Randomized Trial of an Oral Platelet Glycoprotein IIb/IIIa Antagonist, Sibrafiban, in Patients After an Acute Coronary Syndrome

Results of the TIMI 12 Trial

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Background—Inhibitors of the platelet glycoprotein IIb/IIIa receptor given intravenously have been shown to be effective in reducing ischemic complications after coronary angioplasty and in unstable angina, making this a promising new class of agents for the treatment and prevention of ischemic events in patients with acute coronary syndromes. Sibrafiban (Ro 48–3657) is an oral, peptidomimetic, selective antagonist of the glycoprotein IIb/IIIa receptor.

Methods and Results—The Thrombolysis in Myocardial Infarction (TIMI) 12 trial was a phase II, double-blind, dose-ranging trial designed to evaluate the pharmacokinetics (PK), pharmacodynamics (PD), safety, and tolerability of sibrafiban in 329 patients after acute coronary syndromes. In the PK/PD cohort of TIMI 12, 106 patients were randomized to receive one of seven dosing regimens of sibrafiban, ranging from 5 mg daily to 10 mg twice daily for 28 days. In the safety cohort, 223 patients were randomized to one of four dose regimens of sibrafiban (ranging from 5 mg twice daily to 15 mg once daily) or aspirin for 28 days. High levels of platelet inhibition were achieved: mean peak values ranged from 47% to 97% inhibition of 20 μmol/L ADP-induced platelet aggregation on day 28 across the seven doses. Twice-daily dosing provided more sustained platelet inhibition (mean inhibition, 36% to 86% on day 28), whereas platelet inhibition returned to baseline levels by 24 hours with once-daily dosing. Major hemorrhage occurred in 1.5% of patients treated with sibrafiban and in 1.9% of patients treated with aspirin. Protocol-defined “minor” bleeding, usually mucocutaneous, occurred in 0% to 32% of patients in the various sibrafiban groups and in none of the patients treated with aspirin. Minor bleeding was related to total daily dose (P=.002), once- versus twice-daily dosing (P<.0001), renal function (P<.0001), and presentation with unstable angina (P<.01).

Conclusions—The oral glycoprotein IIb/IIIa antagonist sibrafiban achieved effective, long-term platelet inhibition with a clear dose-response but at the expense of a relatively high incidence of minor bleeding. Oral IIb/IIIa inhibition deserves further study as a new treatment strategy in patients after acute coronary syndromes. (Circulation. 1998;97:340-349.)

Key Words: platelet aggregation inhibitors ▪ aspirin ▪ myocardial infarction ▪ angina

Antithrombotic therapy plays a major role in the prevention and acute treatment of ischemia in patients with acute coronary syndromes.1 Aspirin, despite being a relatively weak platelet inhibitor, has a dramatic effect in reducing death or (MI) in all acute ischemic syndromes.2 Antagonists of platelet surface glycoprotein IIb/IIIa receptors are more potent antplatelet agents that inhibit the final common pathway of platelet aggregation. Intravenous IIb/IIIa antagonists have been effective in reducing ischemic complications after angioplasty and in unstable angina.6–8 However, recent trials with 24- to 36-hour infusions of shorter-acting IIb/IIIa antagonists have shown early benefit in reducing ischemic complications after angioplasty but loss of benefit after the infusions were stopped.9,10 These data suggest a need for prolonged IIb/IIIa inhibition, which could potentially be obtained by oral administration. It has also been proposed that oral IIb/IIIa antagonists
may be useful as secondary prevention of death or recurrent ischemic events in patients with acute coronary syndromes. Sibrafiban (also known as Ro 48–3657 or G7333) is a peptidomimetic, selective antagonist of the platelet glycoprotein IIb/IIIa receptor. Sibrafiban is a double produg, which is converted in two enzymatic steps (by an esterase and by an amidoxime reductase) to the active compound Ro 44–3888. In Phase I studies in normal volunteers, sibrafiban was found to have 39% bioavailability and to achieve relatively predictable drug levels and degrees of platelet inhibition. The goals of the TIMI 12 trial, carried out in patients after acute coronary syndromes, were (1) to evaluate the tolerability and safety profile of different dosing regimens of sibrafiban, (2) to evaluate the PK and PD (ie, degree of inhibition of platelet aggregation and bleeding time) of sibrafiban, (3) to define doses that achieved different target ranges of inhibition of platelet aggregation (using 20 μmol/L ADP as an agonist) for >75% of the day; >50% inhibition (medium grade) and >80% inhibition (high grade), and (4) to observe the effects of sibrafiban on recurrent ischemic events in this initial cohort of patients. These two levels of inhibition were sought because the "high-grade" inhibition would be similar to that achieved by abciximab (ReoPro) and the "medium-grade" inhibition might be better tolerated.

Methods

Study Population

Between January 12 and August 2, 1996, patients were screened for enrollment at 46 hospitals (see the "Appendix"). Inclusion criteria for the trial were the onset of an acute coronary syndrome (unstable angina, non-Q-wave MI, or Q-wave MI) in the preceding 24 hours to 7 days. Patients were required to have documented evidence of coronary artery disease, defined as the presence of a positive creatine kinase-MB fraction or ECG changes (ST-segment deviation ≥0.5 mm or T-wave inversion in two or more leads or new left bundle-branch block) with the acute event; a history of prior MI; or a prior coronary angiogram demonstrating ≥70% stenosis. In addition, patients had to be stable for ≥24 hours after the initial event, ie, no ongoing ischemia, congestive heart failure, and not be receiving intravenous heparin. If cardiac catheterization and revascularization were planned, randomization took place after the procedure. Exclusion criteria were concomitant serious illness (active cancer or significant liver or renal disease with creatinine >1.5 mg/dL), history of cerebrovascular accident, transient ischemic attack or any central nervous system lesion, recent surgery or biopsy of a parenchymal organ within the preceding 30 days, documented peptic ulcer disease within the preceding month, past or present bleeding disorder or significant gastrointestinal bleeding within the preceding 12 months, poorly controlled hypertension, need for therapeutic anticoagulation (eg, deep venous thrombosis or atrial fibrillation), need for long-term daily nonsteroidal antiinflammatory drugs, positive pregnancy test, heavy alcohol use, coronary bypass surgery or coronary stent within 6 months, serum aspartate aminotransferase or alanine aminotransferase more than twice the upper limit of normal, thrombocytopenia (platelet count <140,000 per 1 μL), baseline prothrombin time international normalized ratio ≥1.4 or bleeding time ≥15 minutes, concurrent use of an investigational device or investigational drug within 5 half-lives of that drug, history of aspirin intolerance (safety study only), use of abciximab (ReoPro) or ticlopidine within 14 days (PK/PD study only), or previous participation in TIMI 12. Prior thrombolytic therapy or percutaneous coronary interventions were not exclusion criteria for the trial.

Trial Design

The trial consisted of two parts, a "PK/PD study" carried out at 18 hospitals and a "safety study" carried out at 46 hospitals, 6 of which also participated in the PK/PD portion of the study. The study protocol was reviewed and approved by each hospital's Institutional Review Board, and written informed consent was obtained from each patient before enrollment. In the PK/PD study, patients were randomized to one of seven doses of sibrafiban and underwent frequent testing of platelet aggregation. On the basis of these results, doses were selected for testing in a larger cohort of patients in the safety study, which included a concurrent aspirin control arm.

In the PK/PD study, patients were initially randomized to receive one of four doses of sibrafiban: 3 mg twice daily, 5 mg once daily, 5 mg twice daily, and 10 mg once daily. The results of the platelet inhibition achieved by each dose were reviewed on a minimum of seven patients by the Operations Committee to choose doses that achieved at least medium-grade platelet inhibition (>50% inhibition of ADP-induced platelet aggregation for >75% of the day). Doses that did not meet this criterion were dropped from further testing, and additional doses were added into the randomization scheme: 7 mg twice daily, 15 mg once daily, and 10 mg twice daily. From these doses, four were chosen for testing in the safety study: Patients were randomized to receive either aspirin or sibrafiban 5 mg twice daily, 7 mg twice daily, 15 mg once daily, or 10 mg twice daily. Patients received double-blind tablets containing either study drug at the specified dose or aspirin for 28 days.

Concomitant Therapy

Patients receiving sibrafiban did not receive concomitant aspirin. However, for patients in the PK/PD arm, a member of the Operations Committee reviewed the platelet aggregation results on each patient, and if there was <50% inhibition at peak on day 1 of the study, the patient was placed on concomitant aspirin therapy in addition to the study drug beginning usually on day 2.

If heparin was needed for the patient after enrollment, it was allowed, and the study drug was continued. If thrombolytic therapy or warfarin was needed, the patient was referred for coronary bypass surgery, the study drug was permanently discontinued. Other medications were used at the discretion of the treating physician.

Platelet Aggregation Studies

In the PK/PD study, platelet aggregation was assessed at each clinical center at baseline and 2, 4, 6, 9, and 24 hours after study drug initiation. When patients returned for follow-up on day 7, blood samples for determination of platelet aggregation and plasma drug concentration were drawn before the dose of study drug. Patients returned for testing on day 25 to 28, with timing of samples similar to that of day 1 with the addition of a 36-hour sample. All PK/PD centers used their clinical laboratory aggregometer. Platelet aggregation was measured in citrated platelet-rich plasma and was induced by two agonists: 20 μmol/L ADP (BioData Corp) and 25 μmol/L TRAP using the 14–amino acid form (SFLLRNH2, Genentech, Inc). Inhibition of platelet aggregation at a given time point was expressed as the maximal excursion (in millimeters) as a percent of the baseline (prerdug) excursion (in millimeters) subtracted from 100%. The platelet aggregation studies were conducted by the clinical laboratory at each site and overseen by the Core Platelet Aggregation Laboratory, both of which were blinded to the dose received and clinical events.

To ensure well-standardized results between centers, (1) a specific platelet aggregation protocol was developed for the study, (2) a clinical

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**Selected Abbreviations and Acronyms**

- MI = myocardial infarction
- OR = odds ratio
- PD = pharmacodynamics
- PK = pharmacokinetics
- TIMI = Thrombolysis in Myocardial Infarction
- TRAP = thrombolyis in Myocardial Infarction

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laboratory technician from each hospital attended a special platelet aggregation training session, and (3) each center carried out a validation study on plasma obtained from three normal volunteers, with an in vitro dose-response curve with the active form of the study drug. If a center differed widely from the mean standard curve, additional on-site training and further validation studies were carried out. The inter-hospital coefficient of variability for the IC50 (defined as the concentration at which there is 50% inhibition) was 29% for ADP and 20% for TRAP.

Other Blood Tests
Samples for PK analysis were drawn at the same times as the platelet aggregation samples and 1 and 12 hours after study drug initiation. One sample was drawn in a tube containing citrate (to measure the free concentration [not bound to glycoprotein IIb/IIIa] of Ro 44–3888) and one was drawn in EDTA (to measure total blood concentration of Ro 44–3888). Ro 44–3888 and its internal standard Ro 44–3888-d4, were isolated from human plasma by precipitating the proteins with trichloroacetic acid. The supernatant was injected into an automated solid-phase extraction system coupled to a high-pressure liquid chromatography system. The extracts were stored at ≤−20°C until analysis. Analysis was by LC/MS/MS by use of positive ion Turbo IonSpray with multiple reaction monitoring ion detection. This method was validated with a range of 1.00 ng/mL to 200 mg/mL. The samples were kept frozen at 70°C until analysis. Analysis was by LC/MS/MS by use of positive ion Turbo IonSpray with multiple reaction monitoring ion detection.

In addition, a complete blood count, including a platelet count and a chemistry panel, were performed at baseline, 24 hours, and days 7 and 28. IVy bleeding times determined with standard techniques were obtained at baseline, 24 hours (predose), and at day 28. Measurement of bleeding times was discontinued at 20 minutes. In the safety study, no platelet aggregation studies were performed, and a PK sample was drawn only a baseline, 6 hours, and days 7 and 28. Blood was obtained at baseline and days 7 and 28 for hematology and chemistry determination.

Follow-up
During hospitalization, patients were monitored for clinical and adverse events. The patient returned for a follow-up visit at 7 days and again at 28 days; the latter involved 24 hours of testing in the PK/PD study. In addition, telephone contact was made on days 14, 21, and 42.

End Points
The end points in the PK/PD study were the degree of inhibition of platelet aggregation, PK, and IVy bleeding times. The primary safety end point in this trial was major hemorrhage as defined by the standard TIMI criteria15–17: an intracranial hemorrhage or a clinically significant hemorrhage associated with a drop >5 g hemoglobin or >15% points in hematocrit, with each blood transfusion countng for 1 g hemoglobin or 3% hematocrit. Minor bleeding was defined as a clinically significant bleeding event that did not meet criteria for major hemorrhage but did meet the following criteria: any skin or mucosal bleed lasting >20 continuous minutes, gross hematuria, melena, or hematochezia (excluding spotting or blood streaking thought to be from hemorrhoids), a spontaneous bruise >5 cm in diameter, any drop in hemoglobin >3 g/dL or an absolute decrease in hematocrit of at least 9%, or other hemorrhage considered to be clinically equivalent to those above. Other adverse events were also recorded. The efficacy end point for this study, reported only for the randomized safety cohort, was a composite of death, MI, and recurrent ischemia (either with ST-T wave changes or leading to recvascularization) through day 42.

Statistical Considerations
A sample size of 15 patients per dose in the PK/PD study was selected on the basis of an estimated 15% variability in the results of the platelet aggregation studies. This sample size would allow testing differences in inhibition of platelet aggregation of ±1 SD between treatment groups with 80% power. The sample size chosen for the safety cohort was based on predicted bleeding rates between 2% and 25%.

It was prespecified that the efficacy and safety analyses would be carried out only on patients who started the study drug. A total of 329 patients were randomized into the trial. However, study drug was not administered to 6 patients for the following reasons: 3 patients were identified as having an exclusion criterion present after randomization, 1 patient withdrew consent, 1 developed dizziness and the investigator decided not to treat with study drug, and 1 patient did not have intravenous access for the blood sampling. Thus, the analyses were carried out on the 323 patients who were randomized and received double-blind study drug.

Continuous variables were compared with Student’s t test, and categorical variables were compared with χ² analysis. A multiple logistic regression analysis for predictors of major or minor hemorrhage was performed, which included the sibrafiban dose and other clinical variables.

Results
Patient Population
Baseline characteristics of the 323 patients randomized into the trial and who received study drug are shown in Table 1. Seventy-two percent of patients were male. The index acute coronary syndrome was a Q-wave MI in 24% of patients, a non–Q-wave MI in 32%, and unstable angina in 44%. Thrombolytic therapy had been used in 21% of patients, and primary angioplasty was used in 19%. Patients were enrolled in the trial on average 3 to 3 1/2 days after the onset of the acute coronary syndrome.

Pharmacokinetics
There was a dose-dependent increase in the maximum blood concentration of the active drug Ro 44–3888 on day 1 across all the doses, with considerable interpatient variability for a given dose (average coefficient of variation of peak concentration was 32%; range, 20% to 40%; Fig 1). In a multivariate analysis, differences in renal function (calculated glomerular filtration rate) and body weight explained ≈23% and 11%, respectively, of the coefficient of variation. Sex and age were univariate but not multivariate predictors of blood concentra-
tion of active drug. The peak blood level was achieved at \( t \approx 6 \) hours after ingestion of study drug, and the half-life of the active compound was 11 hours.

Fig 2 shows the mean day 1 and 28 plasma concentrations of free active drug for the twice-daily (Fig 2A) and once-daily (Fig 2B) doses of sibrafiban. The peak concentrations of the free active drug on day 28 were on average 66% higher than on day 1. For the twice-daily dosing regimen, the average day 28 trough/peak concentration of free active drug was 45%.

Fig 3 shows a clear correlation between concentration of total active drug and degree of ADP-induced platelet inhibition. For the free active drug, 15 ng/mL gave 50% inhibition (IC\(_{50}\) defined as the concentration at which there is 50% inhibition) on average. In the 76 patients with paired day 1 and 28 PK samples, there was no difference in the IC\(_{50}\) on days 1 and 28 (13.8 and 15.9 ng/mL, respectively), suggesting that the patient’s platelets did not change greatly over time with respect to number or activation state of platelet surface glycoprotein IIb/IIIa receptors.

Pharmacodynamics

The effect of sibrafiban on inhibition of platelet aggregation is shown in Fig 4. There was a clear dose response in the day 1 (after the first dose) and 28 (at steady state) inhibition profiles of ADP- and TRAP-induced platelet aggregation. With the twice-daily dosing, the degree of inhibition was sustained, with 40% and 70% inhibition of ADP-induced platelet aggregation at 24 hours at the 5 mg and 10 mg BID doses, respectively (Fig 4A and 4C). In contrast, the once-daily dosing had a return to baseline in platelet function (Fig 4B and 4D). The effect of the twice-daily dosing regimens of sibrafiban on bleeding time at steady state (measured at trough) is shown in Fig 5. Similar to inhibition of platelet aggregation, there was a dose response demonstrated for prolongation of bleeding time.

There were no apparent differences in the degree of platelet inhibition achieved in several prespecified subgroups compared with the population as a whole (eg, patients with unstable angina versus non–Q-wave MI versus Q-wave MI, and those after thrombolysis versus after primary angioplasty or no reperfusion therapy).

Hemorrhagic Events

Of 271 patients treated with sibrafiban, 4 (1.5%) experienced a major hemorrhage, defined as a hemorrhage associated with a drop in hematocrit of 15 percentage points, as did 1 of 52 patients (1.9%) treated with aspirin. (Table 2) The percentage of patients with minor hemorrhage ranged from 0% at the 3 mg BID dose to 32% in the 15 mg QD dose. The rate of major or minor hemorrhage was higher with once-daily dosing compared with twice-daily dosing for similar total daily doses (eg, 10 mg once daily versus 5 mg twice daily; Table 2), which correlates with the higher peak concentrations achieved with once-daily dosing (Fig 1). The rate of hemorrhage that...
required medical intervention (such as nasal packing) ranged from 0% to 11% and averaged 4.4% among the sibrafiban-treated patients (Table 2). The percentage of patients who required a blood transfusion was 3.4%. The bleeding events were distributed evenly throughout the 28-day treatment period.

Epistaxis was the most common primary site of bleeding, occurring in 6.3% of sibrafiban-treated patients, followed by gastrointestinal hemorrhage in 2.2% and gum bleeding in 1.8%. Only 4 patients (1.5%) experienced minor bleeding at a site of instrumentation or trauma. Of patients with major or minor bleeding events, study drug was stopped in 51%.

One patient treated with sibrafiban (0.3%) developed thrombocytopenia, defined as a platelet count <100 000 per 1 μL. His baseline platelet count was 276 000 per 1 μL, and on day 7, it was 518 000. On day 14, the patient presented with gum bleeding and was found to have a platelet count of 6000 per 1 μL, which required the cessation of the study drug. The patient’s platelet count returned to 288 000 per 1 μL at the next follow-up visit. No other unexpected adverse events were identified in sibrafiban-treated patients.

Degree of Platelet Inhibition and Bleeding

Fig 6 shows a relationship between the median peak percent inhibition of ADP-induced platelet aggregation on day 1 for the BID doses in the PK/PD cohort and the incidence of major or minor hemorrhage observed in the PK/PD and safety

**Figure 4.** Mean degree of inhibition of ADP- and TRAP-induced platelet aggregation on days 1 (after the first dose) and 28 (at steady state) achieved for the twice-daily (A and C) and once-daily (panels B and D) doses.

**Figure 5.** Bleeding times at baseline (left) and predose on day 28 (right) for aspirin and the twice-daily doses of sibrafiban. Box and whisker plots show the median (line), 25th and 75th percentiles (box), and 5th and 95th percentiles (error bars).
study patients receiving the corresponding doses. Fig 7 shows the relationship between the average peak concentration of the free active drug at steady state and the incidence of major or minor hemorrhage in the safety study patients. The median time of major or minor hemorrhage was 5.5 hours after ingestion of a dose of study medication, which supports the hypothesis that bleeding was related to peak drug effect. Taken together, these data suggest that bleeding is associated with the degree of platelet inhibition and drug concentration. Furthermore, the drug concentration level on day 1 in patients who subsequently experienced major or minor hemorrhage was 33.8 compared with 20.3 ng/mL for patients not experiencing hemorrhage (P<.0001).

**Risk Covariates**

By use of multiple logistic regression, the total daily dose of sibrafiban was found to predict major or minor hemorrhage (P=.002), as did treatment with once-daily compared with twice-daily dosing (OR=3.0, P<.0001). In addition, a higher rate of major or minor hemorrhage was observed in patients with calculated creatinine clearance <67 mL/min (OR=2.8, P<.0001) and those with unstable angina compared with MI (Q-wave or non–Q-wave; OR=3.0, P<.01).

**Cardiac Events**

The percentage of patients with recurrent cardiac events while on study drug and up to 42 days in the randomized safety cohort was low (Table 3). Similar event rates were observed in the PK/PD cohort. By 42 days, 1.8% of patients died, 1.4% experienced recurrent MI, and 4.0% had experienced recurrent ischemia. Although cardiovascular end-point events were more frequent in the sibrafiban-treated group, especially the group receiving the 15-mg dose, there was no significant difference between patients treated with one of the four doses of sibrafiban or aspirin (P=.46) or between patients treated with 15 mg QD (P=.29). In the 103 patients in the PK/PD cohort, there was 1 death (1%; in the 15–mg QD dose), 2 MIs (2%; in the 5– and 10–mg BID doses), and 3 patients with recurrent ischemia (3%; 2 patients in the 7–mg BID and 1 in the 15–mg QD group).

**Discussion**

In this first double-blind, randomized trial using an oral IIb/IIIa antagonist in patients after acute coronary syndromes, we observed that a high degree of platelet inhibition could be achieved with sibrafiban, ranging from 50% to 100% platelet inhibition across the doses tested. There was a very predictable relation between the plasma concentration of the active drug and the degree of platelet inhibition at any dose. Some of the variability in both drug concentrations could be explained by minor differences in renal function and body weight. It should be noted, however, that considerable variability also exists in the platelet aggregation assay itself and between patients at baseline or those receiving intravenous IIb/IIIa antagonists, as observed in several previous trials.

In this study, the rate of major hemorrhage was rare and similar to that of aspirin. In addition, the rate appeared to be similar or lower than that reported with other intravenous IIb/IIIa agonists. However, over the 28-day treatment period, protocol-defined “minor” hemorrhage (usually mucocutaneous bleeding) was more common with sibrafiban than with aspirin. Some of these events were only “nuisance bleeds” that did not necessitate cessation of the study drug or any intervention. Thus, we observed that 6% to 10% of patients experienced a clinically significant major or minor hemorrhage at the doses that achieved ~70% to 80% platelet inhibition (5 to 10 mg BID). The mucocutaneous bleeds appeared to be related to plasma drug concentrations, the degree of platelet inhibition, and other patient factors (weight or renal function) that might be more closely controlled in future clinical trials. Our data also suggest that if a reliable assay is available, monitoring of the degree of platelet inhibition might help improve the overall safety profile of this class of agents.

**PK/PD**

We observed a good correlation between the blood level and the degree of platelet inhibition (Fig 3). Interestingly, there was...
no difference in the blood concentration required to achieve 50% inhibition on day 1 versus 28, suggesting no major change in dosing is needed as patients recover from their acute coronary syndrome.

**Relationship of Bleeding to Platelet Inhibition and Drug Concentration**

Correlations were observed between the dose of sibrafiban administered, the peak active drug concentration achieved (Figs 1 and 2), the degree of platelet inhibition (Figs 3 and 4), and the rate of hemorrhage (major plus minor) (Fig 5 and 6). Such an increase in the risk of bleeding dependent on the degree of platelet inhibition has also been observed with intravenous IIb/IIIa antagonists.20–22 Similarly, with anticoagulant therapy, higher degrees of anticoagulation are associated with increased bleeding.23–26 Both plasma drug concentration and the risk of bleeding were increased in patients with renal dysfunction, which suggests that dose adjustments based on renal function might reduce the risk of bleeding. The risk of bleeding appeared to be low in patients who had <50% platelet inhibition.

The clinical pattern of bleeding was largely mucocutaneous characterized by epistaxis, gingival bleeding, gastrointestinal bleeding or bruising. This is a different clinical pattern than is usually observed with anticoagulants but is similar to that seen with thrombocytopenia or in Glanzmann’s thrombasthenia.27 Because 6% of patients in this trial experienced gastrointestinal hemorrhage, one might consider using antacids or H2 blockers as prophylactic medication when using IIb/IIa antagonists.

We also observed increased risk of bleeding with once-daily dosing, which may be related to the high peaks that were observed. The bleeding appeared to occur ≥6 hours after study drug ingestion, which correlates with the peak blood level. Thus, using dosing regimens that avoid high peaks may decrease the risk of bleeding. In addition, given the interpatient variability observed in drug level and degree of platelet inhibition, another potential strategy for dosing any IIb/IIIa antagonist is to monitor the degree of platelet inhibition or drug level achieved in individual patients and to adjust the dose to a target level, as is currently done with anticoagulant therapy. By avoiding higher levels of platelet inhibition, this strategy may reduce bleeding complications.

**Clinical Events**

This study was not powered to detect differences in clinical events among the treatment groups, and none were observed. The clinical efficacy of IIb/IIIa inhibition in angioplasty has been shown in other studies, with a dramatic beneficial effect seen with the long-acting agent abciximab (ReoPro).3–5 More recently, one trial in unstable angina showed that a 2- to 4-day infusion of tirofiban improved 7- and 30-day clinical outcomes.8 In contrast, shorter infusions (24 to 36 hours) of selective IIb/IIIa antagonists were shown to have significant early reduction in recurrent ischemic events after angioplasty.

**TABLE 3. Recurrent Ischemic Events in the Randomized Safety Cohort to 42 Days**

<table>
<thead>
<tr>
<th>Events of Study Drug</th>
<th>Aspirin (n=52), %</th>
<th>5 mg BID (n=50), %</th>
<th>7 mg BID (n=37), %</th>
<th>10 mg BID (n=52), %</th>
<th>15 mg QD (n=29), %</th>
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<tbody>
<tr>
<td>Death</td>
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<td>0</td>
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<td>0</td>
</tr>
<tr>
<td>MI</td>
<td>0</td>
<td>2.0</td>
<td>0</td>
<td>0</td>
<td>3.4</td>
</tr>
<tr>
<td>Recurrent ischemia</td>
<td>3.8</td>
<td>2.0</td>
<td>5.4</td>
<td>3.8</td>
<td>6.9</td>
</tr>
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<td>Any of the above</td>
<td>3.8</td>
<td>4.0</td>
<td>5.4</td>
<td>3.8</td>
<td>10.3</td>
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</table>

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<tr>
<th>Events to 42 days</th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>0</td>
<td>2.0</td>
<td>0</td>
<td>1.9</td>
<td>3.4</td>
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<td>5.4</td>
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<td>6.9</td>
</tr>
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<td>5.4</td>
<td>7.7</td>
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</tbody>
</table>

**Figure 7.** Rate of major and minor hemorrhage vs peak blood concentration of the active drug at steady state (day 28).
with a loss of significance of the reduction at the later time points.9,10 One difference between the monoclonal antibody and the selective IIb/IIIa antagonists is that the former has a very long duration of action on the platelet with antiplatelet activity detected up to 1 week after administration of abciximab.28 This suggests that the prolonged antiplatelet effect of the antibody may be responsible for its sustained beneficial effect. Thus, early and continued dosing with oral IIb/IIIa antagonists may demonstrate better efficacy than shorter-term intravenous infusions of IIb/IIIa antagonists. However, it is not known for this class of agents what degree of inhibition of platelet function is needed to prevent recurrent cardiac events and to provide additional clinical benefit compared with aspirin.

**Lessons Learned Regarding Dosing of IIb/IIa Antagonists**

In balancing the potential benefit in reducing ischemic events with the risk of hemorrhage, it may be optimal to treat patients with a higher degree of platelet inhibition early in the course of an acute coronary syndrome followed by a lower level of inhibition for prolonged secondary prevention. This would match the degree of inhibition (and the potential reduction in recurrent ischemic events and risk of bleeding) with the overall absolute risk of recurrent ischemic events. To improve the safety profile of oral IIb/IIIa antagonists, several strategies may be considered. First, the dose may be adjusted on the basis of patient characteristics that influence drug concentrations and degree of platelet inhibition, such as renal function and body weight. Second, if a reliable bedside assay for platelet inhibition were developed, one may be able to titrate the dose of the IIb/IIIa antagonist to a target degree of platelet inhibition (potentially measured with a rapid bedside assay29). Third, one could use fixed dosing initially but lower the dose if the patient experienced repeated minor bleeding. Such strategies may improve the overall safety profile of these potent platelet antagonists.

**Conclusions**

In this study, sustained platelet inhibition was achieved for 28 days with an oral IIb/IIIa antagonist. We observed a low rate of major hemorrhage with this drug, despite the high degree of platelet inhibition. Minor mucocutaneous hemorrhages were more common, and they appeared to be dose related. This is the first multicenter, randomized, double-blind, dose-ranging experience that provides many clues as to how to better use these potent drugs. Given the promising effects of intravenous IIb/IIIa antagonists in other studies,3–5,8–10 prolonged oral IIb/IIIa inhibition may be a useful new strategy for the reduction of recurrent cardiac events in patients after acute coronary syndromes.

**Appendix**

**TIMI 12**

TIMI Study Chairman’s Office: Harvard Medical School, Boston, Mass. Study chairman: Eugene Braunwald, MD; principal investigator: Christopher P. Cannon, MD; project director: Carolyn H. McCabe, BS; coinvestigator: Elliott M. Antman, MD. Sponsor: Genentech, Inc, South San Francisco, Calif.; William F. Novotny, MD; Joel M. Rothman, BS; and Scott A. Hamilton, PhD.

Platelet Aggregation Core Laboratory: Maine Medical Research Institute, South Portland: Kenneth Ault, MD, and Jane Mitchell, MTASCP.

Coagulation Core Laboratory: University of Vermont, Colchester: Russell Tracy, PhD; Edwin G. Bovill, MD; and Elaine Cornell, BS.

ECG Core Laboratory: St Louis (Mo) University: Bernard Chatman, MD, and Karen Stocke, MS.

**PK/PD Centers in Order of Number of Patients Enrolled**

- Henry Ford Hospital, Detroit, Mich. Principal investigator: Steven Borzak, MD; coinvestigator: David Chang, MD; and research coordinator: Theresa Cruz, RN.
- Hennepin County Medical Center, Minneapolis, Minn. Principal investigator: Timothy D. Henry, MD; research coordinators: Charlene Boisjolie, RN, and Lorri Knox, RN.
- Montefiore Medical Center, Bronx, NY. Principal investigator: Hiltrud S. Mueller, MD; research coordinators: Linda Kunkel, RN, and Joseph Cosico, RN.
- University of Vermont/Fletcher Allen HealthCare, Burlington (PK/PD and safety studies). Principal investigator: Marc D. Tischler, MD; research coordinator: Michaelanne Rowen, RN; Liz Golden.
- University of Miami (Fla)/Jackson Memorial Hospital. Principal investigator: Rafael F. Sequeira, MD; coinvestigators: Eduardo de Marchena, MD, Manuel R. Mayor, MD, and Mohammed I. Awaad, MD; research coordinator: Gayatri Girwarr, MD, and Pura Teixeiro, RN.
- Baystate Medical Center, Springfield, Mass. Principal investigator: Marc J. Schweiger, MD; research coordinator: Barbara Burkott, RN.
- Loyola University Medical Center, Maywood, Ill. Principal investigator: Eric Grasman, MD; research coordinator: Ellen Galbraith, RN.
- Brigham and Women’s Hospital, Boston, Mass (PK/PD and safety studies). Principal investigator: Robert N. Piana, MD; coinvestigator, Christopher P. Cannon, MD; research coordinator: Lisa Cook.
- Vancouver Hospital and Health Sciences Center, Vancouver, BC, Canada (PK/PD and safety studies). Principal investigator: Anthony Fung, MD; research coordinators: Heather Abbey, RN, and Catherina van Beek.
- University of Alabama at Birmingham (PK/PD and safety studies). Principal investigator: William J. Rogers, MD; coinvestigators: Vera Gittner, MD, Robert Bourge, MD, and Gilbert Perry, MD; research coordinator: Nancy Grady, RN.
- Midwest Heart Research Foundation/Elmhurst (Ill) Memorial Hospital. Principal investigator: R. Andrew Rauh, MD; research coordinator: Ellen Reynolds, RN.
- University of Massachusetts Medical Center, Worcester. Principal investigator: Richard C. Becker, MD; research coordinator: Steven Ball, RN.
- Jewish General Hospital, Montreal, Quebec, Canada. Principal investigator: Jean G. Diodati, MD; research coordinators: Eileen Shalit, RN, and Desneiges Beauvais, RN.
- St. Paul’s Hospital, Vancouver, BC, Canada. Principal investigator: Christopher Thompson, MD; research coordinator: Karen MacDonald, RN.
- University of Connecticut, Farmington. Principal investigator: Michael Azrin, MD; research coordinators: Erin Proctor, RN, and MaryBeth Barry, RN.
- Christ Hospital, Cincinnati, Ohio (PK/PD and safety studies). Principal investigator: Dean Kereakes, MD; research coordinator: Nancy Highy, RN.
- Deaconess Hospital, Evansville, Ind (PK/PD and safety studies). Principal investigator: Jerry Becker, MD; research coordinator: Sheila Nalley, RN.
- Iowa Heart Center/Mercy Medical Center, Des Moines, Iowa. Principal Investigator: Magdi Ghali, MD; research coordinator: Teresa Coulson, RN.

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Safety Centers in Order of Number of Patients Enrolled

Munroe Regional Medical Center/Mediquest, Ocala, Fla. Principal investigator: Robert Feldman, MD; research coordinator: Brandi Merchant, RN.

Robert Wood Johnson Medical School, New Brunswick, NJ. Principal investigator: Sebastian Palmeri, MD; research coordinator: Laurie Casaza, RN.

Sacred Heart and Baptist Hospitals, Pensacola, Fla. Principal investigators: Brent Videau, MD, and Michael Stein, MD; coinvestigators: G. Ramon Aycock, MD, and Stephen M. Teague, MD; research coordinators: Elizabeth Steck, RN, and Claire Niebuhr, RN.

Sarasota Memorial Hospital, Sarasota, Fla. Principal investigator: Martin Frey, MD; research coordinator: Torey Browning, RN.

Hartford (Conn) Hospital. Principal investigator: Raymond McKay, MD; research coordinator: Jill Cloutier, RN.

Broward General Medical Center, Fort Lauderdale, Fla. Principal investigator: Alan Niederman, MD; research coordinator: Terri Kellerman, RN.

St John’s Hospital/Prairie Cardiovascular Consultants, Springfield, Ill. Principal investigator: Charles Lucore, MD; research coordinator: Linda Pianfetti, RN, and Claire Niebuhr, RN.

Alta Bates Medical Center, Berkeley, Calif. Principal investigator: Robert Greene, MD; research coordinators: Eileen Healy, RN, and Vickie Perry, RN.

New England Deaconess Hospital, Boston, Mass. Principal investigator: David E. Leeman, MD; research coordinator: Sally Pickett, RN.

Baptist Medical Center, Montgomery, Ala. Principal investigator: Paul Moore, MD; research coordinators: Mark Platt, RN, Ernest Parker, RN, and Rena Grimes, RN.

Ohio State University Hospitals, Columbus. Principal investigator: Raymond Maguron, MD; research coordinators: Laurie McCloud, RN, and Ann Marie Nordgren, RN.

St Luke’s Hospital, New York, NY. Principal investigators: Judith Hochman, MD, and Angela Palazzo, MD; research coordinators: Mary McAnulty, RN, and Deborah Tormey, RN.

Winthrop University Hospital, Mineola, NY. Principal investigator: Richard Steingart, MD; research coordinators: Suzanne Bilodeau, RN, and MaryEileen Coglanese, RN.

Hospital of the Good Samaritan, Los Angeles, Calif. Principal investigator: Thomas Shook, MD; research coordinator: Lorraine Evangelista, RN.

Presbyterian Hospital of Dallas (Tex). Principal investigator: Darryl Kwaslasky, MD; research coordinator: Malou Armod, RN.

Cedars-Sinai Medical Center, Los Angeles, Calif. Principal investigator: Prediman Shah, MD; research coordinator: Mitchell Gheorghiu, MD.

St Vincent Hospital, Worcester, Mass. Principal investigator: Richard Bishop, MD; research coordinators: Tammy Brunelle, RN, and Patricia Arsenault, RN.

Brookdale University Hospital and Medical Center, Brooklyn, NY. Principal investigator: Hal L. Chadow, MD; research coordinator: Lorraine Giarraffa, RN.

Doylestown (Pa) Hospital. Principal investigator: James Kmetzo, MD; research coordinator: Dawn Shaddinger, RN.

Indiana University/Krannert/Wishard/VAMC, Indianapolis. Principal investigator: Elizabeth VonDerLohse, MD; research coordinator: Laura Perkins, RN.

Lakeland (Fla) Regional Medical Center/Watson Clinic. Principal investigator: Kevin Browne, MD; research coordinator: Debra McKinney, RN.

Ochsner Clinic of Baton Rouge (La). Principal investigator: Andrew Rees, MD; research coordinator: Helen Penfield, RN.

Rhode Island Hospital, Providence. Principal investigator: George McKendall, MD; research coordinator: Mary Jane McDonald, RN.

Emerson Hospital, Concord, Mass. Principal investigator: Paul Boffetti, MD; research coordinator: Gail Carey, RN.

Parkview Memorial Hospital/Stucky Research Center, Fort Wayne, Ind. Principal investigator: William Collins, MD; research coordinator: Jane Cuttitta, RN.

SUNY/Downstate University Hospital, Brooklyn, NY. Principal investigator: Louis Salciccioli, MD; research coordinator: Rosa Julen, RN.

University of Cincinnati (Ohio) Medical Center. Principal investigator: John Runyon, MD; research coordinator: Nancy Higby, RN.

West Roxbury (Mass) Veterans Affairs Medical Center. Principal investigator: C. Michael Gibson, MD; research coordinator: Christine McLean, RN.

Veterans Affairs Medical Center/Decatur (Ga). Principal investigator: J. Jeffrey Marshall, MD; research coordinator: Alberta Lane, RN.

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References


Randomized Trial of an Oral Platelet Glycoprotein IIb/IIIa Antagonist, Sibrafiban, in Patients After an Acute Coronary Syndrome: Results of the TIMI 12 Trial


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