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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

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Objectives This study sought to determine if the efficacy of bivalirudin alone versus heparin plus a glycoprotein (GP) IIb/IIIa inhibitor is dependent upon the duration of clopidogrel pre-treatment in patients undergoing percutaneous coronary intervention (PCI) in the ACUITY (Acute Catheterization and Urgent Intervention Triage strategY) trial.

Background The administration of a clopidogrel loading dose several hours before PCI reduces the risk of periprocedural thrombotic events.

Methods Patients with an acute coronary syndrome were randomized to heparin plus a GP IIb/IIIa inhibitor (control), bivalirudin plus a GP IIb/IIIa inhibitor, or bivalirudin alone. Dose and timing of clopidogrel were left to the investigator's discretion.

Results Of 13,819 patients randomized, 7,789 underwent PCI. When clopidogrel was initiated at any time before angiography or within 30 min after PCI, randomization to bivalirudin alone (n = 2,284) or control (n = 2,189) was associated with similar ischemic outcomes (8.2% vs. 8.3%, risk ratio: 0.98, 95% confidence interval: 0.81 to 1.20). Those patients who received clopidogrel >30 min after PCI or not at all experienced an increase in ischemic events when randomized to bivalirudin alone (n = 290) versus control (n = 317) (14.1% vs. 8.5%, risk ratio: 1.66, 95% confidence interval: 1.05 to 2.63). Major bleeding was significantly less frequent in patients treated with bivalirudin alone.

Conclusions This post-hoc analysis suggests that in acute coronary syndrome patients, as long as clopidogrel is administered before or within 30 min of PCI treatment with bivalirudin alone is similarly effective to heparin plus a GP IIb/IIIa inhibitor in suppressing 30-day ischemic events with significantly less bleeding. If it is anticipated that clopidogrel will be given late or not at all after PCI, bivalirudin alone may be associated with worse ischemic outcomes. (Comparison of Angiomax Versus Heparin in Acute Coronary Syndromes; NCT00093158) (J Am Coll Cardiol Intv 2008;1:639–48)

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The administration of clopidogrel before percutaneous coronary intervention (PCI), typically as a loading dose of at least 300 mg, has been found in a wide variety of studies to decrease the incidence of periprocedural thrombotic events (1). In the majority of these studies, adjunctive antithrombotic therapy has included aspirin and unfractionated heparin (UFH) with or without a glycoprotein (GP) IIb/IIIa receptor inhibitor. There are theoretical reasons why adjunctive antithrombotic therapy may influence the benefit of clopidogrel pre-treatment. For example, because unfractionated heparin (2) and even platelet GP IIb/IIIa antagonists (3) may increase platelet activation, inhibition of platelet activation with clopidogrel may be of particular benefit in patients receiving UFH with or without a GP IIb/IIIa antagonist. Alternatively, because the direct thrombin inhibitor bivalirudin does not directly inhibit platelet aggregation as do the GP IIb/IIIa inhibitors, additional specific antiplatelet protection may be advantageous in patients receiving only bivalirudin. This may be particularly true in a troponin-positive acute coronary syndrome (ACS) patient, in whom the addition of a GP IIb/IIIa inhibitor has been shown to be most beneficial (4).

Abbreviations and Acronyms

ACS = acute coronary syndrome
GP = glycoprotein
IV = intravenous
NSTE = non–ST-segment elevation
PCI = percutaneous coronary intervention
UFH = unfractionated heparin

Previous analysis of a large randomized trial among patients undergoing nonurgent PCI found that bivalirudin was not inferior to heparin plus a GP IIb/IIIa inhibitor in reducing ischemic events and that the efficacy of bivalirudin was not influenced by the timing of clopidogrel administration (5). In contrast, preliminary analysis of the ACUITY (Acute Catheterization and Urgent Intervention Triage strategY) trial found an interaction of borderline significance ($p = 0.054$) between clopidogrel exposure and randomized therapy on the incidence of 30-day composite ischemia, leading to the suggestion that the use of bivalirudin monotherapy should be limited to those non–ST-segment elevation (NSTE) ACS patients in whom clopidogrel pre-treatment is given (6–8).

In this post-hoc analysis of the ACUITY trial, we specifically evaluated the timing of the initiation of clopidogrel treatment in patients undergoing PCI to determine whether clopidogrel pre-treatment is especially beneficial or necessary in patients not receiving a GP IIb/IIIa antagonist.

Methods

Study design and patients. The design of the ACUITY trial has been previously described in detail (9,10). In brief, patients with symptoms of unstable angina lasting ≥10 min within the preceding 24 h were eligible if 1 or more of the following criteria were met: new ST-segment depression or transient elevation ≥1 mm; troponin I, T, or creatine kinase-myocardial band elevation; known coronary artery disease; or all 4 other Thrombolysis In Myocardial Infarction (TIMI) unstable angina risk criteria (11). The overall study population was therefore composed of patients with NSTE ACS who were at moderate-to-high ischemic risk. Major exclusion criteria included acute ST-segment elevation myocardial infarction or shock; bleeding diathesis or major bleeding episode within 2 weeks; thrombocytopenia; calculated creatinine clearance <30 ml/min; recent administration of abciximab, warfarin, fondaparinux, fibrinolytic agents, bivalirudin or 2 or more doses of low molecular weight heparin; and allergy to study drugs or iodinated contrast that could not be adequately pre-medicated. The study was approved by the institutional review board or ethics committee at each participating center, and all patients provided written, informed consent.

Randomization and study medications. Telephone randomization was stratified by site and the prior use or intent to administer a thienopyridine before angiography. Patients were assigned in a 1:1:1 ratio to 1 of 3 antithrombin

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regimens started immediately after randomization: heparin (either unfractionated or enoxaparin) plus a GP IIb/IIIa inhibitor (the control group), bivalirudin plus a GP IIb/IIIa inhibitor, or bivalirudin alone. Unfractionated heparin was administered as an intravenous (IV) bolus of 60 international units (IU)/kg plus infusion of 12 IU/kg/h to target an activated partial thromboplastin time of 50 to 75 s before angiography and an activated clotting time of 200 to 250 s during PCI. Enoxaparin 1 mg/kg subcutaneously every 12 h was administered before angiography, with an additional 0.3 mg/kg or 0.75 mg/kg IV bolus administered before PCI if the most recent subcutaneous dose had been given more than 8 or 16 h earlier, respectively. Bivalirudin was initiated with an IV bolus of 0.1 mg/kg and an infusion of 0.25 mg/kg/h. Before PCI an additional bivalirudin IV bolus of 0.5 mg/kg was administered, and the infusion was increased to 1.75 mg/kg/h. Bivalirudin, UFH, and enoxaparin were routinely discontinued per protocol at the completion of angiography or PCI. Provisional GP IIb/IIIa antagonist use was permitted in patients randomized to bivalirudin monotherapy for severe breakthrough ischemia or procedural complications during PCI.

Angiography was performed by protocol within 72 h after randomization, after which the decision was made regarding treatment with PCI versus surgical or further medical management. This analysis considers only patients who underwent PCI. Aspirin 300 to 325 mg orally or 250 to 500 mg IV was administered daily during the hospitalization.

Clopidogrel treatment. The initial dosing and timing of clopidogrel were left to the investigator's discretion per local standards, though a ≥300-mg loading dose was recommended no later than 2 h after completing PCI in all patients per protocol. Clopidogrel 75 mg daily was recommended for 1 year in all patients after PCI.

Data regarding timing of clopidogrel administration were recorded in the case report form. Timing of the initiation of clopidogrel treatment was based on the earliest exposure as documented on the case report form For this analysis, clopidogrel pre-treatment was prospectively categorized as: 1) pre-angiography, which was further categorized as: a) pre-hospital—received before presentation to the randomization hospital, b) pre-randomization—received pre-randomization but at the randomization hospital, or c) post-randomization, pre-angiography—received after study randomization and before angiography; 2) peri-PCI—initiated after angiography and either before or within 30 min (determined a priori to reflect loading in the catheterization laboratory) after PCI; or 3) post-PCI—initiated >30 min after PCI. Patients who did not receive clopidogrel at any time before or after PCI were classified as receiving no clopidogrel. Only in patients who initially received clopidogrel after randomization (44% of clopidogrel-treated PCI patients) was the precise dose and timing of clopidogrel initiation documented. Patients who received ticlopidine were excluded from this analysis.

End points and statistical methods. The primary 30-day efficacy end point for this analysis was composite ischemia (death from any cause, myocardial infarction, or unplanned revascularization for ischemia) end point. Composite ischemia was also measured at 1 year. Major bleeding (not related to a coronary artery bypass graft) at 30 days as defined in the study protocol was also evaluated as the principal safety end point; bleeding events beyond 30 days were not measured. The component definitions of the primary end points have been previously detailed (12). A clinical events committee blinded to treatment assignment adjudicated all primary end point events.

Categorical variables were compared by chi-square test. Continuous variables were compared by the nonparametric Wilcoxon rank sum test. All primary categorical binary event rate analyses were performed in the intention-to-treat population, with patients lost to follow-up (23 of 13,819 patients, 0.17%) included in the denominator and considered nonevents. A secondary analysis was performed using time-to-event data (for which patients were censored at the time of study withdrawal or at last follow-up) displayed using Kaplan-Meier methodology and compared with the log-rank test.

To explore the relationship between the time from clopidogrel initiation to PCI and composite ischemia, the 30-day rate of composite ischemia was converted to the logarithmic odds so that a linear regression model could be fit using a spline transformation. All statistical analyses were performed by SAS software, version 8.2 (SAS Institute Inc., Cary, North Carolina).

Results

Of the entire 13,819 patients enrolled in the ACUITY trial, 7,789 underwent PCI during the index hospitalization. Exposure to clopidogrel was documented in 97% (n = 7,517) of all patients undergoing PCI. Overall, 5,131 patients received clopidogrel pre-angiography (pre-hospital + pre-randomization + post-randomization and pre-angiography), and 1,572 patients first received it peri-PCI (Fig. 1). Only 814 patients had clopidogrel initiated >30 min after the end of the PCI procedure and 129 never received clopidogrel.

Ischemic outcomes. Among all patients combined, initiating clopidogrel in the pre-angiography versus peri-PCI period was associated with similar 30-day composite ischemic event rates (8.6% vs. 8.3%, respectively, p = 0.78). In contrast, compared with these 2 groups combined, 30-day composite ischemic event rates were significantly higher among those in whom clopidogrel was initiated only in the post-PCI period (10.6%, p = 0.049) and markedly higher in

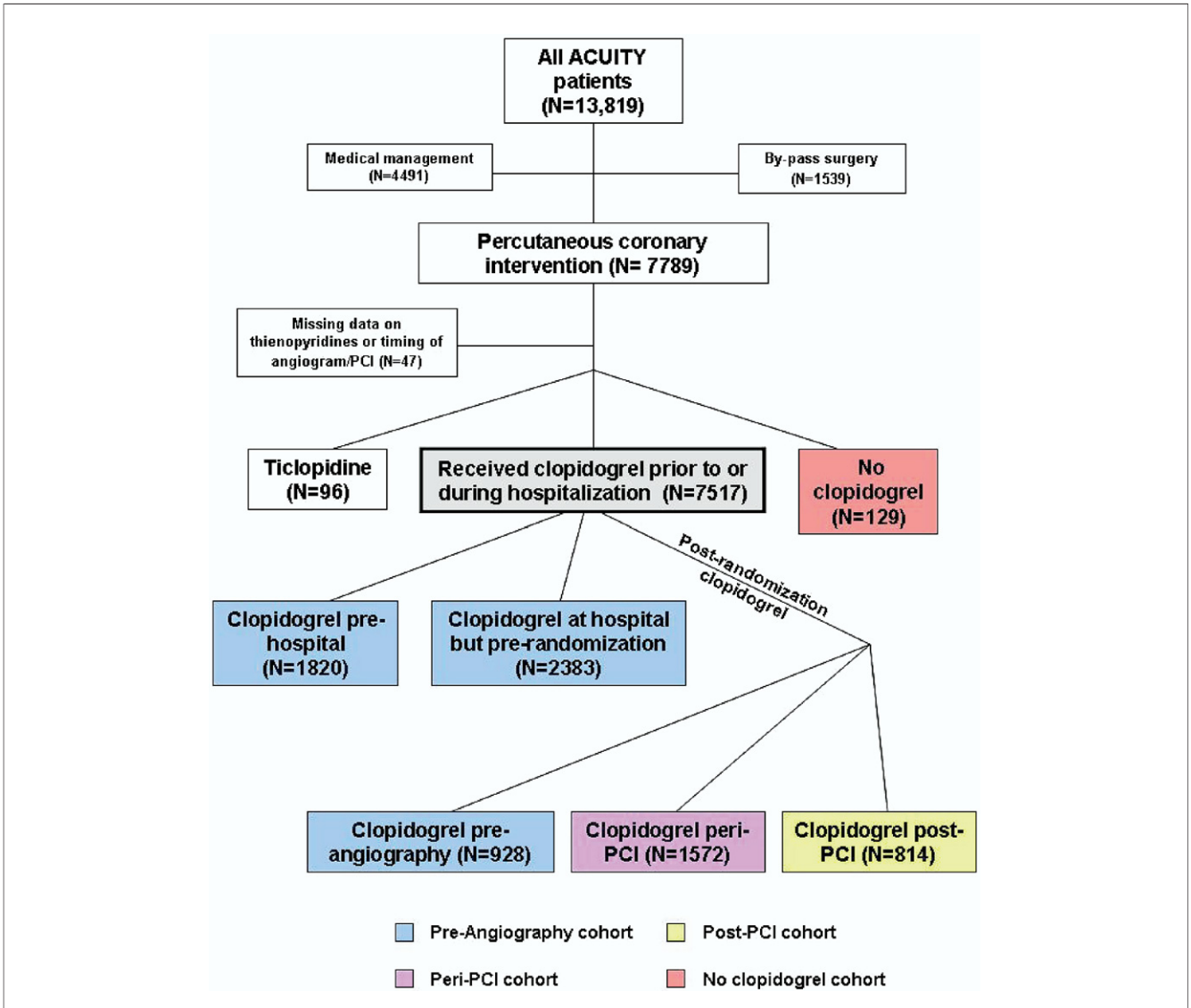

Figure 1. Study Population

Flow diagram of all ACUITY patients and identification of those included in this analysis, broken down by their earliest exposure to clopidogrel. Only in patients who had clopidogrel initiated post-randomization was the dose and time known. PCI = percutaneous coronary intervention.

those in whom clopidogrel was never started (17.1%, $p < 0.001$).

Outcome with regard to the composite ischemic end point according to the timing of clopidogrel initiation and randomization arm is illustrated in Figure 2. For patients in whom the first dose of clopidogrel was administered pre-angiography or peri-PCI, there were no differences in the incidence of the ischemic end point among the 3 randomized treatment arms. When the first dose of clopidogrel was given more than 30 min after PCI (post-PCI), there was no difference in outcomes among those who had received heparin with a GP IIb/IIIa inhibitor ($p = 0.13$). Among patients who never received clopidogrel, a numerically higher ischemic event rate that approached significance (10% absolute increased, $p = 0.08$) was observed in the bivalirudin-alone arm compared with the heparin plus GP IIb/IIIa inhibitor arm.

To increase the power to evaluate specifically whether patients not receiving a GP IIb/IIIa antagonist are particularly dependent upon clopidogrel treatment pre-PCI, patients in the pooled GP IIb/IIIa inhibitor arms (heparin/enoxaparin or bivalirudin) were compared with those randomized to bivalirudin monotherapy. Ischemic event rates were similar among patients in whom clopidogrel was initiated in the pre-angiography or peri-PCI period with either bivalirudin monotherapy or a GP IIb/IIIa inhibitor-based regimen (Fig. 3). However, among patients in whom clopidogrel was initiated beyond 30 min after PCI or not at all, event rates tended to be

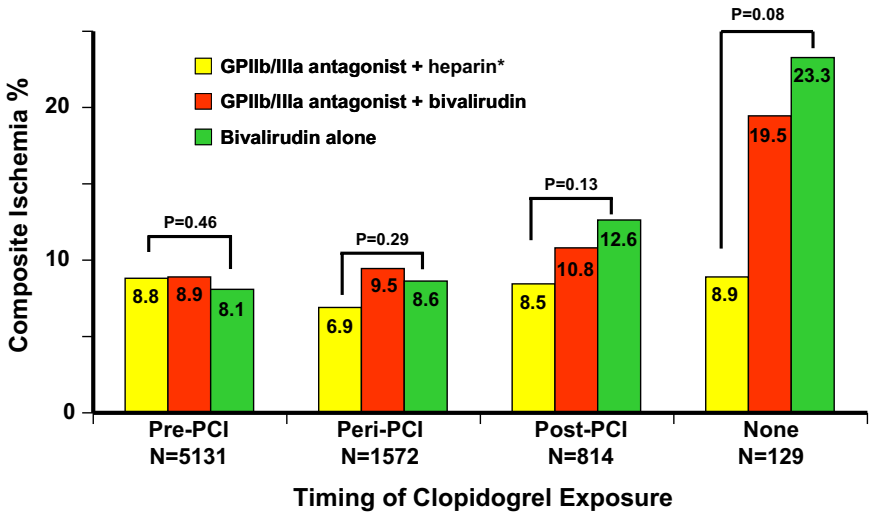

Figure 2. 30-Day Composite Ischemic Outcomes by Randomized Treatment Group

Incidence of the 30-day composite ischemic outcome based on randomized therapy and the timing of clopidogrel initiation among patients undergoing PCI. The p values are for the control arm of a glycoprotein (GP) IIb/IIIa antagonist plus a heparin versus bivalirudin alone. *Either unfractionated heparin or low molecular weight heparin was used. Abbreviations as in Figure 1.

higher in patients randomized to bivalirudin alone, although differences did not reach statistical significance. Moreover, given the small number of patients in these latter 2 subgroups, significant imbalances in baseline and procedural characteristics existed (Table 1).

The benefit of clopidogrel treatment before PCI in placebo-controlled trials has been shown to be time-dependent (13). To further explore the association between clopidogrel timing and randomized treatment in the ACUITY trial, the relationship between ischemic event rates and time of initiation was evaluated with time as a continuous variable. Among the 928 patients in whom the actual time between clopidogrel initiation and angiography was known (those treated after randomization), a spline transformation of the logarithmic odds of the ischemic end point was performed with the duration

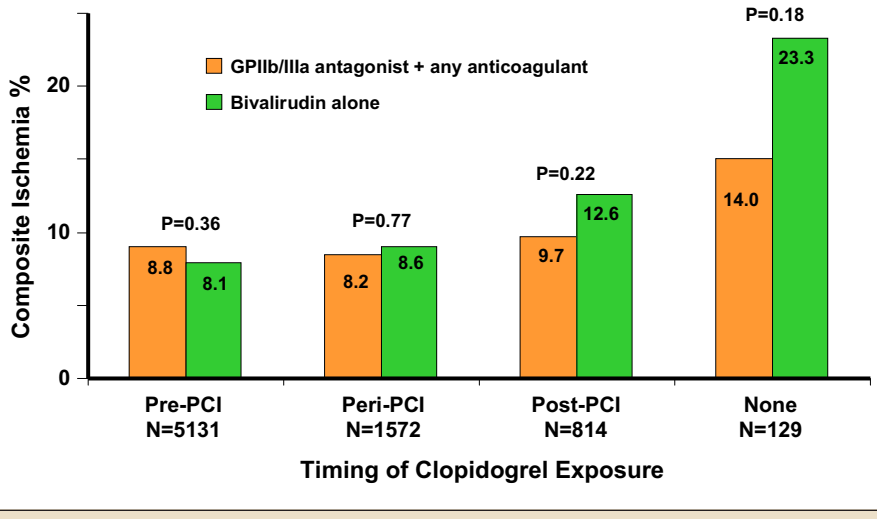

Figure 3. 30-Day Composite Ischemic Outcomes by GP IIb/IIIa Inhibitor Use

Incidence of the 30-day composite ischemic outcome based on randomization to bivalirudin alone versus the combination of the 2 cohorts randomized to a platelet GP IIb/IIIa antagonist plus either bivalirudin or a heparin (unfractionated or low-molecular-weight) and the timing of clopidogrel initiation among patients undergoing PCI. Abbreviations as in Figures 1 and 2.

Table 1. Baseline and Procedural Characteristics of Patients in Whom Clopidogrel Was Initiated Post-PCI or Not at All

	Clopidogrel Pre-Angiography or Peri-PCI			Clopidogrel >30 min After PCI or No Clopidogrel		
	Heparin or Bivalirudin + GP IIb/IIIa Inhibitor (n = 4,419)	Bivalirudin Alone (n = 2,284)	p Value	Heparin or Bivalirudin + GP IIb/IIIa Inhibitor (n = 653)	Bivalirudin Alone (n = 290)	p Value
Age, median [range], yrs	63.0 [21, 91]	62.0 [30, 92]	0.17	62.0 [32, 95]	64.0 [35, 92]	0.01
Age ≥65	45.7%	43.6%	0.10	40.0%	49.3%	0.01
Female	27.0%	26.2%	0.51	26.8%	31.0%	0.18
Diabetes	27.1%	27.3%	0.89	30.2%	30.9%	0.84
Hypertension	65.8%	65.5%	0.80	62.5%	65.4%	0.39
Hyperlipidemia	56.4%	56.3%	0.92	53.0%	52.5%	0.88
Current smoker	30.6%	31.1%	0.63	33.6%	29.8%	0.25
Prior myocardial infarction	30.0%	31.1%	0.34	30.2%	29.8%	0.92
Prior PCI	38.4%	40.2%	0.16	34.6%	34.8%	0.94
Prior coronary artery bypass graft surgery	17.2%	18.0%	0.41	17.5%	15.5%	0.46
Weight, median [IQR], kg	84.0 [73.0, 95.3]	84.0 [75.0, 95.3]	0.07	85.0 [75.0, 97.6]	83.76 [74.0, 96.0]	0.10
Renal insufficiency*	19.0%	17.6%	0.19	16.5%	19.0%	0.36
Baseline cardiac biomarker elevation†	64.4%	66.0%	0.21	64.9%	68.5%	0.30
Attempted vessels per patient						0.44
1	83.3%	84.5%		84.7%	80.9%	
2	14.9%	13.9%		13.9%	17.7%	
≥3	1.8%	1.5%		1.2%	1.4%	
Stent implanted—any	92.5%	92.4%	0.88	87.7%	88.3%	0.82
Thrombectomy or atherectomy	2.3%	2.3%	0.88	2.0%	2.4%	0.68

*Calculated creatinine clearance using the Cockcroft-Gault equation <60 ml/min. There were no significant differences between groups. †Defined as baseline troponin above local laboratories upper limit of normal (ULN). If troponin was not available then creatine kinase-myocardial band above the ULN was used.
GP = glycoprotein; IQR = interquartile range; PCI = percutaneous coronary intervention.

of treatment as a continuous function (Fig. 4). Greater durations of pre-treatment were not associated with improved rates of ischemic events, irrespective of randomized therapy.

In a post-hoc analysis, when only those patients who received clopidogrel either in the pre-angiography or peri-PCI period were analyzed in combination, no significant differences were found between randomized therapies in the 30-day or 1-year composite ischemic end points or their components (Table 2). Alternatively, patients in whom clopidogrel loading was delayed or neglected experienced a significantly higher incidence of the 30-day composite ischemic end point as well as the individual component of myocardial infarction (p value for interaction 0.32). However, there was no difference in the combined ischemic end point or mortality at 1 year (Table 3).

Bleeding outcomes. Regardless of the timing of clopidogrel initiation, major bleeding events were significantly decreased in patients randomized to bivalirudin alone, with relative reductions of ~50% compared with bleeding events in the control arm (Tables 2 and 3).

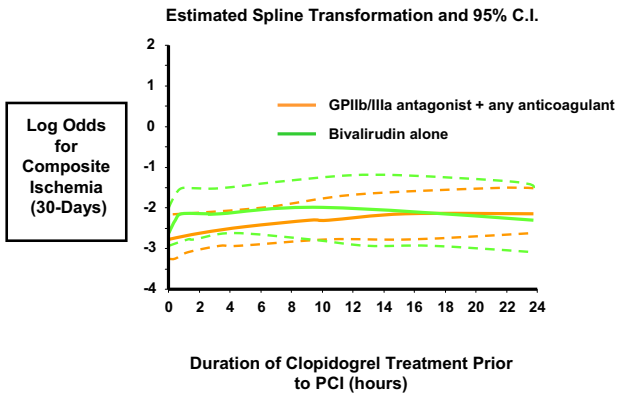

Figure 4. 30-Day Composite Ischemic Outcomes by Duration of Clopidogrel Pre-Treatment

Spline transformation with 95% confidence intervals (CI) of the logarithmic odds of the composite ischemic end point at 30 days based on time of initiation of clopidogrel treatment before PCI. The 928 patients in whom the dose and timing of clopidogrel initiation before PCI was known are divided into those randomized to bivalirudin alone or to a GP IIb/IIIa receptor antagonist. Abbreviations as in Figures 1 and 2.

Table 2. 30-Day and 1-Year Risk Ratios for the Composite Ischemic End Point and Its Components for Patients Who Received Clopidogrel at Any Time Before or Up to 30 Min After PCI

	Arm A UFH/Enox +GP IIb/IIIa Inhibitor (n = 2,189) %	Arm B Bivalirudin +GP IIb/IIIa Inhibitor (n = 2,230) %	B/A Risk Ratio (95% CI)	Arm C Bivalirudin Alone (n = 2,284) %	C/A Risk Ratio (95% CI)
30-day					
Composite ischemia*	8.3	9.0	1.08 (0.90–1.31) p = 0.41	8.2	0.98 (0.81–1.20) p = 0.88
Death	0.8	1.1	1.36 (0.75–2.49) p = 0.31	1.0	1.22 (0.66–2.26) p = 0.52
MI	5.8	6.4	1.11 (0.88–1.40) p = 0.39	6.0	1.05 (0.83–1.33) p = 0.69
Unplanned revascularization	3.3	3.7	1.12 (0.82–1.53) p = 0.48	2.8	0.87 (0.62–1.20) p = 0.39
Major bleeding	6.6	7.8	1.18 (0.95–1.46) p = 0.13	3.5	0.53 (0.41–0.69) p < 0.0001
1-year					
Composite ischemia*	17.9	19.7	1.10 (0.97–1.25) p = 0.12	18.7	1.05 (0.93–1.19) p = 0.45
Death	3.0	3.2	1.07 (0.77–1.49) p = 0.68	3.1	1.05 (0.75–1.46) p = 0.79

*Death, myocardial infarction (MI), or unplanned ischemia-driven revascularization.
CI = confidence intervals; Enox = enoxaparin; UFH = unfractionated heparin; other abbreviations as in Table 1.

Troponin-positive patients. When the subset of patients who were troponin-positive at the time of randomization were evaluated for the influence of the timing of clopidogrel treatment and randomization to bivalirudin alone or combination treatment with a GP IIb/IIIa antagonist (with heparin or bivalirudin), the results were concordant with the overall results. Among troponin-positive patients who received clopidogrel before or immediately after PCI, no differences were apparent between those randomized to an anticoagulant plus a GP IIb/IIIa inhibitor versus bivalirudin monotherapy (Fig. 5). Among troponin-positive patients receiving clopidogrel late after their PCI or not at all, the absolute difference in ischemic event rates between patients receiving a GP IIb/IIIa inhibitor and bivalirudin alone tended to be substantially greater.

Table 3. 30-Day and 1-Year Risk Ratios for the Composite Ischemic End Point and Its Components for Patients Who Received Clopidogrel >30 Min After PCI or Not at All

	Arm A UFH/Enox +GP IIb/IIIa Inhibitor (n = 317) %	Arm B Bivalirudin +GP IIb/IIIa Inhibitor (n = 336) %	B/A Risk Ratio (95% CI)	Arm C Bivalirudin Alone (n = 290) %	C/A Risk Ratio (95% CI)
30-day					
Composite ischemia*	8.5	11.9	1.40 (0.88–2.22) p = 0.16	14.1	1.66 (1.05–2.63) p = 0.03
Death	1.9	1.2	0.63 (0.18–2.21) p = 0.47	1.7	0.91 (0.28–2.95) p = 0.88
MI	5.0	8.0	1.59 (0.87–2.90) p = 0.13	10.3	2.05 (1.14–3.68) p = 0.02
Unplanned revascularization	3.2	3.9	1.23 (0.55–2.76) p = 0.62	6.6	2.08 (0.98–4.39) p = 0.06
Major bleeding	7.3	6.3	0.86 (0.49–1.53) p = 0.61	3.4	0.48 (0.23–0.98) p = 0.04
1-year					
Composite ischemia*	18.0	17.9	0.99 (0.72–1.38) p = 0.97	21.7	1.21 (0.88–1.67) p = 0.25
Death	5.0	3.6	0.71 (0.34–1.47) p = 0.35	3.1	0.61 (0.28–1.37) p = 0.23

*Death, myocardial infarction, or unplanned ischemia-driven revascularization.
Abbreviations as in Tables 1 and 2.

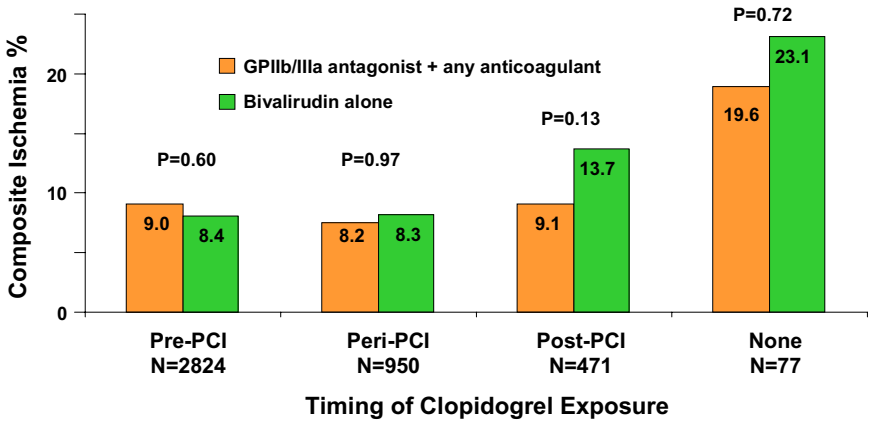

Figure 5. 30-Day Composite Ischemic Outcomes Among Troponin-Positive Patients

Incidence of the 30-day composite ischemic outcome among patients who were troponin-positive at baseline based on randomization to bivalirudin alone versus the combination of the 2 cohorts randomized to a platelet GP IIb/IIIa antagonist plus either bivalirudin or heparin (unfractionated or low-molecular-weight) and the timing of clopidogrel initiation among patients undergoing PCI. Abbreviations as in Figures 1 and 2.

Discussion

This post-hoc analysis of NSTE ACS patients undergoing PCI in the ACUITY trial suggests that as long as clopidogrel is administered no later than 30 min after PCI, ischemic outcomes remain similar in patients treated with bivalirudin monotherapy or heparin plus a GP IIb/IIIa inhibitor while a significant reduction in major bleeding is maintained. These findings clarify the initially published results of the ACUITY trial, which suggested that patients who were randomized to bivalirudin alone and who were not pre-treated with clopidogrel experienced more ischemic events. Those initial findings were rapidly interpreted to imply that prolonged (i.e., ≥6 h) pre-treatment with clopidogrel was needed if bivalirudin was to be used in the NSTE ACS setting (7,8). This current, more focused, analysis of the ACUITY trial reveals that initial findings were driven primarily by the results in a small number of patients who received no clopidogrel or by those who first received clopidogrel more than 30 min after PCI.

In contrast to the findings from other studies (14), pre-treatment with clopidogrel did not provide a protective effect in patients randomized to a heparin plus a GP IIb/IIIa inhibitor in the ACUITY trial; ischemic event rates in that treatment arm were nearly identical regardless of whether patients received clopidogrel before PCI, after PCI, or not at all. Conversely, and more in line with expectations from prior studies, patients in the bivalirudin monotherapy or bivalirudin plus a GP IIb/IIIa inhibitor arms experienced ischemic event rates 2 to 3 times higher if they had not received clopidogrel than if clopidogrel was administered pre-PCI. Because of this apparent differential effect of clopidogrel, which may have in part been due to chance, direct comparison between the heparin plus GP IIb/IIIa inhibitor arm versus the bivalirudin-alone arm suggested that ischemic event rates were different if clopidogrel was not administered before PCI. In the present analysis, we more thoroughly explored whether a NSTE ACS patient undergoing a PCI without concomitant platelet inhibition with a GP IIb/IIIa inhibitor is especially dependent on clopidogrel pre-treatment. These results suggest that patients who received clopidogrel at any time before the PCI or within 30 min thereafter experienced similar ischemic event rates whether randomized to bivalirudin alone or a GP IIb/IIIa antagonist plus an anticoagulant. On the other hand, patients randomized to bivalirudin alone consistently tended to have substantially higher ischemic event rates than did GP IIb/IIIa inhibitor-treated patients if clopidogrel was initiated more than 30 min after the completion of PCI or not at all.

"Pre-treatment" with clopidogrel typically implies administration of a loading dose with an adequate duration of time before the PCI to decrease periprocedural ischemic events. For a 300-mg loading dose, the best available data suggest that maximal clinical benefit occurs after as long as 15 to 24 h (13). For a 600-mg loading dose, the best available data suggest that at least 2 h of pre-treatment is necessary (15). Whether there is any benefit of initiating clopidogrel at "inadequate" doses or duration before a PCI compared with treatment at the time of the procedure remains unproven, but at least 1 analysis of a placebo-controlled, blinded trial would suggest there is not (13). It is important, however, to acknowledge that in the ACUITY trial, the percentage of patients "adequately" pre-treated was not characterized, but as the average durations between admission and randomization before PCI were 19.5 and 4 h, respectively, it is

possible that a substantial proportion of patients in this analysis would not be considered to have been adequately pre-treated.

Initial analyses of the ACUITY trial concentrated primarily on the results of 2 of the 3 study arms, namely bivalirudin alone versus the active control arm of heparin plus a GP IIb/IIIa inhibitor. In this present study, we also performed an analysis in which patients in the 2 arms randomized to a GP IIb/IIIa inhibitor were combined and compared with the 1 arm of bivalirudin alone. This secondary analysis was carried out to focus on whether patients not receiving additional antiplatelet protection beyond aspirin were particularly likely to benefit from the addition of clopidogrel compared with those receiving a GP IIb/IIIa antagonist. Pooling of the heparin plus GP IIb/IIIa and bivalirudin plus GP IIb/IIIa arms is justifiable for an exploratory analysis; 30-day ischemic event rates in these 2 groups were nearly identical, and there are no prior data to suggest or a priori reasons to believe that among patients treated with GP IIb/IIIa inhibitors, clopidogrel treatment would be any more or less beneficial with bivalirudin versus heparin. The findings of this pooled analysis were confirmatory of those of the comparison between the heparin plus GP IIb/IIIa inhibitor versus bivalirudin-only treatments arms.

Although it may be assumed that adding a thienopyridine to a GP IIb/IIIa inhibitor might offer no additional benefit due to a lack of any further inhibition of measurable platelet aggregation, clinical data suggest otherwise (16). Moreover, it has been shown that in troponin-positive patients with ACS, addition of a GP IIb/IIIa inhibitor results in further reduction in ischemic events beyond that provided by pre-treatment with a thienopyridine in combination with high-dose heparin (4). It is therefore reassuring that in this present analysis of the troponin-positive cohort in the ACUITY trial, patients randomized to bivalirudin alone experienced similar ischemic event rates as those randomized to a GP IIb/IIIa inhibitor, irrespective of whether clopidogrel was administered before PCI or in the periprocedural period. This finding is important in that many patients with an NSTE ACS are not preloaded with clopidogrel before diagnostic angiography and can therefore only receive the drug just before or after completion of PCI.

An important question is whether the high event rates in the patients who never received clopidogrel despite undergoing a PCI were due to complications that occurred at the time of the procedure. Because patients who received no clopidogrel also had no major bleeding events (data not shown), it seems unlikely that a bleeding complication was a reason for not ever receiving clopidogrel. Only 11 of the 129 patients who received no clopidogrel underwent a coronary artery bypass graft during their index hospitalization; thus clopidogrel was not withheld to prevent perioperative bleeding in the vast majority of patients. Given the lack of information regarding reasons why clopidogrel was not administered after PCI, we can provide no clear explanation for this differential in outcomes, although it is possible that this finding is due to the play of chance in a small subgroup.

Study limitations. The primary limitations of this analysis are those inherent with any post-hoc, nonrandomized analysis. Also, as randomized therapy was not blinded, it is possible that the investigators may have treated patients differently, including the use of adjunctive antiplatelet therapies such as clopidogrel, based on their biases toward the use of a GP IIb/IIIa receptor inhibitor in the setting of PCI. Although the use of clopidogrel and its timing seemed to be well balanced between treatment groups, biases based upon open-label allocation to the randomized therapies may have contributed to undetected imbalances in the underlying risk of patients in the various cohorts of clopidogrel pre-treatment. Also, patients randomized into clinical trials represent a unique cohort of patients whose treatment does not always reflect real-world clinical practice, including the potential for shorter delays to PCI and therefore shorter durations of pre-treatment. Finally, it is important to re-emphasize that the dose or duration of clopidogrel treatment before the time of their PCI was unknown in the majority of patients in the ACUITY trial, requiring estimation of time intervals as described in this report.

Conclusions

The results of this analysis suggest that with initiation of clopidogrel treatment before or within 30 min of the performance of PCI, bivalirudin has similar efficacy in preventing short-term and long-term ischemic complications as does a GP IIb/IIIa inhibitor with UFH, enoxaparin, or bivalirudin among NSTE ACS patients, while maintaining a significant reduction in major bleeding. However, among patients in whom it is anticipated that clopidogrel will be given more than 30 min or not at all after PCI, an antithrombotic regimen that includes GP IIb/IIIa inhibition may provide better protection against ischemic events than does bivalirudin alone. These data are reassuring for the treatment of patients with NSTE ACS who undergo diagnostic catheterization with bivalirudin alone without clopidogrel pre-loading. If a PCI is indicated, such patients may be treated with a clopidogrel loading dose just before or immediately after the PCI, with the expectation of a similar risk of ischemic complications but a lower risk of bleeding compared with the risk of bleeding in patients treated with a GP IIb/IIIa antagonist.

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Key Words: clopidogrel ■ acute coronary syndromes ■ anticoagulants ■ percutaneous coronary intervention ■ bivalirudin.