Randomized, Placebo-Controlled Trial of Titrated Intravenous Lamifiban for Acute Coronary Syndromes

The Platelet IIb/IIIa Antagonist for the Reduction of Acute coronary syndrome events in a Global Organization Network (PARAGON)-B Investigators

**Background**—Platelet glycoprotein IIb/IIIa inhibitors reduce the rate of death or myocardial infarction among patients with acute coronary syndromes without persistent ST-segment elevation, but their effects may depend on plasma concentrations. We tested whether the addition of lamifiban, titrated to achieve target plasma concentrations, to standard care would improve clinical outcomes.

**Methods and Results**—We randomized 5225 patients at 389 centers in 29 countries to receive a bolus and 72-hour infusion of lamifiban or placebo, adjusted for renal function, with aspirin and heparin. The primary end point was the composite of death, myocardial infarction, or severe, recurrent ischemia at 30 days. Baseline characteristics did not differ significantly by treatment. The primary end point occurred in 11.8% of lamifiban-treated patients and in 12.8% of placebo-treated patients (OR, 0.914; 95% CI, 0.769 to 1.087; P=0.329). Bleeding was more common in lamifiban-treated patients, but intracranial hemorrhage was not increased. Among the subgroup who had plasma lamifiban concentrations measured, 91% had a concentration >18 ng/mL at steady state, but their outcomes did not differ from those with lower concentrations.

**Conclusions**—Lamifiban showed no significant effects on clinical outcomes in patients with non–ST-elevation acute coronary syndromes, despite achievement of adequate plasma concentrations. (Circulation. 2002;105:316-321.)

**Key Words:** angina myocardial infarction platelets

The putative mechanism behind acute coronary syndromes (ACS) is atherosclerotic plaque rupture, fissuring, or erosion followed by coronary thrombosis mediated through the platelet and coagulation systems.1 In addition to myocardial necrosis resulting from the obstruction of coronary blood flow, myocardial infarction (MI) may occur through distal embolization of thrombotic material, resulting in obstruction of coronary microcirculation.2 Treatment of this condition has focused on antiplatelet and antithrombin therapies. Both types of agents have improved the clinical outcomes of patients with ACS without persistent ST-segment elevation.3-5

Particularly striking have been the data from trials of platelet glycoprotein (GP) IIb/IIIa antagonists. In aggregate, GP IIb/IIa inhibitors consistently have reduced the composite incidence of death or MI at 30 days and 6 months among patients with ACS without persistent ST-segment elevation.6-10 In a recent systematic overview, their use was associated with 13% fewer deaths or MIs at 30 days.3

Lamifiban is a peptidomimetic, highly specific inhibitor of platelet GP IIb/IIa. Parenteral administration produces rapid, dose-dependent inhibition of platelet aggregation in response to various agonists.10 It is excreted predominantly renally and has no known metabolites. The Platelet IIb/IIIa Antagonist for the Reduction of Acute coronary syndrome events in a Global Organization Network (PARAGON)-A trial tested two lamifiban doses, with and without unfractionated heparin (UFH), versus placebo with heparin and aspirin, in ACS patients without persistent ST-segment elevation.9 The 30-day incidence of death or MI was not reduced with either lamifiban dose, but retrospective, nonrandomized pharmacokinetic analyses showed a 40% reduction in the end point with steady-state lamifiban concentrations of 18 to 42 ng/mL.11

Pharmacokinetic modeling suggested that with appropriate dose adjustments, plasma lamifiban concentrations within this range could be achieved for most patients. The PARAGON-B trial was designed to test whether the addition of such titrated lamifiban dosing to standard care would improve clinical outcomes.11

**Methods**

**Study Organization**
PARAGON-B was a randomized, double-blind, placebo-controlled trial conducted at 389 centers in 29 countries (see http://dcri.mc.duke.edu/research/publications.html). Enrollment continued from February 1998 to June 1999.
Infarctions were classified as baseline (randomization) or postrandomization (end point) events. Baseline MI was defined as CK-MB >ULN <16 hours after randomization or total CK >2×ULN if CK-MB was unavailable. Postrandomization MI was defined as any new, significant Q waves in 2 contiguous leads, CK-MB (or CK, if CK-MB was unavailable) >2×ULN if no revascularization procedure had been performed, or CK-MB (or total CK, if CK-MB was unavailable) >3× or >5× ULN after PCI or bypass, respectively.

The protocol recommended cardiac-enzyme measurement at baseline, 8 and 16 hours after the infusion began, and every 8 hours for 24 hours after PCI, bypass surgery, or angioplasty episodes. Laboratory results were collected on all patients and verified centrally against data collection forms. All ECGs were collected on all patients and read centrally by the CEC.

The definition of severe, recurrent ischemia required (1) recurrent angina at rest lasting ≥20 minutes and occurring >2 hours after study drug began, (2) new or increased ischemic ECG changes as determined by the core laboratory, and (3) unplanned or urgent revascularization <24 hours after the ischemic episode.

Safety End Points

The primary safety assessment was bleeding, including hemorrhagic and ischemic stroke, major or life-threatening bleeding, and intermediate bleeding. Other safety measures included bleeding during study treatment in patients not undergoing bypass surgery, blood product transfusions, minor bleeding, and thrombocytopenia. All suspected strokes were adjudicated by a CEC including neurologists and cardiologists.

Major or life-threatening bleeding was defined as any intracranial hemorrhage or bleeding leading to hemodynamic compromise requiring intervention. Intermediate bleeding was bleeding requiring transfusion or a decrease in hemoglobin ≥5 g/dL (or decrease in hematocrit ≥15% when hemoglobin was unavailable). Platelet counts were monitored throughout study drug infusion; thrombocytopenia was defined as <50,000 platelets/μL, after excluding diagnosis of pseudothrombocytopenia.

Plasma Lamifiban Concentrations

Blood was collected on a subset of patients at steady state (before infusion end) to determine plasma concentrations of lamifiban.

Statistical Methods

We assumed an incidence of the primary 30-day end point of 16% for control subjects and a 25% reduction with lamifiban. A sample of 4000 patients (2000 per arm) would provide 96% power to detect such a difference at \( \alpha = 0.05 \) (2-sided); 87% power at \( \alpha = 0.01 \). This size also would provide 87% power at \( \alpha = 0.05 \) to detect a 25% reduction in the composite of death or MI, assuming a 12% incidence for control subjects.

The Data and Safety Monitoring Board, during a blinded review of the overall event rate in March 1999, recommended that 1600 additional patients be enrolled. At that time, 1639 patients had been accrued, and the incidence of the 30-day primary end point (based on the limited numbers of events adjudicated) was estimated at 10%. After consultation between the sponsor and the Steering Committee, it was decided to augment the original sample by 1200 patients. The primary analysis of the 30-day efficacy data were performed with logistic regression techniques and included all patients randomized who received ≥1 dose of study drug. For patients who lacked follow-up data, we based calculations of efficacy variables on the last data collected within the period. We assumed patients to be event-free when lost to follow-up if no event had occurred by then.

Dichotomous variables were summarized as frequencies and percentages, and continuous variables as medians and interquartile ranges. Univariable analysis first was used to compare the incidence of the primary efficacy end point by treatment. The analysis was repeated after adjustment for variables contributing the most predictive information for the composite of 30-day death or MI in logistic regression: enrollment region, age, sex, index-event diagnosis, phase of enrollment (European patients), and body mass index. Odds ratios
and 95% CI for the primary end point were constructed by treatment for major subgroups and for the nonrandomized subgroup of patients undergoing early PCI (<72 hours while receiving study drug). We generated survival curves for the cumulative incidence of the 6-month composite of death or MI. Log-rank tests were used to compare lamifiban with placebo over time.

We also tested for an interaction between treatment assignment and PCI on 30-day outcomes. To account for the known selection bias in performance of PCI after randomization, a Cox proportional hazards model was developed that included the propensity score for PCI, treatment, early PCI, and an interaction term (early PCI x treatment). The early PCI and interaction terms were included as time-dependent covariates to account for timing of PCI. The interaction terms were used to describe any differential treatment effect among patients who did and did not undergo PCI during the period of treatment allocation.

Results

In all, 5225 patients were randomized. Follow-up data were 99.8% complete for the primary end point (99.9% for placebo, 99.7% for lamifiban). Placebo and lamifiban patients were enrolled a median 7.4 (4.3 to 10.8) hours and 7.3 (4.3 to 10.8) hours after symptom onset, respectively. Most patients had ST-segment depression or T-wave inversion on the prerandomization ECG, not mutually exclusive (Table 1). At baseline, 56.6% of placebo patients and 57.3% of lamifiban patients had MI by enzymatic criteria. The median duration of lamifiban infusion was 72.0 (59.0 to 72.1) hours. Other medication use is displayed in Table 2. Table 3 contains data on the use and timing of cardiac procedures.

Efficacy End Points

The incidence of the primary end point did not differ significantly by treatment: lamifiban, 11.8% and placebo, 12.8% (OR, 0.914; 95% CI, 0.769 to 1.087; P = 0.329) (Table 4). Survival curves for the composite of death or MI to 6 months showed no attenuation or amplification of benefit over time (Figure 1).

Figure 2 shows odds ratios for major subgroups of patients. In a prospective subgroup analysis (n = 1160), a positive baseline troponin T level correlated with markedly amplified treatment benefit. Treatment effect appeared not to differ substantially by presenting ECG (15.8% placebo, 16.7% lamifiban for ST depression; 13.4%, 11.8% for T-wave inversion; 15.2%, 14.0% for transient ST elevation). Treat-
ment effect likewise did not differ significantly by the performance or timing of PCI (Table 5).

**Safety End Points**

Stroke occurred in 15 placebo-treated patients and in 28 lamifiban-treated patients (0.6% versus 1.1%; \(P = 0.051\)). Two patients in each group had intracranial hemorrhage. Red cell transfusions were used more often in the lamifiban group (10.3% versus 8.9%; \(P = 0.088\)) (Table 6). Thrombocytopenia occurred infrequently in both the placebo (n=14, 0.5%) and lamifiban groups (n=18, 0.7%). One placebo-treated patient and 5 lamifiban-treated patients (0.2%) had a nadir platelet count <20 000/μL.

**Plasma Concentration and Outcomes**

Steady-state plasma lamifiban concentrations were available for 1264 patients (48.1%). Of these, 109 (8.6%) had concentrations \(\geq 18\) ng/mL, 914 (72.3%) had concentrations of 18 to 42 ng/mL, and 241 (19.1%) had concentrations >42 ng/mL. Plasma concentration and the primary end point showed no significant relation.

**Discussion**

Titrated lamifiban did not significantly reduce the incidence of death, MI, or severe, recurrent ischemia compared with placebo.

### TABLE 5. Effects of Treatment and PCI on 30-Day End Points

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo</th>
<th>Lamifiban</th>
<th>OR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial infarction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No PCI (n=3729)</td>
<td>165 (8.9)</td>
<td>153 (8.2)</td>
<td>0.92 (0.72–1.16)</td>
</tr>
<tr>
<td>Early PCI (n=678)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before PCI</td>
<td>3 (0.85)</td>
<td>1 (0.31)</td>
<td>0.34 (0.03–3.32)</td>
</tr>
<tr>
<td>After PCI</td>
<td>44 (12.5)</td>
<td>27 (8.3)</td>
<td>0.63 (0.38–1.05)</td>
</tr>
<tr>
<td>Late PCI (n=749)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before PCI</td>
<td>15 (4.3)</td>
<td>18 (4.5)</td>
<td>1.06 (0.52–2.14)</td>
</tr>
<tr>
<td>After PCI</td>
<td>24 (6.9)</td>
<td>30 (7.5)</td>
<td>1.10 (0.63–1.93)</td>
</tr>
<tr>
<td>Death</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No PCI (n=3729)</td>
<td>70 (3.8)</td>
<td>68 (3.6)</td>
<td>0.97 (0.68–1.36)</td>
</tr>
<tr>
<td>Early PCI (n=678)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before PCI</td>
<td>6 (1.7)</td>
<td>2 (0.62)</td>
<td>0.34 (0.08–1.79)</td>
</tr>
<tr>
<td>After PCI</td>
<td>9 (2.6)</td>
<td>6 (1.5)</td>
<td>0.58 (0.20–1.63)</td>
</tr>
<tr>
<td>Late PCI (n=749)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before PCI</td>
<td>15 (4.3)</td>
<td>18 (4.5)</td>
<td>1.06 (0.52–2.15)</td>
</tr>
<tr>
<td>After PCI</td>
<td>26 (7.5)</td>
<td>34 (8.5)</td>
<td>1.16 (0.67–1.97)</td>
</tr>
</tbody>
</table>

*Odds of having the event during the specified period vs not within 30 days. \(P\) values for interaction of treatment and early PCI.

### TABLE 6. In-Hospital Bleeding

<table>
<thead>
<tr>
<th>Placebo</th>
<th>Lamifiban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall (n=2564)</td>
<td>(n=2594)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>23 (0.9)</td>
</tr>
<tr>
<td>Intermediate bleeding</td>
<td>299 (11.5)</td>
</tr>
<tr>
<td>Bypass surgery (n=385)</td>
<td>(n=400)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>127 (4.9)</td>
</tr>
<tr>
<td>Intermediate bleeding</td>
<td>1573 (60.5)</td>
</tr>
<tr>
<td>No bypass surgery (n=2173)</td>
<td>(n=2189)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>3 (0.1)</td>
</tr>
<tr>
<td>Intermediate bleeding</td>
<td>75 (2.9)</td>
</tr>
</tbody>
</table>

*\(P=0.002\).
when both were given with heparin and aspirin. Bleeding was increased with lamifiban compared with placebo, though not intracranial hemorrhage or thrombocytopenia.

**Patient Population**

Patients enrolled in PARAGON-B were typical of those enrolled in trials of moderate- to high-risk ACS. Patients were predominantly male, in their mid-sixties, and had multiple cardiac risk factors. Considerable numbers had undergone previous PCI or surgical revascularization. Most had abnormal ECGs at presentation, and most showed plasma markers of myocardial injury at enrollment. Almost all were treated with aspirin and some form of heparin, either UFH or low-molecular-weight heparin. As with other protocols that have not encouraged or required angiography, ~64% of patients underwent diagnostic angiography a median of 3 days after entry. Overall, then, the enrolled patients were similar to those of other ACS trials, representative of the patients seen in clinical practice, and treated according to global practice patterns.

**Efficacy Outcomes**

Despite the best contemporary therapies, including aspirin, heparin, β-blockers, ACE inhibitors, lipid-lowering agents, and coronary revascularization, the rate of death or MI at 30 days remained high (>10%) among these patients with ACS without persistent ST-segment elevation. Because MI was defined conservatively in PARAGON-B, requiring a CK-MB level ≥2×ULN, the true event rates may be even higher. Similarly, the 30-day incidence of severe, recurrent ischemia was much lower than anticipated; the stringent definition probably identified patients only at the highest end of the risk spectrum. Armstrong et al. have shown that patients with ACS with recurrent ischemia have a significantly higher 1-year mortality rate than those without recurrent ischemia. The most appropriate definition of recurrent ischemia, and thus the ability to better identify those at greatest risk, requires more investigation.

Optimal dosing and timing of platelet GP IIb/IIIa inhibitors remains uncertain. Previous work suggested that enhancement of plasma lamifiban concentrations could maximize treatment effect. This idea was supported by similar observations for UFH used as an adjunct to fibrinolysis for acute ST-segment elevation MI. Since lamifiban is primarily excreted renally, a dosing strategy using calculated creatinine clearance seemed reasonable. Among the subset of PARAGON-B patients with plasma lamifiban measurements, most achieved steady-state lamifiban concentrations within the desired range, but 28% had a concentration outside this range, most often >42 ng/mL. Despite adjusting the dose for age, sex, weight, and renal function, these variables remained most predictive of failure to achieve therapeutic lamifiban concentrations.

Unlike the PARAGON-A investigators, we noted no significant relation between plasma concentration and outcomes. Given that almost 30% of the sampled patients remained outside the targeted pharmacokinetic window despite adjusted dosing, questions remain about whether more precise dosing can maximize the likelihood of achieving the desired concentration and amplify treatment effects. Recent preliminary data suggest that there may be optimal levels of platelet inhibition, as measured by a point-of-care device, that correlate with improved outcomes in patients undergoing PCI. Whether this finding applies to treatment of patients with ACS is unknown but warrants investigation.

**Safety Outcomes**

As with other trials of platelet GP IIb/IIIa antagonists in this population, bleeding was increased among lamifiban-treated patients, manifested mainly as increased blood transfusions. Importantly, the risk of intracranial hemorrhage was not increased among lamifiban-treated patients beyond the low baseline risk of this population. Most bleeding occurred in patients undergoing bypass surgery, and treatment with lamifiban did not add to this increased risk. Likewise, the overall incidence of severe or profound thrombocytopenia was quite low and not appreciably increased with lamifiban.

**Trials of GP IIb/IIIa Inhibitors**

More than 40 000 patients have been randomized in major trials of intravenous GP IIb/IIIa inhibition versus standard therapy for ACS or with PCI. Individually or together, the overall aggregated data suggest that treatment with this class of therapeutics improves clinical outcomes of these patients. A systematic overview of parenterally administered small-molecule IIb/IIIa inhibitors shows that all randomized trials trend in the same direction, that is, that there appears to be a modest gain from using these therapies. However, in the current trial, lamifiban showed no benefit despite achievement of target drug concentrations.

**Acknowledgments**

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**References**


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