511 (51.3%)	540 (54.2%)	790 (79.0%)	
Risk Factors					
Diabetes mellitus	202 (20.0%)	206 (20.7%)	193 (19.4%)	216 (21.6%)	0.65
Hypercholesterolemia	438 (43.5%)	444 (44.5%)	449 (45.1%)	470 (47.0%)	0.44
Hypertension	628 (62.3%)	634 (63.6%)	615 (61.7%)	607 (60.7%)	0.61
Current smoker	344 (34.2%)	325 (32.6%)	356 (35.8%)	307 (30.9%)	0.11
Family history of CAD	323 (32.0%)	358 (35.9%)	308 (30.9%)	343 (34.3%)	0.08
Past Cardiovascular disease					
Previous PCI	148 (14.7%)	161 (16.1%)	156 (15.7%)	188 (18.8%)	0.078
Previous CABG	57 (5.7%)	49 (4.9%)	56 (5.6%)	49 (4.9%)	0.78
Previous MI	130 (12.9%)	143 (14.3%)	142 (14.3%)	156 (15.6%)	0.39
NSTEMI severity					
Ischemic changes on ECG	570 (57.2%)	537 (54.4%)	516 (52.1%)	538 (54.3%)	0.16
Baseline Troponin level, ≥ 10 x ULN	508 (50.7%)	510 (51.4%)	464 (46.8%)	459 (46.2%)	0.041*
Grace Score ≥ 140	232 (23.4%)	225 (22.9%)	207 (21.3%)	229 (23.8%)	0.59
Killip Class 1	972 (96.4%)	964 (96.7%)	962 (96.6%)	954 (95.4%)	0.40

CABG means Coronary Artery Bypass Graft; CAD, Coronary Artery Disease; MI=Myocardial Infarction; PCI, Percutaneous Coronary Intervention.

Table 2. Time delays, strategy and antithrombotic therapy within the four groups of the global population n=4001 patients. Values are given in Mean ± SD or n (%).

| Pre Treatment Time	Quartile 1 (0.1 - 2.5 hr) (n=1008)	Quartile 2 (2.5 - 3.9 hr) (n=997)	Quartile 3 (3.9 - 13.6 hr) (n= 996)	Quartile 4 (> 13.6 hr) (n=1000)	p value
Time delays (hrs)					
Symptoms Onset to First Dose	17.8 ± 16.4	20.2 ± 29.5	18.9 ± 17.6	21.5 ± 70.9	0.19
Time from First Dose to Angiography	2.1 ± 0.4	3.10 ± 0.4	6.9 ± 2.9	23.3 ± 43.5	< 0.001*
Treatment Sub-cohort at 7 Days					
PCI Only	760 (75.4%)	695 (69.7%)	677 (68.0%)	637 (63.7%)	< 0.001*
CABG Only	49 (4.9%)	54 (5.4%)	58 (5.8%)	77 (7.7%)	
PCI + CABG	2 (0.2%)	4 (0.4%)	3 (0.3%)	2 (0.2%)	
Medical management	197 (19.5%)	244 (24.5%)	258 (25.9%)	284 (28.4%)	
Antithrombotic therapy					
Aspirin	989 (98.1%)	972 (97.5%)	984 (98.8%)	985 (98.5%)	0.14
Unfractionated heparin	509 (77.4%)	460 (72.6%)	446 (65.8%)	279 (45.8%)	< 0.001*
Low-molecular-weight heparin	125 (19.0%)	138 (21.8%)	208 (30.7%)	293 (48.1%)	< 0.001*
Bivalirudin	5 (0.8%)	9 (1.4%)	3 (0.4%)	2 (0.3%)	0.13
Multiple antithrombin therapy	231 (22.9%)	248 (24.9%)	215 (21.6%)	299 (29.9%)	< 0.001*
No antithrombin therapy	119 (11.8%)	115 (11.5%)	103 (10.3%)	92 (9.2%)	0.21
GP IIb/IIIa inhibitor	130 (12.9%)	123 (12.3%)	97 (9.7%)	107 (10.7%)	0.98

CAD means Coronary Artery Disease; GP, Glycoprotein; MI=Myocardial Infarction; PCI, Percutaneous Coronary Intervention.

Table 3. Procedural characteristics in the four groups of the PCI population. Values are given in Mean ± SD or n (%). Pretreatment quartile are slightly different from the global population as they only concern the PCI population (n= 2769) in this table.

Pre Treatment Time	Quartile 1 (0.1 - 2.45 hr) (n=691)	Quartile 2 (2.45 - 3.68 hr) (n=693)	Quartile 3 (3.68 - 12.25 hr) (n= 693)	Quartile 4 (≥ 12.25 hr) (n=692)	p value
PCI Procedure					
Duration of PCI procedure (hrs)	0.52 ± 0.37	0.49 ± 0.35	0.49 ± 0.38	0.50 ± 0.39	0.30
Arterial Sheath Location					
Femoral	637 (63.3%)	591 (59.3%)	523 (52.7%)	525 (52.7%)	< 0.001*
Radial or Brachial	370 (36.7%)	406 (40.7%)	470 (47.3%)	472 (47.3%)	
Stents					
Number of vessels treated	1.3 ± 0.6	1.3 ± 0.7	1.3 ± 0.7	1.5 ± 0.8	< 0.001*
2 or more vessels treated	159 (20.8%)	161 (23.0%)	165 (24.3%)	217 (34.0%)	< 0.001*
Total number of stents	1.2 ± 0.6	1.2 ± 0.7	1.2 ± 0.6	1.4 ± 0.9	< 0.001*
No stent implanted	45 (5.9%)	45 (6.4%)	34 (5.0%)	34 (5.3%)	< 0.001*
Bare metal stent only	290 (38.1%)	264 (37.8%)	261 (38.4%)	172 (26.9%)	
Drug eluting stent only	409 (53.7%)	364 (52.1%)	362 (53.2%)	399 (62.4%)	
Both BMS & DES	18 (2.4%)	26 (3.7%)	23 (3.4%)	34 (5.3%)	

BMS means Bare Metal Stent; DES, Drug Eluting Stent; PCI, Percutaneous Coronary Intervention.

Primary Safety Endpoint
(All TIMI Major Bleeding)
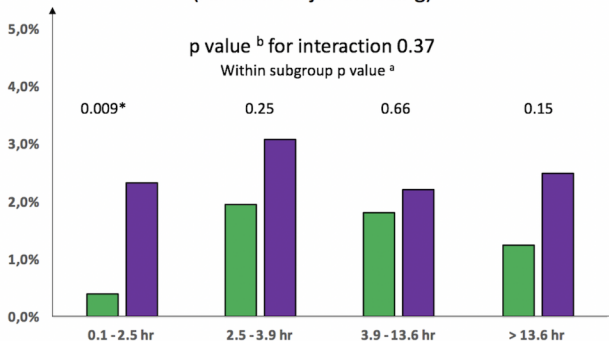
(Non CABG TIMI Major Bleeding)
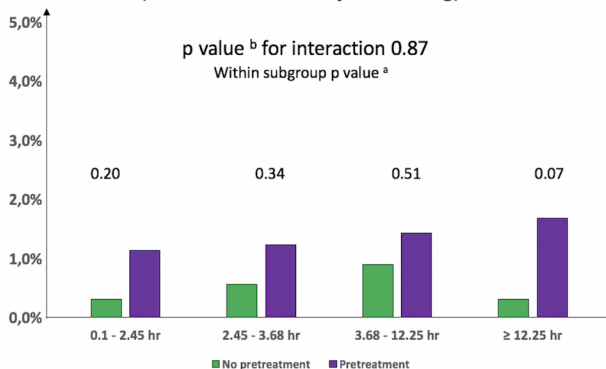
a Within subgroup p-value is from a two-sided log rank test
b Interaction p-value is from a Cox proportional hazards model with treatment, subgroup, and treatment-by-subgroup interaction as fixed effects