Attenuation of Rebound Ischemia After Discontinuation of Heparin Therapy by Glycoprotein IIb/IIIa Inhibition With Eptifibatide in Patients With Acute Coronary Syndromes
Observations From the Platelet IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) Trial

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Background—A reactivation of ischemia after the discontinuation of intravenous heparin in acute coronary syndromes has been described. The effect of glycoprotein IIb/IIIa blockade on heparin rebound is unknown.

Methods and Results—Patients with acute coronary syndromes who received heparin therapy but not initial revascularization in the Platelet IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) trial were analyzed. Rates of death or myocardial (re)infarction while on heparin therapy and in 12-hour periods in the 2 days after heparin discontinuation were compared between eptifibatide and placebo. There was no difference between study groups in event rates during heparin infusion. In the 12 hours after heparin discontinuation, there was a 2.5-fold increase in all events, an 8-fold increase in death, and a 2-fold increase in myocardial infarction. However, in the 12 hours after heparin discontinuation, there was a significantly lower rate of events (1.68% versus 2.53%, P<0.03) and death (0.77% versus 0.21%, P=0.002) in the eptifibatide group compared with the placebo group. When only considering patients who were on study drug at the time of heparin discontinuation, the reduction in the combined end point was marginally significant, but the difference in the rate of death remained significant (0.68% versus 0.06%, P=0.004). In logistic regression analyses, the multivariate predictors of rebound events were the duration of heparin therapy, age, North American site, and lack of eptifibatide treatment.

Conclusions—An increase in death or myocardial infarction occurs in the 12 hours after heparin discontinuation in patients with acute coronary syndromes. This rebound is attenuated by glycoprotein IIb/IIIa inhibition with eptifibatide. (Circulation. 2001;104:2772-2777.)

Key Words: heparin ■ ischemia ■ glycoproteins ■ platelets ■ mortality

A reactivation of unstable angina after the discontinuation of intravenous heparin therapy has been described in patients with acute coronary syndromes.1–4 In the original observation by Théroux et al.,1 the rebound in ischemic events was ameliorated by the concomitant administration of aspirin. Clustering of events in the hours after heparin discontinuation was noted despite the consistent use of aspirin in patients with ST-segment elevation myocardial infarction (MI) in the Global Utilization of Streptokinase and Tissue plasminogen activator for Ocluded coronary arteries (GUSTO)-I;1 and those with non–ST-segment elevation acute coronary syndromes in the GUSTO-II;1 and the Efficacy and Safety of Subcutaneous Enoxaparin in Non–Q-wave Coronary Events (ESSENCE)3 trials. The effect of platelet inhibition by glycoprotein IIb/IIIa blockade on heparin rebound has not been reported. Therefore, it was our goal to confirm that an increase in death or MI in the hours after heparin discontinuation occurs in patients with acute coronary syndromes and to determine whether this rebound ischemia may be attenuated by glycoprotein IIb/IIIa inhibition with eptifibatide. To test this hypothesis, data from the Platelet IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) trial of eptifibatide versus placebo were analyzed.

Methods

Patient Selection
The PURSUIT trial enrolled 10 948 patients who presented within 24 hours of symptoms of ischemia at rest accompanied by ST-
segment depression, transient ST elevation, T-wave inversion, or a creatine kinase-MB level above the upper limit of normal. The study was approved by the institutional review committee at each site, and all subjects gave informed consent. Patients were randomized in a double-blind manner to receive either intravenous eptifibatide or placebo. High-dose eptifibatide was administered as a 180 µg/kg bolus followed by a 2.0 µg · kg⁻¹ · min⁻¹ infusion that was continued up to the time of hospital discharge or 72 hours, whichever came first. Enrollment in a low-dose eptifibatide group was stopped as planned when the Data and Safety Monitoring Committee determined that the high-dose regimen had an acceptable safety profile. This low-dose eptifibatide group was excluded from both the main study and present analyses.

All patients received aspirin (80 to 325 mg per day) at the discretion of the treating physicians. Patients who were allergic to or intolerant of aspirin received ticlopidine. Intravenous or subcutaneous heparin was recommended. Intravenous heparin was to be given as a bolus dose of 5000 U, followed by an infusion at a rate of 1000 U/hr, with the activated partial-thromboplastin time (aPTT) maintained in the range of 50 to 70 seconds. For patients weighing <70 kg, lower doses were recommended.

Patients who did not receive intravenous heparin were excluded from the analysis, as were all patients who underwent revascularization during the initial hospitalization due to the confounding effects of procedural complications and intraprocedural heparin boluses.

End Point Definition
The primary end point of the trial was a composite of death from any cause or nonfatal myocardial (re)infarction at 30 days. The end point for the current analysis was death or MI occurring either during heparin infusion or in the 48 hours after heparin discontinuation. Suspected infarctions were evaluated by a blinded clinical events committee.

MI within 18 hours after enrollment was diagnosed by ischemic chest pain lasting 30 minutes associated with new ST-segment elevation in at least 2 contiguous leads. After 18 hours, MI was diagnosed by a new elevation of the creatine kinase-MB fraction above the upper limit of normal (or the total creatine kinase concentration >2 times the upper limit of normal if creatine kinase-MB values were unavailable) or by new Q-waves in 2 electrocardiographic leads.

Secondary end points included all-cause mortality or a first or recurrent MI while on heparin therapy or in the 48 hours after its discontinuation. Repeated analysis was performed excluding patients in whom eptifibatide or placebo was discontinued before heparin discontinuation.

Statistical Analysis
Baseline characteristics were summarized for categorical variables with frequencies and percentages and for continuous factors with medians and interquartile ranges. Frequency data were analyzed using χ² tests, and median values were compared using Wilcoxon analysis. Events were categorized as occurring during heparin therapy or as during 1 of 4 12-hour periods after its discontinuation. The events on heparin therapy were divided by the mean number of hours of therapy for the group and multiplied by 12 to normalize the number of events to a 12-hour period for comparison purposes. Differences in event rates between eptifibatide and placebo were determined by χ² analysis for each 12-hour period. Similar analyses were performed for 6-hour periods. Univariate and multivariate logistic regression analyses were performed to determine predictors of rebound ischemic events occurring in the 12 hours after heparin discontinuation. All statistical tests were 2-tailed, with a significance level of 0.05.

Results
Baseline Characteristics
The sample size for this study was 6186 after defined exclusions, with 3068 patients in the placebo group and 3118 in the eptifibatide group. Baseline characteristics of patients are listed in Table 1. The 2 treatment groups were evenly matched in age and in the percentage of patients with a history of diabetes, hypertension, or prior MI. The placebo group had a higher percentage of female patients and a lower percentage of current smokers. In terms of clinical presentation, there was more frequent angina during the 6 weeks before the qualifying episode in the placebo group, particularly for postinfarct angina. Patients randomized to placebo were also more likely to have ST-segment depression as the qualifying ECG abnormality, as opposed to transient ST-segment elevation or T-wave inversion. The percentages of patients who received aspirin were similar between the groups at presentation and during infusion. The 2 groups were similar in terms of the duration of heparin therapy, with a median of 78 hours in the placebo group and 75 hours in the eptifibatide group.

Event Rates for All Patients in Relation to Heparin Infusion
The rates of death or MI that occurred during heparin infusion and in 12-hour periods of time after heparin discontinuation are shown in Figure 1A. There was no difference in the event rate during heparin infusion between patients in the eptifibatide group (0.82% per 12 hours) compared with the placebo group (0.90% per 12 hours). In both groups, the event rate in the period 0 to 12 hours after heparin discontinuation was more than twice the rate while on heparin. The event rate in the 0 to 12 hour period was significantly lower in the eptifibatide group (1.68%) compared with the placebo group (2.53%, P=0.03). The event rate in both groups returned to the on-heparin rate in the 12- to 24-hour period and to below the on-heparin rate in the 24- to 36- and 36- to 48-hour periods.

The rate of death rose from 0.09% while on heparin to 0.77% in the 0- to 12-hour period with placebo; with
epitifibatide, the rate rose to only 0.21% in the 0- to 12-hour period after heparin from the on-heparin rate of 0.04%. (Figure 1B). The difference in death rates between the placebo group and the epitifibatide group 0 to 12 hours after heparin discontinuation was statistically significant ($P = 0.002$). There were no significant differences in the rates of death between placebo and epitifibatide during any other 12-hour period.

Analyses performed using 6-hour periods rather than 12-hour periods showed that the event rates were similar in the periods 0 to 6 hours and 6 to 12 hours after heparin discontinuation (data not shown). The smaller number of events in these shorter periods of time reduced the statistical significance of the differences.

Event Rates in Patients on Study Drug at Heparin Discontinuation

After excluding patients for whom study drug was discontinued before heparin discontinuation, there remained 1651 patients in the epitifibatide group and 1536 patients in the placebo group. In this subset, similar but more marked changes were observed. There was an increase in death or MI in the placebo group from 0.77% while on heparin to 1.62% in the 0 to 12 hour period (Figure 2A). There was only a small increase in death or MI in the epitifibatide group, from 0.63% while on heparin to 0.94% in the 0 to 12 hour period. The difference in event rates between the placebo and epitifibatide groups in the 0- to 12-hour period was of borderline significance ($P = 0.09$).

When considering only those patients on study drug treatment at the time of heparin withdrawal, the reduction in death was marked. In the placebo group, the rate of death rose from 0.13% while on heparin to 0.68% in the 0 to 12 hour period, but there was only a minimal increase in the death rate in the epitifibatide group, from 0.04% while on heparin to 0.06% in the 0 to 12 hour period (Figure 2B). The difference in death rates between the placebo group (0.68%) and the epitifibatide group (0.06%) was statistically significant ($P = 0.004$). In this subset, the small rise in the rate of MI, from 0.64% to 0.95%, in the placebo group was not reduced in the epitifibatide group (0.59% while on heparin to 0.87% in the 0 to 12 hour period; Figure 2C).

Regression Analysis

The univariate predictors of death or MI in all patients in the 12 hours after heparin withdrawal according to logistic regression analysis included heparin duration, age, higher peak aPTT, and North American as opposed to European site (Table 2). Treatment with epitifibatide was associated with a lower risk of events. None of the variables relating to prior symptoms or qualifying electrocardiographic characteristics were predictive of rebound events.

In the multivariate analysis, duration of heparin therapy, age, and North American site remained significant predictors of rebound events (Table 3). Treatment with epitifibatide remained associated with a lower risk of death or MI.

Discussion

This study supports the presence of a rebound in ischemic events after the discontinuation of heparin therapy in patients with acute coronary syndromes. In this study of 6186 such patients treated with intravenous heparin but not initially undergoing revascularization, an 8-fold increase in death and a 2-fold increase in MI in the placebo group led to a 2.5-fold increase in the combined end point in the 12 hours immedi-
After heparin discontinuation. The event rates returned toward on-heparin rates at 12 to 24 hours and were at or below on-heparin rates at 24 to 48 hours.

This is the first report of the effect of glycoprotein IIb/IIIa inhibition on post-heparin rebound ischemia. We found that intravenous eptifibatide administered as a 180 µg/kg bolus followed by a 2.0 µg·kg⁻¹·min⁻¹ infusion continued up to 72 hours or hospital discharge attenuated rebound ischemic events. There was a 34% reduction with eptifibatide in the combined end point of death and non-fatal infarction in the first 12 hours after heparin discontinuation (1.68% versus 2.53%, P<0.03) and a 79% reduction in death (0.21% versus 0.77%, P<0.002) during the same period. Nevertheless, there was a residual increase in death and the combined end point in the entire eptifibatide group in this time period.

Because the inhibition of platelet aggregation by eptifibatide is decreased to <50% by 4 hours after it is stopped, it would be reasonable to assume that the infusion of eptifibatide should be ongoing at the time of heparin discontinuation and perhaps even longer to prevent events that tend to occur up to 12 hours later. Indeed, when the analysis was limited to patients on study drug at the time of heparin cessation, eptifibatide seemed to reduce the incidence of death and the combined end point of death or MI to essentially baseline levels. There was a 91% reduction in the rate of death in the eptifibatide group compared with placebo (0.68% versus 0.06%), such that the rebound in death after heparin discontinuation was essentially eliminated. The reduction of death remained statistically significant even in this small subset of patients.

A reactivation of unstable angina after the discontinuation of intravenous heparin was first described by Théroux et al in patients with unstable angina randomized to aspirin versus placebo and to intravenous heparin versus placebo. Both therapies were continued until catheterization at day 6 and then stopped. At the end of 6 days, the incidence of death, MI, or recurrent angina was reduced in the aspirin/heparin and heparin-only groups compared with the aspirin-only group.

TABLE 2. Univariate Predictors of Death or MI in the 12 Hours After Heparin Withdrawal in All Patients

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eptifibatide therapy</td>
<td>0.66</td>
<td>0.46–0.95</td>
</tr>
<tr>
<td>Heparin duration (per hour)</td>
<td>1.003</td>
<td>1.001–1.005</td>
</tr>
<tr>
<td>Age (per year)</td>
<td>1.02</td>
<td>1.004–1.040</td>
</tr>
<tr>
<td>Peak aPTT</td>
<td>1.10</td>
<td>1.002–1.210</td>
</tr>
<tr>
<td>North American site</td>
<td>2.77</td>
<td>1.89–4.07</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.16</td>
<td>0.80–1.71</td>
</tr>
<tr>
<td>Diabetes, insulin-treated</td>
<td>0.59</td>
<td>0.24–1.45</td>
</tr>
<tr>
<td>Current smokers</td>
<td>0.93</td>
<td>0.62–1.40</td>
</tr>
<tr>
<td>Prior MI</td>
<td>1.33</td>
<td>0.92–1.92</td>
</tr>
<tr>
<td>History of CHF</td>
<td>1.41</td>
<td>0.67–1.94</td>
</tr>
<tr>
<td>Angina in prior 6 wk</td>
<td>1.29</td>
<td>0.79–2.11</td>
</tr>
<tr>
<td>Rest pain in prior 6 wk</td>
<td>1.23</td>
<td>0.74–2.07</td>
</tr>
<tr>
<td>Postinfarct angina</td>
<td>2.27</td>
<td>0.76–6.81</td>
</tr>
<tr>
<td>ST-segment depression</td>
<td>1.22</td>
<td>0.83–1.81</td>
</tr>
<tr>
<td>Transient ST-segment elevation</td>
<td>1.06</td>
<td>0.64–1.78</td>
</tr>
<tr>
<td>T-wave inversion</td>
<td>0.96</td>
<td>0.65–1.42</td>
</tr>
</tbody>
</table>

TABLE 3. Multivariate Predictors of Death or MI in All Patients in the 12 Hours After Heparin Withdrawal

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>P (χ²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eptifibatide therapy</td>
<td>0.66</td>
<td>0.45–0.96</td>
<td>0.03</td>
</tr>
<tr>
<td>Heparin duration (per hr)</td>
<td>1.004</td>
<td>1.002–1.005</td>
<td>0.0001</td>
</tr>
<tr>
<td>Age (per year)</td>
<td>1.02</td>
<td>1.002–1.037</td>
<td>0.03</td>
</tr>
<tr>
<td>Peak aPTT</td>
<td>1.10</td>
<td>0.99–1.22</td>
<td>0.07</td>
</tr>
<tr>
<td>North American site</td>
<td>3.30</td>
<td>2.20–4.95</td>
<td>0.0001</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.31</td>
<td>0.88–1.96</td>
<td>0.16</td>
</tr>
</tbody>
</table>
which had an event rate lower than the double-placebo group. In the day after treatment discontinuation, however, there was a sharp increase in events in the heparin-only group, with a clustering of events 9 to 10 hours after heparin cessation, such that all advantage over the aspirin-only group was lost. There was a persistent protection from rebound events in the group that received both heparin and aspirin.1

The existence of ischemic rebound was also observed in the GUSTO trial of thrombolytic strategies in patients with ST-segment elevation. In this trial, it was noted that there was a clustering of reinfarctions in the 10 hours after heparin discontinuation, with a peak incidence at 2 to 4 hours. These reinfarctions were associated with a higher aPTT and occurred despite the constant use of aspirin.2

An analysis of patients with non-ST-segment elevation acute coronary syndromes in the GUSTO IIb trial demonstrated a clustering of MI or re-MI in the first 12 hours after heparin discontinuation, with the greatest risk during the first 8 hours.4 Such an early clustering was not observed in the patients receiving hirudin.

A 174-patient, ST-segment monitoring substudy of the ESSENCE trial showed that patients with rest angina receiving low-molecular-weight enoxaparin were less likely than patients receiving unfractionated heparin to experience ST-segment deviation in the 48 hours after study drug discontinuation. There was definite rebound in those patients treated with unfractionated heparin, because ischemia was more frequent in the 48 hours after discontinuation than in the initial 48 hours of treatment. Although there was no such increase in ischemia in the enoxaparin group, complete attenuation of rebound could not be determined, because there was no ST-segment recording in the period immediately before study drug discontinuation if heparin duration was >48 hours.5

It is interesting that eptifibatide treatment seemed to have a greater effect on reducing the incidence of death than on the rate of nonfatal MI. It is plausible that some of the deaths that are prevented with eptifibatide represent patients who still experienced a recurrent ischemic event. If the number of patients converted from a fatal to a nonfatal infarction was similar to the number of nonfatal infarctions avoided, the net effect on the infarction rate would be neutral.

In Théroux et al’s original observation, the rebound in ischemic events was ameliorated by the concomitant administration of aspirin. In the GUSTO-I, ESSENCE, and GUSTO-II trials and in the present analysis, however, rebound ischemia was noted despite the consistent use of aspirin.2–4 Perhaps the reason that aspirin therapy ameliorated the rebound events in the original report is that aspirin was given at a dose of 325 mg twice daily, as opposed to the once-daily dosing used in other trials, although other studies have not confirmed such a dose response.

A possible mechanism underlying the interaction between heparin rebound and antiplatelet therapy is offered by a study showing that platelet activation and aggregation is increased during therapy with heparin. It is possible that this platelet activation effect of heparin may outlive its therapeutic anticoagulant effect.6

A substudy of hemostatic markers in the GUSTO-IIb trial showed that thrombin activity is suppressed during heparin therapy but rises above baseline levels by 6 hours after discontinuation. Thrombin generation remained stable relative to baseline during the heparin infusion, but it also increased 6 hours after heparin discontinuation. An increase in thrombin generation and activity after therapy discontinuation was also observed in the hirudin group, but the increase was of lesser magnitude and more delayed. These laboratory findings correlate well with the timing of clinical events in the 2 treatment groups. These findings suggest that the accumulation of prothrombotic factors during antithrombin therapy leads to a relative hypercoagulable state after drug withdrawal.7

One of the strongest predictors of rebound events in the multivariate analysis was prolonged duration of heparin infusion. Because the infusion of eptifibatide was limited to 72 hours and the mean heparin infusion duration was >94 hours, a long heparin infusion may simply be a surrogate for heparin discontinuation without the protective effects of eptifibatide. Alternatively, prolonged heparin duration may cause more pronounced platelet activation or buildup of thrombin or identify a subset of patients with more unstable symptoms requiring prolonged heparin therapy. A prior study, however, found that the increase in thrombin generation and activation seen after heparin discontinuation was not associated with duration of heparin therapy,8 which argues against this as a mechanism for the observed risk of prolonged therapy in our study. A repeat multivariate analysis in our population limited to those who were on study drug at the time of heparin withdrawal (data not shown) showed that prolonged heparin infusion actually provided a protective effect. This finding supports the theory that the risk of prolonged heparin infusion in the overall population is due to heparin therapy that extends beyond the protective period of eptifibatide therapy.

A higher peak aPTT also seemed to confer an additional risk of experiencing rebound ischemia in the univariate analysis, but it did not remain a significant predictor of risk in the multivariate analysis. In several trials of direct thrombin inhibitors, there has been a correlation between higher doses and higher rates of rebound events.9–10 In the GUSTO-I trial, patients experiencing rebound ischemic events had higher aPTT levels during heparin infusion than those who did not experience an event.2

In the multivariate analysis, patients from North America were more likely to experience a rebound event than those from Europe (odds ratio, 3.28; 95% confidence interval, 2.20 to 4.94). This is consistent with the finding in the entire PURSUIT cohort that the observed treatment effect varied among geographic regions, with the greatest benefit observed in North America; this can be explained by differences in patient characteristics and management.11 There was no difference in the peak aPTT ratio between patients from North America and Europe. Similar variations in outcome have been observed in other large international trials of cardiovascular therapy.12

This analysis is limited by virtue of being a subset analysis that was not predefined at the time of study design and by the
fact that heparin was not controlled as part of the protocol. The analysis is further limited by the baseline imbalances in treatment groups, although the regression analysis should adjust, in part, for this effect. Finally, it is difficult to analyze the necessity of therapy overlap because of the small numbers of events when the sample is limited to examine this issue.

In conclusion, this study offers further evidence that an increase in death or MI in the 12 hours after heparin discontinuation occurs in patients with acute coronary syndromes. Furthermore, this rebound seems to be attenuated by glycoprotein IIb/IIIa inhibition with eptifibatide. These findings are relevant to the therapy of patients with unstable coronary syndromes and suggest that the timing of antithrombin and IIb/IIIa inhibition therapy should be studied further.

References
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