Point-of-Care Measured Platelet Inhibition Correlates With a Reduced Risk of an Adverse Cardiac Event After Percutaneous Coronary Intervention

Results of the GOLD (AU-Assessing Ultegra) Multicenter Study

Steven R. Steinhubl, MD; J. David Talley, MD; Gregory A. Braden, MD; James E. Tcheng, MD; Peter J. Casterella, MD; David J. Moliterno, MD; Frank I. Navetta, MD; Peter B. Berger, MD; Jeffrey J. Popma, MD; George Dangas, MD; Richard Gallo, MD; David C. Sane, MD; Jorge F. Saucedo, MD; Gang Jia, MA; A. Michael Lincoff, MD; Pierre Theroux, MD; David R. Holmes, MD; Paul S. Teirstein, MD; Dean J. Kereiakes, MD

Background—The optimal level of platelet inhibition with a glycoprotein (GP) IIb/IIIa antagonist necessary to minimize thrombotic complications in patients undergoing a percutaneous coronary intervention (PCI) is currently unknown.

Methods and Results—Five hundred patients undergoing a PCI with the planned use of a GP IIb/IIIa inhibitor had platelet inhibition measured at 10 minutes, 1 hour, 8 hours, and 24 hours after the initiation of therapy with the Ultegra Rapid Platelet Function Assay (Accumetrics). Major adverse cardiac events (MACEs: composite of death, myocardial infarction, and urgent target vessel revascularization) were prospectively monitored, and the incidence correlated with the measured level of platelet function inhibition at all time points. One quarter of all patients did not achieve ≥95% inhibition 10 minutes after the bolus and experienced a significantly higher incidence of MACEs (14.4% versus 6.4%, P = 0.006). Patients whose platelet function was <70% inhibited at 8 hours after the start of therapy had a MACE rate of 25% versus 8.1% for those ≥70% inhibited (P = 0.009). By multivariate analysis, platelet function inhibition ≥95% at 10 minutes after the start of therapy was associated with a significant decrease in the incidence of a MACE (odds ratio 0.46, 95% CI 0.22 to 0.96, P = 0.04).

Conclusions—Substantial variability in the level of platelet function inhibition is achieved with GP IIb/IIIa antagonist therapy among patients undergoing PCI. The level of platelet function inhibition as measured by a point-of-care assay is an independent predictor for the risk of MACEs after PCI. (Circulation. 2001;103:2572-2578.)

Key Words: angioplasty ■ platelets ■ complications

Early animal models evaluating platelet glycoprotein (GP) IIb/IIIa inhibitors demonstrated a clear dose-response relationship with these agents. On the basis of these studies, initial dose-finding trials in humans attempted to identify the appropriate dosing regimen necessary to achieve and maintain ≥80% receptor blockade, or <20% of baseline ADP-induced platelet aggregation. Because of the technical constraints of receptor-binding assays and standard turbidimetric platelet aggregometry, however, these studies were limited to only a small number of patients.

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Although in large populations of patients, treatment with GP IIb/IIIa inhibitors is clearly beneficial, it is unknown whether all patients achieve similar levels of platelet inhibition with currently recommended dosing regimens and what level of platelet inhibition optimizes efficacy and safety. The recent development of a rapid, whole-blood, point-of-care platelet function assay, the Ultegra Rapid Platelet Function Assay (RPFA) (Accumetrics, Inc), whose results correlate well with turbidimetric aggregometry and receptor-binding...
Clinical End Points

The primary clinical end point was major adverse cardiac events (MACEs: death, MI, or urgent target vessel revascularization) occurring either in hospital or within 7 days of the PCI. MIs were identified as Q-wave if new pathological Q waves developed after the procedure or as non-Q-wave if there were no new Q waves but a new elevation in creatine kinase (CK) or CK-MB ≥3 times the laboratory’s upper limit of normal, and a ≥50% increase over the baseline. Myocardial enzyme elevations were systematically monitored 8, 16, and 24 hours after the procedure. The diagnosis of MI was determined by the site investigators and through blinded adjudication of myocardial enzyme elevations by 2 of the authors (S.R.S. and G.J.). To be eligible for evaluation, patients had to have had a baseline and 2 of 3 post-PCI CK and CK-MB determinations. To be considered an urgent target vessel revascularization, a repeat PCI or coronary artery bypass surgery had to be initiated within 24 hours of an episode of objective myocardial ischemia and had to occur after completion of the index procedure and guidewire removal.

The definition of a bleeding complication was not prespecified in the study protocol, but site investigators were asked to identify on the case report form any patient with a bleeding complication.

Statistical Analysis

The following patients were considered nonevaluable and were excluded from statistical analysis: patients with no baseline PAU, patients with a baseline PAU <50 (previous studies found the lower limit of normal PAUs among cardiac patients to be 120), patients who received their GP IIb/IIIa bolus before baseline sample collection, and patients who did not undergo a PCI. All other patients were included in all statistical analyses. The definition of “evaluable patients” was decided before any data analysis occurred.

All continuous variables are reported as means with SD if their distributions are normal, or medians with 25th and 75th percentiles otherwise. The Shapiro-Wilk statistics are used to test normality. Discrete variables are expressed as frequencies and/or percentages. Group comparisons between patient subsets use 2-sample t tests for normally distributed variables, Wilcoxon rank sum tests for other continuous variables, and χ² tests for discrete variables. This protocol was designed as a preliminary investigation and was not powered to achieve statistical significance with regard to patient subset comparisons. Probability values of 0.05 were considered statistically significant, and no adjustment for multiple comparisons was made.

Generalized additive models (GAMs) were used to describe the relationship between risk of MACEs and percent platelet function inhibition. Spline smoothing methods were used in GAM. GAM also served as the guide to deciding the cut point of platelet inhibition, along with the classification tree method.

All demographic factors, medical histories, and lesion/procedure information collected in the case report form were screened in building the multivariate logistic models. Stepwise selection methods and 0.05 significance level criteria were used to decide the final models.

All statistical analyses were performed with SAS software.

Results

A total of 503 patients were enrolled who met all inclusion and exclusion criteria, and 498 underwent their planned PCI with the use of a GP IIb/IIIa inhibitor. Thirteen patients were not considered evaluable because the baseline platelet function study either was not drawn or was drawn after the GP IIb/IIIa infusion had been started. Therefore, a total of 485 patients were evaluated for the primary end point. Their baseline characteristics are shown in Table 1. The site investigator determined clinical diagnosis.

The majority of patients (84%) received abciximab, with 9% receiving tirofiban and 7% epifibatide. All patients treated with abciximab received a 0.25-mg/kg bolus followed...
by a 0.125-μg · kg⁻¹ · min⁻¹ infusion (maximum of 10 μg/min), with a mean duration of infusion of 12.±1.8 hours. Tirofiban-treated patients all received the bolus and infusion rate evaluated in the Randomized Efficacy Study of Tirofiban for Outcomes and Restenosis (RESTORE) trial—a 10-μg/kg bolus followed by a 0.15-μg · kg⁻¹ · min⁻¹ infusion. The mean duration of infusion in this cohort was 12.8±5.4 hours. The eptifibatide bolus dose and infusion rate were as in the Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) trial, with a 180-μg/kg bolus followed by a 2-μg · kg⁻¹ · min⁻¹ infusion with a mean infusion time of 19.4±5.5 hours. Eighty-two percent of patients received a stent, and 46% underwent multivessel intervention. The procedure was successful in all but 2 patients. All patients received unfractionated heparin during the procedure, with a mean activated coagulation time of 258±54 seconds. After the procedure, 275 patients (59%) were started on clopidogrel and 108 patients (23%) began ticlopidine.

A total of 42 patients (8.9%) experienced an in-hospital MACE within 7 days of the PCI. There were 3 deaths: 1 due to a large recurrent MI ±20 hours after the procedure, 1 due to multiorgan failure several days after the procedure not believed to be directly related to the PCI, and 1 due to pericardial tamponade secondary to wire-tip perforation. There was 1 urgent surgical revascularization due to an unsuccessful PCI. There were no Q-wave MIs, but there were 38 non–Q-wave MIs. Twenty-two (58%) of the non–Q-wave MIs were considered large, with CK or CK-MB elevations ≥5 times normal. Site investigators identified 12 patients (2.5%) as having a bleeding complication.

**Platelet Inhibition**

Ten minutes after the bolus dose of a GP IIb/IIIa antagonist, the mean level of platelet inhibition was 96±9%. At 1 hour after the bolus, while patients were still receiving an infusion of the drug, the mean level of inhibition was 95±8%. At 8 hours after starting therapy, the mean level of inhibition for

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**TABLE 1. Baseline Patient Characteristics of Evaluable Patients**

| Characteristic               | n   | Female sex | 26   | Age >65 y | 47   | Diabetes mellitus | 29   | LVEF <45% | 17*   | Hypertension | 66   | Current smoker | 24   | Previous CABG | 23   | Previous MI | 29   | Previous GP IIb/IIIa therapy | 16   | Recent MI (>3, <7 d) | 7    | Unstable angina | 55   | Preprocedure heparin | 26   |
|-----------------------------|-----|------------|------|-----------|------|-------------------|------|------------|------|-------------|------|------------------|------|--------------|------|-------------|------|------------------|------|------------------|------|-------------------|------|

Values are percentages.

*Left ventricular ejection fraction (LVEF) known in 350 patients.

**TABLE 2. Platelet Inhibition for the Individual GP IIb/IIIa Antagonists**

<table>
<thead>
<tr>
<th>Antagonist</th>
<th>10 Minutes</th>
<th>1 Hour</th>
<th>8 Hours</th>
<th>24 Hours</th>
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</thead>
<tbody>
<tr>
<td>Abciximab</td>
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<td>96±7</td>
<td>90±11†</td>
<td>75±14</td>
</tr>
<tr>
<td>Tirofiban</td>
<td>97±5</td>
<td>95±6</td>
<td>93±16</td>
<td>47±40‡</td>
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<tr>
<td>Eptifibatide</td>
<td>90±9*</td>
<td>89±9*</td>
<td>93±6</td>
<td>77±21</td>
</tr>
</tbody>
</table>

Values are percent, mean±SD.

*P<0.001 for eptifibatide vs abciximab or tirofiban.

†P<0.001 for abciximab vs eptifibatide or tirofiban.

‡P<0.001 for tirofiban vs abciximab and eptifibatide.

**TABLE 3. Relationship Between Clinical, Hematologic, and Procedural Characteristics and Level of Platelet Inhibition**

<table>
<thead>
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<th>Characteristic</th>
<th>n</th>
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<th>24 Hours</th>
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</tbody>
</table>

*P<0.05 by nonparametric testing.

†P<0.05 vs patients with stable angina by nonparametric testing.
those patients still receiving a GP IIb/IIIa antagonist infusion had decreased to 91±11%. At 24 hours after the start of therapy, mean inhibition had decreased to 73±20%, with wide variability at least partially influenced by variation in sampling times and infusion durations. The mean level of platelet inhibition at the various time points did vary based on the antagonist used (Table 2).

All clinical, hematologic, and procedural data were evaluated for their relationship to the level of inhibition at the sampled time points. By nonparametric testing, a number of variables were found to be associated with a significant difference in the degree of platelet inhibition at various time points during and after the GP IIb/IIIa inhibitor treatment (Table 3).

Platelet Inhibition and the Incidence of MACEs

Those patients in the lowest quartile of platelet function inhibition (<95%) at 10 minutes after the GP IIb/IIIa antagonist bolus had a 14.4% incidence of in-hospital MACEs, whereas patients whose platelet function was inhibited ≥95% had an incidence of 6.4% (P=0.006) (Figure 1A). When the percent platelet function inhibition was plotted as a continuous relationship with the probability of MACEs, the greatest risk was seen in those between 85% and 95% inhibition (Figure 1B). With the data obtained 1 hour after the bolus dose, no significant relationship was found between the level of inhibition and risk of an adverse cardiac event, although patients with <80% inhibition did experience the highest MACE rate (Figure 2). Data obtained 8 hours after the bolus dose showed a strong correlation between platelet function inhibition and the occurrence of MACEs (Figure 3A), with patients with <70% platelet function inhibition experiencing 3 times the event rate of those with ≥70% inhibition (25% versus 8.1%, P=0.009). When expressed as a continuous relationship, the probability of a MACE was found to increase with lower levels of platelet inhibition (Figure 3B). This general correlation appeared to be consistent between abciximab and the small-molecule GP IIb/IIIa inhibitors (Figure 3C). Those patients whose platelet function was ≥90% inhibited at 24 hours experienced the lowest event rate, 2.0%, compared with 9.7% for all others (P=0.13), but in contrast to the data obtained at 8 hours, there was no significant linear correlation of risk of MACEs with lower levels of platelet function inhibition (Figure 4).

By multivariate logistic modeling, when evaluated individually, the levels of inhibition achieved at 10 minutes and at 8 hours after the GP IIb/IIIa inhibitor bolus were found to correlate with the probability of MACEs (Table 4). A low level of inhibition at 8 hours was associated with a low level of inhibition at 10 minutes postbolus, with 58% of those with <70% inhibition at 8 hours also having <95% inhibition at 10 minutes (P<0.001). Therefore, when both time points were entered into the logistic model, percent inhibition at 10

Figure 1. Incidence of MACEs in relation to level of platelet function inhibition at 10 minutes after GP IIb/IIIa inhibitor bolus (A). Additive model demonstrating a continuous relationship between level of platelet function inhibition at 10 minutes and probability of MACEs (data for 8 patients with <80% inhibition of platelet function are not shown) (B).

Figure 2. Incidence of MACEs in relation to level of platelet function inhibition at 1 hour after GP IIb/IIIa inhibitor bolus, but while infusion continued.
minutes remained statistically significant, whereas 8-hour inhibition was of only borderline significance.

Patients identified as having a bleeding complication did not have greater levels of platelet inhibition than patients without bleeding complications at all time points.

**Discussion**

This is the first study to demonstrate that the level of platelet inhibition achieved with currently used, weight-adjusted GP IIb/IIIa antagonists in patients undergoing a PCI is significantly associated with the risk of experiencing a MACE. Our observations also reinforce the findings of previous smaller studies that used various techniques to analyze platelet function inhibition and found substantial interpatient variability in response to GP IIb/IIIa antagonist therapy.3–7,12

GP IIb/IIIa antagonists prevent thrombus formation in proportion to their blockade of the ~80 000 GP IIb/IIIa receptors present on the platelet surface.13 Early studies found that inhibition of > ~50% of the GP IIb/IIIa receptors was needed to detect significant inhibition of ADP-induced platelet aggregation, whereas blockade of ~80% of the receptors completely abolished ADP-induced platelet aggregation, suggesting a steep dose-response curve.14 Moreover, the GP IIb/IIIa receptor blockade necessary to produce an antithrombotic effect depended on the thrombotic challenge. Thus, in a monkey model of cyclic flow reductions due to platelet thrombus formation, the cyclic flow reductions could be abolished without complete inhibition of platelet aggregation and with ~80% GP IIb/IIIa receptor blockade.15 In contrast, ~80% receptor blockade, with nearly 100% inhibition of platelet aggregation, was necessary to prevent thrombotic reocclusion after thrombolysis in a dog model of coronary thrombosis.16 Which model best reflects the degree of local thrombogenicity in humans undergoing a PCI or experiencing an acute coronary syndrome is unknown.

Indirect evidence from several placebo-controlled trials of GP IIb/IIIa antagonists in PCI has suggested the importance of the level of platelet inhibition at 24 hours after GP IIb/IIIa inhibitor bolus, after completion of infusion.
of achieving and maintaining a specific level of platelet inhibition to minimize thrombotic complications. In the Evaluation of 7E3 for the Prevention of Ischemic Complications (EPIC) trial, patients undergoing a high-risk PCI were randomized to receive either a bolus and infusion of placebo, a bolus of abciximab and an infusion of placebo, or a bolus and infusion of abciximab. Patients receiving placebo started to need urgent interventions immediately after the initial PTCA, whereas patients receiving a bolus alone of abciximab were nearly completely protected for the first 4 to 6 hours (during which time receptor blockade was likely to be ≥80% in most patients), and patients treated with a bolus and 12-hour infusion of abciximab were protected from ischemic complications almost throughout the infusion period. At 30 days, patients who received a bolus and infusion of abciximab had almost a 33% reduction in ischemic events compared with those treated with a bolus alone. This benefit of a bolus and infusion of abciximab versus a bolus alone was maintained for ≥3 years.

The importance of achieving a high level of receptor blockade with eptifibatide at the time of a PCI is suggested by the discrepant results of 2 trials that used very different doses of this agent. In the Integrilin to Minimize Platelet Aggregation and Coronary Thrombosis (IMPACT-II) trial, randomization to a 135-μg/kg bolus and a 0.5-μg · kg⁻¹ · min⁻¹ infusion of eptifibatide at the time of PCI led to an 18% relative decrease in the composite end point compared with placebo (9.2% versus 11.4%, P=0.063). Later, this dosing regimen was found to produce only ≈50% receptor blockade. In the Enhanced Suppression of Platelet Receptor IIb/IIIa using Integrilin Therapy (ESPIRIT) trial, a much higher dose of eptifibatide was evaluated, with two 180-μg/kg boluses and a 2-μg · kg⁻¹ · min⁻¹ infusion. This higher dose was associated with almost a doubling of the relative benefit of eptifibatide treatment compared with placebo, with a 35% reduction in the 30-day composite clinical end point of death, MI, or urgent revascularization (6.8% versus 10.5%, P=0.0034).

The clinical importance of achieving a high level of platelet inhibition at the initiation of a PCI, as reflected by comparison of the IMPACT-II and ESPIRIT data, is confirmed in the present study by the significant increase in the incidence of MACEs among the nearly 25% of patients who did not achieve >95% platelet inhibition immediately after the GP IIb/IIIa inhibitor bolus. The significance of our finding showing a decreasing risk of MACEs if platelet function is inhibited <85% at 10 minutes is unclear. It probably represents a sampling aberrancy, because that portion of the curve is made up of <5% of the patient population, but its clinical importance cannot be completely discounted without further study.

The importance of maintaining >70% inhibition at 8 hours after the start of therapy shown in this study is consistent with the difference in outcomes found in the bolus alone versus the bolus plus 12-hour infusion treatment arms of the EPIC trial. It is unclear whether maintaining a high level of platelet inhibition during the infusion of a GP IIb/IIIa antagonist is protective against late thrombotic complications, or rather, whether a lower level of inhibition during the infusion is due to a more thrombogenic environment and greater systemic platelet activation and is therefore representative of a population of patients at higher risk for a thrombotic event. The present study highlights the fact that currently used dosing regimens do not ensure that optimal levels of platelet inhibition are achieved or maintained in a substantial number of patients undergoing a PCI.

Importantly, no clinical, procedural, or hematologic factors were clearly predictive of the level of platelet function inhibition achieved by GP IIb/IIIa antagonist therapy. Patients with angiographic thrombus, however, were found to have significantly lower levels of inhibition at all times. The significance of these differences is unclear, but they suggest that in the setting of a greater thrombogenic stimulus, more GP IIb/IIIa antagonist is necessary to achieve high levels of inhibition.

Study Limitations
A relatively small patient population and, therefore, a small number of outcome events limit this study. The overall MACE rate in our study (8.9%) is higher than what has been reported in the GP IIb/IIIa antagonist treatment arms of PCI trials, but it probably reflects a more diverse patient population and variety of procedural techniques. Also, as in previous trials, most adverse cardiac events were non-Q-wave MIs, although the majority of these were large.

Importantly, the results of this trial do not establish a cause-and-effect relationship and do not allow for the establishment of an algorithm for treatment in response to measured platelet function inhibition. Although a significant association was found between the level of platelet inhibition achieved with a GP IIb/IIIa antagonist in patients undergoing a PCI and the incidence of a MACE, whether titrating therapy to a specific level of inhibition will decrease this risk remains unknown. In addition, the inability to achieve and maintain a specific level of platelet inhibition may be a marker that identifies a subgroup of patients with a greater degree of platelet activation at baseline who may therefore be more prone to thrombotic complications.

Conclusions
The degree of inhibition of platelet function through treatment with a GP IIb/IIIa antagonist can be easily measured with a rapid, point-of-care assay and correlates with the risk of MACEs in patients undergoing a PCI. With a large proportion of patients in the United States now receiving a GP IIb/IIIa antagonist at the time of a PCI and an expanding population receiving them in the primary treatment of acute coronary syndromes, the results of this study could have substantial clinical implications for the future treatment of patients. Further evaluation with a dose-adjustment trial is needed to delineate the value of monitoring platelet function inhibition in patients treated with GP IIb/IIIa antagonists.

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References


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