ORIGINAL ARTICLE

Pretreatment with Prasugrel in Non–ST-Segment Elevation Acute Coronary Syndromes

Gilles Montalescot, M.D., Ph.D., Leonardo Bolognese, M.D., Dariusz Dudek, M.D., Ph.D., Patrick Goldstein, M.D., Christian Hamm, M.D., Jean-Francois Tanguay, M.D., Jurrien M. ten Berg, M.D., Ph.D., Debra L. Miller, R.N., Timothy M. Costigan, Ph.D., Jochen Goedicke, M.D., Johanne Silvain, M.D., Ph.D., Paolo Angioli, M.D., Jacek Legutko, M.D., Ph.D., Margit Niethammer, M.D., Zuzana Motovska, M.D., Ph.D., Joseph A. Jakubowski, Ph.D., Guillaume Cayla, M.D., Ph.D., Luigi Oltrona Visconti, M.D., Eric Vicaut, M.D., Ph.D., and Petr Widimsky, M.D., D.Sc., for the ACCOAST Investigators*

ABSTRACT

BACKGROUND

Although $P2Y_{12}$ antagonists are effective in patients with non–ST-segment elevation (NSTE) acute coronary syndromes, the effect of the timing of administration — before or after coronary angiography — is not known. We evaluated the effect of administering the $P2Y_{12}$ antagonist prasugrel at the time of diagnosis versus administering it after the coronary angiography if percutaneous coronary intervention (PCI) was indicated.

METHODS

We enrolled 4033 patients with NSTE acute coronary syndromes and a positive troponin level who were scheduled to undergo coronary angiography within 2 to 48 hours after randomization. Patients were randomly assigned to receive prasugrel (a 30-mg loading dose) before the angiography (pretreatment group) or placebo (control group). When PCI was indicated, an additional 30 mg of prasugrel was given in the pretreatment group at the time of PCI and 60 mg of prasugrel was given in the control group.

RESULTS

The rate of the primary efficacy end point, a composite of death from cardiovascular causes, myocardial infarction, stroke, urgent revascularization, or glycoprotein IIb/IIIa inhibitor rescue therapy (glycoprotein IIb/IIIa bailout) through day 7, did not differ significantly between the two groups (hazard ratio with pretreatment, 1.02; 95% confidence interval [CI], 0.84 to 1.25; P=0.81). The rate of the key safety end point of all Thrombolysis in Myocardial Infarction (TIMI) major bleeding episodes, whether related or not related to coronary-artery bypass grafting (CABG), through day 7 was increased with pretreatment (hazard ratio, 1.90; 95% CI, 1.19 to 3.02; P=0.006). The rates of TIMI major bleeding and life-threatening bleeding not related to CABG were increased by a factor of 3 and 6, respectively. Pretreatment did not reduce the rate of the primary outcome among patients undergoing PCI (69% of the patients) but increased the rate of TIMI major bleeding at 7 days. All the results were confirmed at 30 days and in prespecified subgroups.

CONCLUSIONS

Among patients with NSTE acute coronary syndromes who were scheduled to undergo catheterization, pretreatment with prasugrel did not reduce the rate of major ischemic events up to 30 days but increased the rate of major bleeding complications. (Funded by Daiichi Sankyo and Eli Lilly; ACCOAST ClinicalTrials.gov number, NCT01015287.)

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Montalescot at the ACTION Study Group, Institut de Cardiologie, Centre Hospitalier Universitaire Pitié–Salpêtrière, 47 Blvd. de l'Hôpital, 75013 Paris, France, or at gilles.montalescot@psl.aphp.fr.

*Investigators in the Comparison of Prasugrel at the Time of Percutaneous Coronary Intervention (PCI) or as Pretreatment at the Time of Diagnosis in Patients with Non-ST Elevation Myocardial Infarction (ACCOAST) are listed in the Supplementary Appendix, available at NEJM.org.

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Clopidogrel does not become biologically and clinically effective until several hours after administration.[1,2] Although a loading dose of clopidogrel is required in patients undergoing percutaneous coronary intervention (PCI), it is uncertain whether pretreatment with clopidogrel (with treatment given early enough before catheterization to be effective) is efficient when the coronary-artery anatomy in a patient with a non–ST-segment elevation (NSTE) acute coronary syndrome is not known. Pretreatment can delay a coronary-artery bypass grafting (CABG) procedure or increase unnecessarily the risk of bleeding in patients who do not need to undergo PCI. Two randomized studies, one involving patients with NSTE acute coronary syndromes and one involving patients undergoing elective PCI, suggested that pretreatment with clopidogrel could reduce the rate of ischemic events at the cost of an increase in the rate of major bleeding.[3,4] On the basis of those studies, current guidelines from the European Society of Cardiology and the American College of Cardiology Foundation–American Heart Association give a class I recommendation for pretreatment in patients with NSTE acute coronary syndromes who are scheduled to undergo an invasive procedure.[5,6] More recent observational studies and a meta-analysis have challenged the benefit of routine pretreatment with clopidogrel in patients with NSTE acute coronary syndromes.[7-9]

Prasugrel and ticagrelor are more potent and have a more rapid onset of action than clopidogrel.[10-13] These drugs were shown to be more effective than clopidogrel in patients with acute coronary syndromes but were associated with an increase in bleeding complications.[14,15] Pretreatment was given before catheterization in one of the studies,[15] whereas in the other study, $P2Y_{12}$-receptor antagonists were started after the coronary angiography was performed and the indication of PCI was confirmed.[14] We designed the Comparison of Prasugrel at the Time of Percutaneous Coronary Intervention (PCI) or as Pretreatment at the Time of Diagnosis in Patients with Non-ST Elevation Myocardial Infarction (ACCOAST) trial to compare systematic pretreatment with prasugrel at the time of diagnosis of an NSTE acute coronary syndrome with prasugrel treatment given selectively after the angiography to patients undergoing PCI. Pretreatment was restricted to a maximum of 48 hours before coronary angiography, reflecting contemporary practice.[16-19]

METHODS

STUDY OVERSIGHT

The ACCOAST trial was a phase 3, randomized, double-blind, event-driven study. We conducted the study at 171 centers in 19 countries (see the Supplementary Appendix, available with the full text of this article at NEJM.org). The trial was sponsored by Daiichi Sankyo and Eli Lilly, and was led by the ACTION Study Group at the Institute of Cardiology of Pitié-Salpêtrière Hospital. The trial was approved by the national regulatory authorities in all participating countries and by the local review board at each participating site. All patients provided written informed consent.

Data were collected in a blinded fashion and were analyzed after the database was locked according to the protocol and a predefined statistical analysis plan; the data were analyzed by a clinical research organization contracted by Eli Lilly. End points were adjudicated by an independent end-point adjudication committee (see the Supplementary Appendix). The study chair (first author) had a copy of the database and prepared all drafts of the manuscript, and all the authors provided comments. All the authors made the decision to submit the manuscript for publication and assume responsibility for the accuracy and completeness of the data. The analyses that were performed conform with the study protocol, which is available at NEJM.org.

The executive steering committee (see the Supplementary Appendix) designed and oversaw the conduct of the trial. The trial was monitored by an independent data and safety monitoring committee. This committee met seven times during the course of the trial at scheduled meetings. After the last scheduled meeting, the committee made a recommendation to stop enrollment, since pretreatment was associated with an increased risk of major and life-threatening bleeding with no reduction in cardiovascular events (but no between-group imbalance in mortality). Enrollment was suspended immediately, on November 16, 2012.

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PATIENTS

Eligible patients were identified for inclusion after they received a diagnosis of an NSTE acute coronary syndrome and were found to have elevated troponin levels. Randomization was to take place as soon as possible after the diagnosis was made and before the patients had received a loading dose of clopidogrel or any dose of prasugrel or ticagrelor. Patients were to be scheduled to undergo coronary angiography and PCI, if indicated, within 2 to 48 hours after randomization.[20]

STUDY PROCEDURES

After the patients were admitted to a study site with a diagnosis of NSTE myocardial infarction, they were randomly assigned, in a 1:1 ratio, to receive pretreatment with prasugrel (pretreatment group) or matching placebo (control group). Patients in the pretreatment group received a 30-mg loading dose of prasugrel before coronary angiography was performed; an additional 30 mg of prasugrel was given at the time of PCI if angiography confirmed the indication for PCI. Patients in the control group received placebo before coronary angiography was performed, and the approved 60-mg loading dose of prasugrel was given after angiography only in patients undergoing PCI. If the results of the angiography suggested that CABG or medical treatment only would be a more appropriate treatment than PCI given the patient's coronary anatomy, the patient did not receive the second loading dose (30 mg in the pretreatment group or 60 mg in the control group). The use of a thienopyridine drug in patients who were receiving medical treatment only or who were undergoing CABG was left to the discretion of the investigator. All patients were treated according to the standard of care at the time, which included the use of aspirin.

A pharmacodynamic substudy involving 23 patients was performed to evaluate the effect of prasugrel on the inhibition of platelet aggregation relative to the time of administration. The primary analysis measure was $P2Y_{12}$ Reaction Units (PRU), as assessed with the use of the VerifyNow P2Y12 test (Accumetrics).

STUDY END POINTS

The primary composite end point was the first occurrence of death from cardiovascular causes, myocardial infarction, stroke, urgent revascularization, or the need for rescue therapy with glycoprotein IIb/IIIa inhibitors (glycoprotein IIb/IIIa bailout) through day 7 after randomization. Secondary efficacy end points included a composite of death from cardiovascular causes, myocardial infarction, or stroke; death from any cause; and stent thrombosis. Safety end points of major and minor bleeding according to Thrombolysis in Myocardial Infarction (TIMI) criteria were evaluated for all bleeding episodes and according to whether the bleeding was related or not related to CABG. Bleeding complications were also adjudicated according to the Safety and Efficacy of Enoxaparin in Percutaneous Coronary Intervention (PCI) Patients, an International Randomized Evaluation (STEEPLE) criteria and the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) criteria.[20]

STATISTICAL ANALYSIS

The efficacy comparisons were performed on the basis of the time to the first event, according to the intention-to-treat principle. Safety analyses were performed on data from all patients who received at least one dose of a study drug. The primary efficacy analysis was performed on the basis of the time from randomization to the first occurrence of a primary composite end-point event, with the use of a two-sided log-rank test. Time-to-event analyses for efficacy and safety end points were performed through day 7 and through day 30 after randomization. Rates are expressed as Kaplan–Meier estimates; hazard-ratio estimates and 95% confidence intervals were obtained from a Cox proportional-hazards model, and two-sided P values were calculated with the use of a log-rank test. For efficacy and safety comparisons, P values of less than 0.05 were considered to indicate statistical significance. Homogeneity of treatment effects across subgroups for safety and efficacy end points were assessed with the use of a Cox proportional-hazards model with terms for treatment, subgroup, and the interaction of treatment with subgroup. For interaction analyses, P values of less than 0.10 were considered to indicate statistical significance.

We calculated that 400 patients would have to

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Table 1. Baseline Characteristics of the Total Study Population.*

Characteristic	Pretreatment (N=2037)	No Pretreatment (N=1996)
Mean age — yr	63.8	63.6
Female sex — no. (%)	552 (27.1)	558 (28.0)
Mean weight — kg†	81.7	81.5
BMI ≥30 — no. (%)‡	591 (29.0)	562 (28.2)
Cardiovascular risk factors — no./total no. (%)		
Diabetes mellitus	413/2037 (20.3)	407/1996 (20.4)
Hypercholesterolemia	914/2037 (44.9)	900/1996 (45.1)
Hypertension	1279/2037 (62.8)	1225/1996 (61.4)
Current smoker	693/2031 (34.1)	647/1992 (32.5)
GRACE score — no./total no. (%)§		
<140	1503/1984 (75.8)	1526/1947 (78.4)
≥140	481/1984 (24.2)	421/1947 (21.6)
Median CRUSADE score¶	34.0	34.0
Creatinine clearance ≤30 ml/min — no./total no. (%)	65/2016 (3.2)	46/1972 (2.3)
Access — no./total no. (%)		
Femoral	1140/2013 (56.6)	1136/1981 (57.3)
Radial	869/2013 (43.2)	842/1981 (42.5)
Median intervals — hr‖		
Symptom onset to first loading dose	14.6	15.2
First loading dose to start of coronary angiography	4.4	4.2
Concomitant medications through day 7 — no./total no. (%)		
Aspirin	2000/2037 (98.2)	1957/1996 (98.0)
Antithrombin monotherapy		
Unfractionated heparin	865/1323 (65.4)	835/1275 (65.5)
Low-molecular-weight heparin	385/1323 (29.1)	390/1275 (30.6)
Bivalirudin	11/1323 (0.8)	8/1275 (0.6)
Fondaparinux	62/1323 (4.7)	42/1275 (3.3)
Proton-pump inhibitor	1116/2037 (54.8)	1114/1996 (55.8)
Beta-blocker	1719/2037 (84.4)	1683/1996 (84.3)
Statin	1823/2037 (89.5)	1787/1996 (89.5)
Angiotensin-receptor blocker	279/2037 (13.7)	239/1996 (12.0)
Angiotensin-converting–enzyme inhibitor	1405/2037 (69.0)	1433/1996 (71.8)
Maintenance dose of clopidogrel**	45/2037 (2.2)	43/1996 (2.2)

* There were no significant differences between the groups in any of the characteristics listed.
† Data were available for 2036 patients in the pretreatment group and 1993 in the no-pretreatment (control) group.
‡ The body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters.
§ The Global Registry of Acute Coronary Events (GRACE) risk scores range from 1 to 372, with higher scores indicating greater risk.
¶ The analysis of the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the ACC/AHA Guidelines) bleeding score (which ranges from 1 to 100, with higher scores indicating a greater risk of bleeding) was a post hoc analysis. Data were available for 1899 patients in the pretreatment group and 1941 in the no-pretreatment group.
‖ Data for the time from symptom onset to first loading dose were available for 2036 patients in the pretreatment group and 1996 in the no-pretreatment group; data for the time from first loading dose to start of coronary angiography were available for 2017 patients in the pretreatment group and 1985 in the no-pretreatment group.
** According to the protocol, patients could be receiving a 75-mg maintenance dose of clopidogrel at the time of randomization.

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Table 2. Major Efficacy End Points through Day 7 and Day 30.*

End Point	Pretreatment (N=2037)	No Pretreatment (N=1996)	Hazard Ratio (95% CI)	P Value
	no. of patients (%)			
7 Days				
Death from cardiovascular causes, myocardial infarction, stroke, urgent revascularization, or glycoprotein IIb/IIIa bailout: primary end point	203 (10.0)	195 (9.8)	1.02 (0.84–1.25)	0.81
Death				
From any cause	8 (0.4)	10 (0.5)	0.78 (0.31–1.98)	0.61
From cardiovascular cause	7 (0.3)	10 (0.5)	0.69 (0.26–1.80)	0.44
Myocardial infarction	119 (5.8)	109 (5.5)	1.07 (0.83–1.39)	0.60
Stroke	8 (0.4)	10 (0.5)	0.78 (0.31–1.98)	0.60
Urgent revascularization	22 (1.1)	26 (1.3)	0.83 (0.47–1.46)	0.52
Glycoprotein IIb/IIIa bailout	76 (3.7)	78 (3.9)	0.96 (0.70–1.31)	0.79
30 Days				
Death from cardiovascular causes, myocardial infarction, stroke, urgent revascularization, or glycoprotein IIb/IIIa bailout	219 (10.8)	216 (10.8)	0.997 (0.83–1.20)	0.98
Death from cardiovascular causes, myocardial infarction, or stroke	144 (7.1)	144 (7.2)	0.98 (0.78–1.23)	0.86
Death from cardiovascular causes or myocardial infarction	135 (6.6)	130 (6.5)	1.02 (0.80–1.30)	0.88
Death from cardiovascular causes, myocardial infarction, or urgent revascularization	157 (7.7)	146 (7.3)	1.06 (0.85–1.33)	0.62
Death from cardiovascular causes	14 (0.7)	22 (1.1)	0.62 (0.32–1.22)	0.16
Myocardial infarction	126 (6.2)	116 (5.8)	1.07 (0.83–1.37)	0.62

* Event rates are raw percentages. Hazard ratios for pretreatment and two-sided 95% confidence intervals were calculated with the use of a Cox proportional-hazards model with treatment as a fixed effect. Two-sided P values were calculated with the use of the log-rank test.

have a primary efficacy end-point event for the study to have 80% power to detect a 24% reduction in relative risk with pretreatment as compared with no pretreatment (control), and we estimated that approximately 4100 patients would need to be enrolled to reach that number of patients with events. Of 4033 patients who underwent randomization, 398 patients had a primary efficacy end-point event.

RESULTS

STUDY PATIENTS

From December 6, 2009, through November 16, 2012, we randomly assigned 4033 patients: 2037 to pretreatment with prasugrel and 1996 to no pretreatment with prasugrel. The baseline characteristics were balanced between the two groups (Table 1, and Table S1 in the Supplementary Appendix), including in the subgroups defined according to whether the acute coronary syndrome was ultimately managed by means of PCI, CABG, or medical treatment alone. Three patients were lost to follow-up through day 30 (Fig. S1 in the Supplementary Appendix). PCI was performed in 68.7% of the patients (2770 of 4033), at a median time of 4.3 hours after the initial loading dose. Through day 7, the strategy chosen was CABG in 6.2% of the patients (249 of 4033) and medical management in 25.1% (1014 of 4033).

CLINICAL END POINTS

The incidence of the primary end point through day 7 after randomization did not differ significantly between the group receiving pretreatment with prasugrel and the control group (10.0% and 9.8%, respectively; P=0.81) (Table 2 and Fig. 1). There was no significant between-group difference in any of the components of the primary end point, in total mortality, in the rate of stent thrombosis, or in prespecified composite secondary end points either at day 7 or at day 30 (Table 2, and Fig. S2 in the Supplementary Appendix). Pretreatment with prasugrel was not associated with

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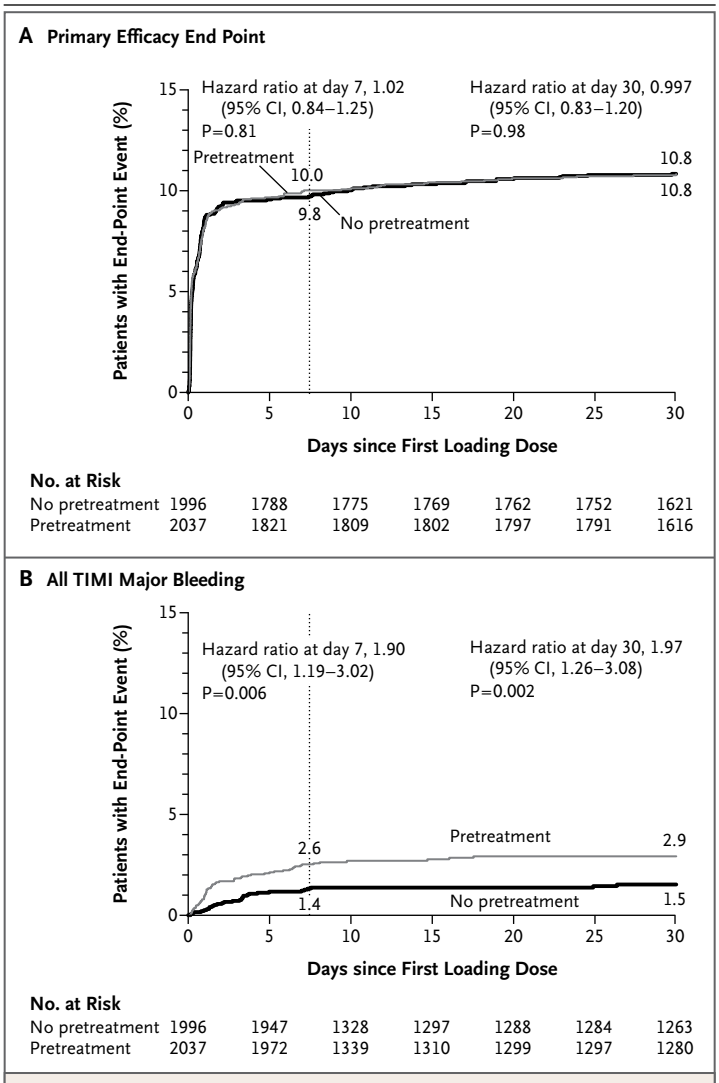

Figure 1. Primary Efficacy and Key Safety End Points in the Total Population.
Panel A shows the incidence of the primary efficacy end point of death from cardiovascular causes, myocardial infarction, stroke, urgent revascularization, or glycoprotein IIb/IIIa inhibitor rescue therapy (glycoprotein IIb/IIIa bailout) at day 7 (dotted line) and to day 30 after the first loading dose, in the total study population, according to pretreatment or no pretreatment with prasugrel. Panel B shows the incidence of the key safety end point of major bleeding (whether related or not related to coronary-artery bypass grafting) according to Thrombolysis in Myocardial Infarction criteria at day 7 (dotted line) and to day 30, in the total study population, according to pretreatment or no pretreatment with prasugrel. CI denotes confidence interval.

a significant decrease in the rate of ischemic events (the primary end point) during the waiting period for coronary angiography: 0.8% (16 of 2014 patients) among those who received pretreatment and 0.9% (18 of 1981 patients) among those who did not receive pretreatment (P=0.93). In most cases, glycoprotein IIb/IIIa bailout therapy was administered to treat an angiographically identified thrombus before PCI or thrombotic complications during PCI. The rates of definite or probable stent thrombosis were low in the two groups through day 30: 0.1% (2 of 1367 patients) in the pretreatment group and 0.4% (5 of 1353 patients) in the control group (P=0.25)

In the cohort of patients who underwent PCI, there was no significant difference between the two groups with respect to the primary end point (Fig. 2) — a finding similar to that in the overall population. There was no benefit of pretreatment in prespecified subgroups of the global population (Fig. S3 in the Supplementary Appendix) or in the PCI cohort.

SAFETY

The incidences of TIMI major bleeding (Table 3 and Fig. 1) and of TIMI major or minor bleeding (Fig. S4 in the Supplementary Appendix) through day 7 after the first loading dose were significantly higher in the pretreatment group than in the control group. There was an increase by a factor of 3 in all major bleeding not related to CABG and an increase by a factor of 6 in life-threatening bleeding not related to CABG (Table 3). TIMI minor bleeding events were also increased with pretreatment as compared with no pretreatment (hazard ratio, 2.50; 95% confidence interval, 1.42 to 4.37; P<0.001). There was, however, no excess of fatal bleeding or intracranial hemorrhage with pretreatment.

Bleeding events were predominantly associated with PCI or CABG and occurred early in patients who underwent PCI (Fig. 2). The results were consistent when more PCI-specific STEEPLE definitions were used. A total of 14 patients in the PCI cohort had TIMI life-threatening bleeding events (12 patients in the pretreatment group and 2 in the control group). The most frequent bleeding complications involved bleeding at the access site (5 patients), pericardial bleeding (4), and retroperitoneal bleeding (3). Although bleeding complications occurred less frequently in some subgroups, such as young patients, patients with high body weight, and patients in whom PCI was performed through radial access, pretreatment, as compared with no pretreatment, was consistently associated with an excess of bleeding in these subgroups (Fig. S5 and S6 in the Supplementary Appendix). There was no significant difference between the groups in the rates of nonhemorrhagic serious adverse events. The rates of epistaxis and hematoma were higher in the pretreat-

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ment group than in the control group (Table S2 in the Supplementary Appendix).

In the pharmacodynamic substudy, we found that at the time of arterial access a median of 4.8 hours after the first loading dose, there was greater platelet inhibition in the pretreatment group than in the control group (Fig. S7 in the Supplementary Appendix), which may have contributed to the increased rate of bleeding complications in the pretreatment group. By 2 hours after the second loading dose, antiplatelet activity was similar in the two groups, with low levels of platelet reactivity observed up to 24 hours.

DISCUSSION

Although pretreatment with aspirin and a $P2Y_{12}$ antagonist has been a class I recommendation in the guidelines and common practice for the treatment of patients with NSTE acute coronary syndromes, we found that pretreatment with prasugrel did not reduce the rate of ischemic events in the overall population or in the cohort that underwent PCI, the cohort that underwent CABG, or the cohort that received medical treatment only. There were significantly more major and life-threatening bleeding complications not related to CABG in the pretreatment group than in the control group — mostly among patients who underwent PCI. However, the rates of stent thrombosis and of death were low in both groups.

The benefit of adding clopidogrel to aspirin in patients with NSTE acute coronary syndromes was shown in the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) study, in which a conservative medical management strategy was evaluated.[4] In the CURE study, a small subgroup of 21% of the patients underwent PCI an average of 10 days after randomization. The significant benefit with respect to ischemic end points with clopidogrel pretreatment in this PCI subgroup set the precedent for clopidogrel treatment before catheterization.[21] Subsequent randomized studies did not confirm the benefit of clopidogrel pretreatment with respect to ischemic events among patients in stable condition who were undergoing elective PCI,[3,22-24] and a recent meta-analysis did not show a survival benefit of clopidogrel pretreatment among more than 37,000 patients undergoing PCI.[9] In our study, prasugrel, when administered as pretreatment, was biologically effective at the time of catheterization or PCI, as shown by the results of the pharmacodynamic substudy, but pretreatment with prasugrel did not reduce the incidence of thrombotic complications in either the overall population or among patients undergoing PCI. The lack of protection against ischemic events was shown

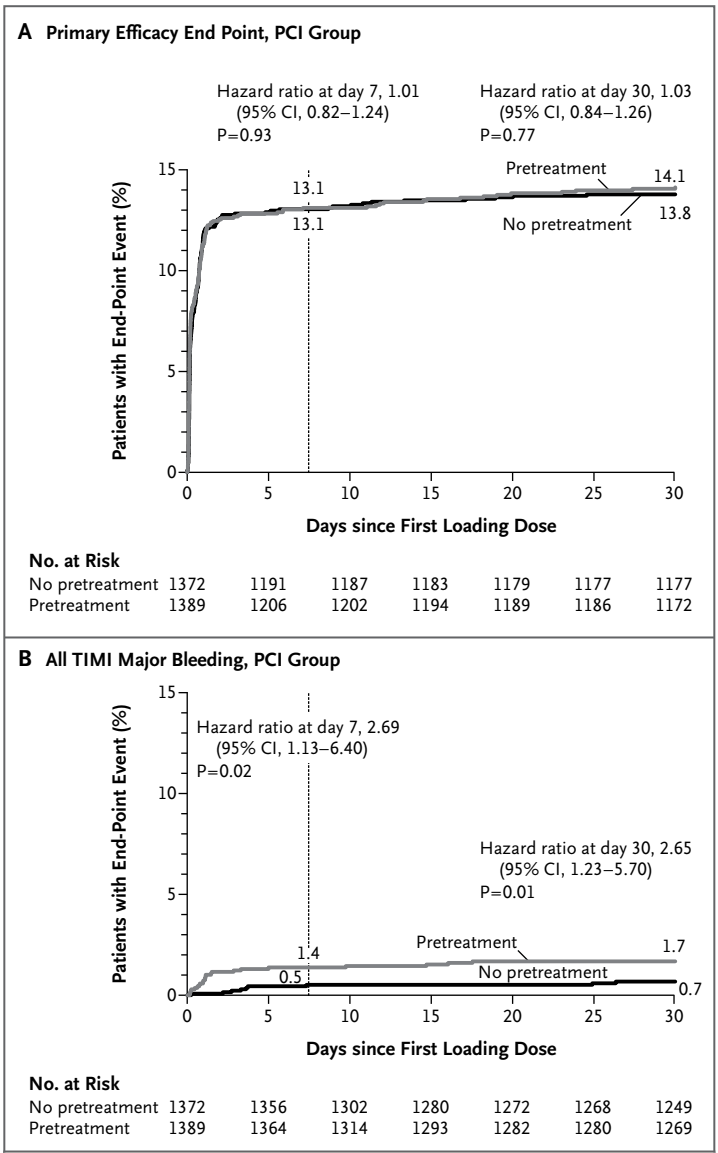

Figure 2. Primary Efficacy and Key Safety End Points in the PCI Cohort. Panel A shows the incidence of the primary efficacy end point of death from cardiovascular causes, myocardial infarction, stroke, urgent revascularization, or glycoprotein IIb/IIIa bailout at day 7 (dotted line) and to day 30 after the first loading dose, in the cohort of patients who underwent PCI, according to pretreatment or no pretreatment with prasugrel. Panel B shows the incidence of the key safety end point of major bleeding (whether related or not related to coronary-artery bypass grafting) according to Thrombolysis in Myocardial Infarction criteria at day 7 (dotted line) and to day 30, in the cohort of patients who underwent PCI, according to pretreatment or no pretreatment with prasugrel.

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consistently across all prespecified subgroups, including the patients who were at the highest risk, such as the elderly, patients with diabetes, and those with a Global Registry of Acute Coronary Events (GRACE) risk score of 140 or higher (with scores ranging from 1 to 372 and higher scores indicating greater risk). This suggests that stronger antiplatelet therapy does not prevent the occurrence of a myocardial infarction before catheterization or after PCI. Our data are consistent with the results of previous studies that evaluated the use of glycoprotein IIb/IIIa inhibitors in a similar clinical situation.[25,26] The absence of $P2Y_{12}$ inhibition in the control group

Table 3. Bleeding End Points through Day 7 and Day 30.*

End Point	Pretreatment (N=2037)	No Pretreatment (N=1996)	Hazard Ratio (95% CI)	P Value
	no. of patients (%)			
7 Days				
All CABG-related or non–CABG-related TIMI major bleeding: key safety end point	52 (2.6)	27 (1.4)	1.90 (1.19–3.02)	0.006
Non–CABG-related TIMI major bleeding	27 (1.3)	9 (0.5)	2.95 (1.39–6.28)	0.003
Fatal bleeding	1 (<0.1)	0	NE	NE
Life-threatening bleeding	17 (0.8)	3 (0.2)	5.56 (1.63–19.0)	0.002
Type of bleeding†				
Intracranial hemorrhage	0	0	NE	NE
Vascular access-site bleeding	9 (0.4)	2 (0.1)	NE	NE
Gastrointestinal	4 (0.2)	3 (0.2)	NE	NE
Hematuria	1 (<0.1)	0	NE	NE
Pericardial	4 (0.2)	2 (0.1)	NE	NE
Other‡	9 (0.4)	2 (0.1)	NE	NE
Non–CABG-related TIMI major or minor bleeding	61 (3.0)	20 (1.0)	3.02 (1.82–5.01)	<0.001
CABG-related TIMI major bleeding§	25 (20.7)	16 (13.7)	1.59 (0.85–2.98)	0.14
GUSTO moderate or severe, CABG-related or non–CABG-related	70 (3.4)	35 (1.8)	1.98 (1.32–2.97)	<0.001
STEEPLE major bleeding, non–CABG-related	46 (2.3)	18 (0.9)	2.52 (1.46–4.35)	<0.001
STEEPLE minor bleeding, non–CABG-related	58 (2.8)	38 (1.9)	1.50 (1.00–2.26)	0.05
Transfusions¶				
Total, for any reason	41 (2.0)	22 (1.1)	1.84 (1.09–3.08)	0.02
For non–CABG-related TIMI major bleeding	20 (1.0)	7 (0.4)	2.81 (1.19–6.63)	0.01
30 Days				
All CABG-related or non–CABG-related TIMI major bleeding	58 (2.8)	29 (1.5)	1.97 (1.26–3.08)	0.002
Non–CABG-related TIMI major bleeding	32 (1.6)	11 (0.6)	2.86 (1.44–5.68)	0.002
Fatal bleeding	3 (0.1)	0	NE	NE
Life threatening bleeding	22 (1.1)	4 (0.2)	5.40 (1.86–15.68)	<0.001
Type of bleeding†				
Intracranial hemorrhage	1 (<0.1)	0	NE	NE
Vascular access-site bleeding	9 (0.4)	2 (0.1)	NE	NE
Gastrointestinal	6 (0.3)	5 (0.3)	NE	NE
Hematuria	1 (<0.1)	0	NE	NE
Pericardial	5 (0.2)	2 (0.1)	NE	NE
Other‡	10 (0.5)	2 (0.1)	NE	NE

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Table 3. (Continued.)

End Point	Pretreatment (N=2037)	No Pretreatment (N=1996)	Hazard Ratio (95% CI)	P Value
	no. of patients (%)			
Non–CABG-related TIMI major or minor bleeding	73 (3.6)	23 (1.2)	3.15 (1.97–5.03)	<0.001
CABG-related TIMI major bleeding§	27 (17.2)	16 (10.2)	1.77 (0.95–3.28)	0.07
GUSTO moderate or severe, CABG-related or non–CABG-related	80 (3.9)	37 (1.9)	2.14 (1.45–3.16)	<0.001
STEEPLE major bleeding, non–CABG-related	56 (2.7)	22 (1.1)	2.52 (1.54–4.12)	<0.001
STEEPLE minor bleeding, non–CABG-related	70 (3.4)	49 (2.5)	1.41 (0.98–2.03)	0.07
Transfusions¶				
Total, for any reason	46 (2.3)	24 (1.2)	1.89 (1.15–3.09)	0.01
For non–CABG-related TIMI major bleeding	24 (1.2)	9 (0.5)	2.62 (1.22–5.63)	0.01

* All event rates are raw percentages. Hazard ratios for pretreatment and two-sided 95% confidence intervals were calculated with the use of a Cox proportional-hazards model with treatment as a fixed effect. Two-sided P values were calculated with the use of the log-rank test. CABG denotes coronary-artery bypass grafting, GUSTO Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries, NE not able to be evaluated, STEEPLE Safety and Efficacy of Enoxaparin in Percutaneous Coronary Intervention (PCI) Patients, an International Randomized Evaluation, and TIMI Thrombolysis in Myocardial Infarction.

† Participants who had more than one bleeding event may be included in more than one TIMI bleeding category. Within each category of type of TIMI bleeding, the first TIMI bleeding episode in that category is reported here.

‡ Other sources of bleeding included the retroperitoneum, the respiratory tract, the surgical incision site, and unknown sites.

§ The percentages for CABG-related TIMI major bleeding were calculated on the basis of the total number of patients who underwent CABG: at 7 days, 121 patients in the pretreatment group and 117 in the group that received no pretreatment, and at 30 days, 157 patients in each of the two groups.

¶ Transfusions included transfusion of any product or transfusion of fresh-frozen plasma, packed red cells, platelets, and whole blood cells.

was not associated with an excess of ischemic events among patients who underwent CABG or among those who received medical treatment alone.

The largest percentage of all TIMI major bleeding complications occurred in the cohort of patients who underwent CABG, with a nonsignificant excess observed with pretreatment in that cohort (Fig. S5 in the Supplementary Appendix). There was a significant increase with pretreatment, by a factor of 3, in the incidence of TIMI major bleeding episodes not related to CABG, including an increase by a factor of 6 in the incidence of life-threatening bleeding, although there was not an excess of intracranial or fatal bleeding. The between-group differences in safety were driven by the PCI cohort, which had the same significant excess of bleeding complications as that observed in the global population. Bleeding in the PCI cohort occurred early, as compared with bleeding in the CABG cohort, in which bleeding was delayed and was dependent on the timing of surgery in relation to the administration of prasugrel. Radial access, as compared with femoral access, was associated with a 61% lower incidence of TIMI major bleeding not related to CABG, but the safety hazard of pretreatment persisted in this subgroup.

Despite the lack of rigorous studies supporting the practice of pretreatment with clopidogrel in patients with NSTE acute coronary syndromes, this practice has become commonplace and has often been extended to new oral $P2Y_{12}$ antagonists. Our results support the administration of prasugrel when the coronary anatomy is known and after PCI is selected as the treatment strategy. Currently, the risk of an ischemic complication before catheterization is extremely low given the short interval between admission and catheterization.[16,17,27-30] Coronary angiography not only confirms the diagnosis but is central for determining the treatment strategy. In our population of patients with NSTE acute coronary syndromes, 32% did not need pretreatment since they underwent CABG or received medical treatment with or without further $P2Y_{12}$ inhibition. In the 69% of patients undergoing PCI, pretreat-

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ment with an effective $P2Y_{12}$ inhibitor at the time of insertion of the sheath exposed patients to a greater risk of bleeding complications without better protection against periprocedural myocardial infarction. The rapid onset of action of oral and intravenous $P2Y_{12}$ inhibitors, together with the short intervals to catheterization, suggests that these drugs should be used only when the coronary anatomy has been defined.[14,28]

There are several aspects of our trial that may limit the conclusions. First, given the safety issues, the data and safety monitoring committee recommended interruption of the enrollment just before completion. However, the power of the trial was not affected, since at the time the trial was stopped, 398 patients had had a primary efficacy end-point event, and this event-driven study was due to stop when 400 patients had an end-point event. Second, since our study tested the concept of pretreatment, receipt of a loading dose of a $P2Y_{12}$ inhibitor before randomization was, according to the study design, an exclusion criterion. Subsequently, pretreatment with clopidogrel was the most frequent reason for screening failure, which we believe was a reflection of the common practice more than a difference in patient profile. Third, one fourth of the study population received medical treatment only, and those patients may not have been the most appropriate subgroup for pretreatment. Fourth, our findings are applicable to most patients presenting with an NSTE acute coronary syndrome, but they cannot be extended to patients requiring urgent or late (>48 hours) catheterization or to patients with ST-segment elevation myocardial infarction.

In conclusion, among patients with NSTE myocardial infarction who were scheduled to undergo catheterization within 48 hours after admission, pretreatment with prasugrel at the time of diagnosis did not reduce the rate of major ischemic events up to day 30 but increased the rate of major bleeding complications. The results were consistent among patients undergoing PCI, supporting the strategy of treatment with prasugrel after the coronary anatomy has been defined.[14]

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APPENDIX

The authors' affiliations are as follows: Institut de Cardiologie, Centre Hospitalier Universitaire Pitié–Salpêtrière (ACTION group, Assistance Publique–Hôpitaux de Paris [AP-HP], Université Paris 6) (G.M., J.S.), and Methodology and Statistical Unit, Centre Hospitalier Universitaire Lariboisière (ACTION group, AP-HP, Université Paris 7) (E.V.), Paris, and Service d'Aide Médicale d'Urgence and Emergency Department, Lille University Hospital, Lille (P.G.), Service de Cardiologie, Centre Hospitalier Universitaire Nîmes (ACTION group, Université Montpellier 1), Montpellier (G.C.) — all in France; Cardiovascular and Neurological Department, Azienda Ospedaliera Arezzo, Arezzo (L.B., P.A.), and the Division of Cardiology, Fondazione IRCCS Policlinico San Matteo, Pavia (L.O.V.) — both in Italy; Institute of Cardiology, Jagiellonian University Medical College, University Hospital (D.D.), and Jagiellonian University Hospital Krakow (J.L.) — both in Krakow, Poland; Kerckhoff Heart and Thoraxcenter, Bad Nauheim and Medical Clinic I, University of Giessen, Giessen (C.H.), Eli Lilly Deutschland, Bad Homburg (J.G.), and Medizinische Klinik, Universitätsmedizin der Johannes Gutenberg-Universität, Mainz (M.N.) — all in Germany; Montreal Heart Institute, Montreal (J.-F.T.); the Department of Cardiology, St. Antonius Hospital, Nieuwegein, the Netherlands (J.M.B.); Eli Lilly, Indianapolis (D.L.M., T.M.C., J.A.J.); and Third Medical Faculty of Charles University and University Hospital Royal Vineyards, Prague, Czech Republic (Z.M., P.W.).

REFERENCES

1. Montalescot G, Sideris G, Meuleman C, et al. A randomized comparison of high clopidogrel loading doses in patients with non-ST-segment elevation acute coronary syndromes: the ALBION (Assessment of the Best Loading Dose of Clopidogrel to Blunt Platelet Activation, Inflammation and Ongoing Necrosis) trial. J Am Coll Cardiol 2006;48:931-8.

2. Steinhubl SR, Berger PB, Brennan DM, Topol EJ. Optimal timing for the initiation of pre-treatment with 300 mg clopidogrel before percutaneous coronary intervention. J Am Coll Cardiol 2006;47:939-43.

3. Steinhubl SR, Berger PB, Mann JT III, et al. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. JAMA 2002;288:2411-20. [Erratum, JAMA 2003;289:987.]

4. The Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med 2001;345:494-502. [Errata, N Engl J Med 2001;345:1506, 1716.]

5. Hamm CW, Bassand JP, Agewall S, et al. ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: the Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J 2011;32:2999-3054.

6. Jneid H, Anderson JL, Wright RS, et al. 2012 ACCF/AHA focused update of the guideline for the management of patients with unstable angina/non-ST-elevation myocardial infarction (updating the 2007 guideline and replacing the 2011 focused update): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2012;60:645-81.

7. Ndrepepa G, Neumann FJ, Deliargyris EN, et al. Bivalirudin versus heparin plus a glycoprotein IIb/IIIa inhibitor in patients with non-ST-segment elevation myocardial infarction undergoing percutaneous coronary intervention after clopidogrel pretreatment: pooled analysis from the ACUITY and ISAR-REACT 4 trials. Circ Cardiovasc Interv 2012;5:705-12.

8. Lincoff AM, Steinhubl SR, Manoukian SV, et al. Influence of timing of clopidogrel treatment on the efficacy and safety of bivalirudin in patients with non-ST-segment elevation acute coronary syndromes undergoing percutaneous coronary intervention: an analysis of the ACUITY (Acute Catheterization and Urgent Intervention Triage strategY) trial. JACC Cardiovasc Interv 2008;1:639-48.

9. Bellemain-Appaix A, O'Connor SA, Silvain J, et al. Association of clopidogrel pretreatment with mortality, cardiovascular events, and major bleeding among patients undergoing percutaneous coronary intervention: a systematic review and meta-analysis. JAMA 2012;308:2507-16. [Erratum, JAMA 2013;309:1461.]

10. Wiviott SD, Trenk D, Frelinger AL, et al. Prasugrel compared with high loading- and maintenance-dose clopidogrel in patients with planned percutaneous coronary intervention: the Prasugrel in Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation-Thrombolysis in Myocardial Infarction 44 trial. Circulation 2007;116:2923-32.

11. Montalescot G, Sideris G, Cohen R, et al. Prasugrel compared with high-dose clopidogrel in acute coronary syndrome: the randomised, double-blind ACAPULCO study. Thromb Haemost 2010;103:213-23.

12. Storey RF, Husted S, Harrington RA, et al. Inhibition of platelet aggregation by AZD6140, a reversible oral P2Y12 receptor antagonist, compared with clopidogrel in patients with acute coronary syndromes. J Am Coll Cardiol 2007;50:1852-6.

13. Gurbel PA, Bliden KP, Butler K, et al. Randomized double-blind assessment of the ONSET and OFFSET of the antiplatelet effects of ticagrelor versus clopidogrel in patients with stable coronary artery disease: the ONSET/OFFSET study. Circulation 2009;120:2577-85.

14. Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2007;357:2001-15.

15. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2009;361:1045-57.

16. Mehta SR, Granger CB, Boden WE, et al. Early versus delayed invasive intervention in acute coronary syndromes. N Engl J Med 2009;360:2165-75.

17. Montalescot G, Cayla G, Collet JP, et al. Immediate vs delayed intervention for acute coronary syndromes: a randomized clinical trial. JAMA 2009;302:947-54.

18. Sorajja P, Gersh BJ, Cox DA, et al. Impact of delay to angioplasty in patients with acute coronary syndromes undergoing invasive management: analysis from the ACUITY (Acute Catheterization and Urgent Intervention Triage strategY) trial. J Am Coll Cardiol 2010;55:1416-24.

19. Katritsis DG, Siontis GC, Kastrati A, et al. Optimal timing of coronary angiography and potential intervention in non-ST-elevation acute coronary syndromes. Eur Heart J 2011;32:32-40.

20. Montalescot G, Bolognese L, Dudek D, et al. A comparison of prasugrel at the time of percutaneous coronary intervention or as pretreatment at the time of diagnosis in patients with non-ST-segment elevation myocardial infarction: design and rationale for the ACCOAST study. Am Heart J 2011;161:650.e1-656.e1.

21. Mehta SR, Yusuf S, Peters RJ, et al. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. Lancet 2001;358:527-33.

22. Widimsky P, Motovská Z, Simek S, et al. Clopidogrel pre-treatment in stable angina: for all patients > 6 h before elective coronary angiography or only for angiographically selected patients a few minutes before PCI? A randomized multicentre trial PRAGUE-8. Eur Heart J 2008;29:1495-503.

23. Di Sciascio G, Patti G, Pasceri V, et al. Effectiveness of in-laboratory high-dose clopidogrel loading versus routine pre-load in patients undergoing percutaneous coronary intervention: results of the ARMYDA-5 PRELOAD (Antiplatelet therapy for Re-

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duction of MYocardial Damage during Angioplasty) randomized trial. J Am Coll Cardiol 2010;56:550-7.
24. Davlouros PA, Arseniou A, Hahalis G, et al. Timing of clopidogrel loading before percutaneous coronary intervention in clopidogrel-naive patients with stable or unstable angina: a comparison of two strategies. Am Heart J 2009;158:585-91.
25. Giugliano RP, White JA, Bode C, et al. Early versus delayed, provisional eptifibatide in acute coronary syndromes. N Engl J Med 2009;360:2176-90.
26. Stone GW, Bertrand ME, Moses JW, et al. Routine upstream initiation vs deferred selective use of glycoprotein IIb/IIIa inhibitors in acute coronary syndromes: the ACUITY Timing trial. JAMA 2007;297:591-602.
27. The CURRENT-OASIS 7 Investigators. Dose comparisons of clopidogrel and aspirin in acute coronary syndromes. N Engl J Med 2010;363:930-42. [Erratum, N Engl J Med 2010;363:1585.]
28. Bhatt DL, Stone GW, Mahaffey KW, et al. Effect of platelet inhibition with cangrelor during PCI on ischemic events. N Engl J Med 2013;368:1303-13.
29. Tricoci P, Huang Z, Held C, et al. Thrombin-receptor antagonist vorapaxar in acute coronary syndromes. N Engl J Med 2012;366:20-33.
30. Cannon CP, Harrington RA, James S, et al. Comparison of ticagrelor with clopidogrel in patients with a planned invasive strategy for acute coronary syndromes (PLATO): a randomised double-blind study. Lancet 2010;375:283-93.
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