Dose-Finding, Safety, and Tolerability Study of an Oral Platelet Glycoprotein IIb/IIIa Inhibitor, Lotrafiban, in Patients With Coronary or Cerebral Atherosclerotic Disease

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Background—Antiplatelet therapy is the mainstay of the treatment and secondary prevention of cardiovascular and cerebrovascular ischemic events. We assessed the safety, tolerability, and pharmacodynamics of lotrafiban, an oral platelet glycoprotein IIb/IIIa inhibitor, as a secondary prevention strategy in patients with cerebrovascular or cardiovascular disease.

Methods and Results—Overall, 451 patients with a recent cardiovascular or cerebrovascular acute ischemic event were randomized in a double-blind fashion to 1 of 5 dosing regimens for 12 weeks: placebo or 5, 20, 50, or 100 mg lotrafiban, both twice daily with 300 to 325 mg/d aspirin. The primary end point was the incidence and tolerability of major and minor bleeding during treatment. Secondary end points included inhibition of platelet aggregation and clinical events. The placebo and lotrafiban 5-mg groups had similarly low rates of minor and major bleeding, but the 100-mg arm was terminated early because of excess major bleeding. Protocol-defined thrombocytopenia (<100 000 platelets/μL) occurred in 5 lotrafiban-treated patients (1.4%, 95% CI 0.2% to 2.7%) and 1 placebo patient (1.1%, 95% CI 0% to 3.1%). Three lotrafiban-treated patients had a nadir platelet count <20 000/μL (0.9%, 95% CI 0% to 1.8%). Lotrafiban produced dose-dependent inhibition of platelet aggregation; 5 mg lotrafiban did not differ significantly from placebo, whereas 100 mg inhibited aggregation by nearly 100%.

Conclusions—Lotrafiban provides dose-dependent platelet inhibition when administered to a range of patients with atherosclerosis. The level of platelet inhibition appears to correlate with bleeding risk and drug tolerability. (Circulation. 2000;102:728-735.)

Key Words: atherosclerosis ■ prevention ■ prognosis ■ platelet aggregation

The acute coronary syndromes (ACSs) of unstable angina and myocardial infarction (MI) and the acute cerebrovascular events of transient ischemic attacks (TIAs) and stroke are major clinical problems with substantial rates of associated morbidity and mortality.1 Because platelet-dependent thrombosis is a key pathophysiological mechanism, antiplatelet therapy is a mainstay of treatment, both acutely and for secondary prevention.2 Aspirin, the typical agent used, is only a relatively weak platelet inhibitor because its effects are specific to the thromboxane A2 pathway. Furthermore, some patients do not respond to aspirin3 and thus are at an increased risk of ischemic complications. Two other antiplatelet agents of the thienopyridine class, ticlopidine and clopidogrel, inhibit platelet aggregation through the ADP receptor,4 but this receptor also represents only 1 of several important pathways to platelet aggregation.

When stimulated by an agonist, platelets aggregate via fibrinogen binding to the surface platelet glycoprotein (GP) IIb/IIIa receptor, the “final common pathway.” Agents that block ligand binding to this receptor provide potent platelet inhibition.5–6 More than 30 000 patients have been randomized in trials of 4 intravenous GP IIb/IIIa inhibitors: abciximab (monoclonal antibody fragment),7–11 eptifibatide (peptide),12,13 lamifiban (nonpeptide),14,15 and tirofiban16–18...
Bleeding Questionnaire Taken from the CRF (Baseline)

The purpose of this questionnaire is to find out whether you have recently experienced any type of bleeding events such as nasal bleed(s), bleeding when brushing your teeth, prolonged bleeding from shaving nicks, or easy bruising. For women, we would like to know of any unusual pattern of menstrual bleeding (if premenopausal) or postmenopausal bleeding (if any).

It is important that you mark your current level of these types of bleeding events since you will be asked several times during the course of the study to compare your level of bleeding at each visit to your level now, when you have not taken study medication.

Have you had:

No       Yes

Nose bleed(s)?
Bleeding during or after brushing your teeth?
Bleeding after shaving nicks?
Easy bruising?
Hemorrhoidal bleeding?
Dark or tarry stools?
Unusual bleeding from other cuts?
Urinary bleeding?
Unusual menstrual bleeding?
Post menopausal bleeding?
Any other new or prolonged bleeding?

If "Yes" please describe: __________________________

If you answered "Yes" to any of the above questions, please answer the following questions.

1. Does this bleeding cause you concern or inconvenience?

No

Yes ——— If "Yes" please list, by number, the bleeding events in order of concern to you, with the bleeding event of greatest concern first.

Which event(s): __________________________

Figure 1. Patient questionnaire to assess major and minor bleeding.

(nonpeptide). A systematic overview of these studies shows a consistent, significant reduction in the acute complications of percutaneous coronary intervention (PCI) or non–ST-segment elevation ACSs.18

Oral GP IIb/IIIa inhibitors offer 2 advantages over intravenous therapy: easier administration and the possibility of chronic therapy.20 The Anti-PLAtelet Useful Dose (APLAUD) study of lotrafiban, an oral GP IIb/IIIa inhibitor, was undertaken with the goals to define safe, tolerable doses of lotrafiban that could then be investigated in larger, definitive outcome studies and to assess the acute and chronic pharmacodynamics of a range of doses (20-fold difference) in patients with cardiovascular or cerebrovascular atherosclerosis.

Methods

Population

Patients >18 years old were eligible if they had had a cardiovascular event (unstable angina or MI) within 42 days, TIA or minor ischemic stroke within 5 days to 6 months, or a major ischemic stroke within 30 days to 6 months before randomization. Unstable angina was defined as typical ischemic symptoms with either ECG changes (ST-segment depression, transient elevation, or T-wave inversion) or other objective evidence of coronary disease (prior MI, significant angiographic cardiovascular disease, or abnormal exercise test). A diagnosis of MI required typical ischemic symptoms with either elevated creatine kinase–MB or troponin values to above the local upper limit of normal or new Q waves. TIA was defined as a focal neurological deficit lasting for <24 hours. Ischemic stroke was defined as a neurological deficit lasting for >24 hours that was not caused by intracerebral hemorrhage and confirmed with CT or MRI.

Major exclusion criteria included National Institutes of Health Stroke Score of ≥2, prior intracranial hemorrhage or aneurysm, severe comorbidities that limit life expectancy, major surgery or trauma <3 months before entry, planned surgery (including carotid endarterectomy or CABG) or PCI within the previous 4 months, pregnancy, peptic ulcer within the past 3 years, platelet count of <150 000/µL, renal insufficiency (creatinine of >2.0 g/dL [288 µmol/L]), hepatic dysfunction (SGOT or SGPT value more than twice the upper limit of normal), abnormal prothrombin time (international normalized ratio of >1.5), uncontrolled hypertension (blood pressure of >180/110 mm Hg), treatment within the previous week with abciximab or within the previous 24 hours with heparin or thrombolysis, aspirin allergy or intolerance, or active drug or alcohol abuse within the past 6 months.

Treatment Assignment and Follow-Up

Patients were randomized in a double-blind fashion, via central telephone service, to receive 1 of 5 treatments: placebo twice daily or 5, 20, 50, or 100 mg lotrafiban BID. All patients received 300 to 325 mg/d aspirin. The study period was 12 weeks with patient visits at days 3, 5, 7, and 10 and weeks 2, 3, 4, 6, 8, and 12. There was a follow-up visit 1 week after the last dose of study drug. Complete blood cell counts, including platelets, were obtained at baseline and all visits. Additional samples were obtained when clinically indicated.
Pharmacodynamic Measurements

Inhibition of platelet aggregation was measured at selected centers with standard aggregometry techniques. The timing of blood sampling and number of samples taken to measure inhibition of platelet aggregation were as follows: baseline and day 14 visits (trough and 1.5, 3, and 6 hours after dose), week 12, early withdrawal, and follow-up visits (trough only). Blood was collected into 3.8% sodium citrate, platelet-rich plasma was prepared, and aggregation was measured with 20 μmol/L ADP as an agonist. The percent maximal aggregation and maximal slope were recorded. Aggregation testing was performed by local laboratory personnel without knowledge of patients’ clinical courses. Aggregation data were transferred and stored separately at the coordinating center and were unavailable to study personnel, except for the statistical group and a coordinating center hematologist. The hematologist reviewed each aggregation curve for technical correctness and calculated the percent inhibition of aggregation versus each patient’s baseline (predrug) value.

Thrombocytopenia Monitoring

Blood samples for platelet counts were obtained from all patients before the evening dosing of study drug. If the count fell to <60% of baseline at any visit, the patient did not take a dose that evening; a follow-up count was performed the next day. Automated platelet counts were confirmed manually to exclude pseudothrombocytopenia; if the manual count was <100 000/μL (thrombocytopenia), the study drug was stopped and a daily platelet count was repeated until it was ≥100 000/μL. If the count was <20 000/μL, it was recommended that the patient be admitted and monitored until the platelet count was ≥30 000/μL.

End Point Definitions

The primary end point was the incidence and tolerability of major and minor bleeding. Major bleeding was defined as intracerebral hemorrhage, blood transfusion, bleeding that required hospitalization, or decreased hemoglobin of ≥3.5 g/dL from baseline. Minor bleeding, as determined with a nurse-administered questionnaire, was defined as any new, prolonged, or more frequent bleeding: epistaxis, gingival bleeding, bruising, surface bleeding from cuts and shaving, melena or hematochezia, genitourinary bleeding (including increased menstrual bleeding), or other bleeding that did not meet the definition of major bleeding.

Patients were given a questionnaire (Figure 1) to assess minor bleeding at baseline; at days 7 and 14; at weeks 3, 4, 6, 8, and 12; and...
at follow-up or early withdrawal. At baseline, patients assessed their usual bleeding pattern. At later visits, patients compared their current bleeding level with this baseline level. If patients reported bleeding, they were asked whether it caused them concern or inconvenience and whether they would still take the study drug if proved to reduce the risk of heart attack, stroke, or vascular procedures.

Secondary end points included death, MI, stroke, or vascular procedures (CABG, PCI, carotid endarterectomy, or vascular surgery).

Safety Monitoring
Independent statisticians monitored individual platelet counts, bleeding, and drug tolerability and provided safety evaluation data on an ongoing basis to the Data Safety and Monitoring Board (DSMB). The DSMB members, who were clinical experts in this drug class and in clinical trial methods, formally reviewed the aggregate safety data. The DSMB charter specified that reviews were to occur after 50, 100, 200, and 350 patients were enrolled. Another review occurred at the recommendation of the committee chairman and trial statistician.

Statistical Methods
We assumed a rate of minor mucocutaneous bleeding of 10% in patients administered aspirin alone and calculated that 400 evaluable patients (80 per treatment arm) would be required to detect an absolute 20% increase in minor bleeding in patients randomized to lotrafiban with aspirin, with 90% power and no adjustments for multiple comparisons (2-tailed \( P = 0.05 \)). Five hundred patients were planned for enrollment, with the assumption of a 20% dropout rate.

Baseline characteristics and efficacy analyses were conducted on an intention-to-treat basis; platelet aggregation and safety assessments were conducted on an as-treated basis. Pairwise comparisons were made between each dose of lotrafiban and placebo and between lotrafiban doses combined and placebo. No adjustments were made for multiple comparisons. Statistical significance was determined to be a value of \( P = 0.05 \).

Results

Patient Characteristics
A total of 451 patients were enrolled at 68 centers in the United States, Canada, The Netherlands, Belgium, and France between April and September 1997 (Table 1). Randomization into the 100 mg lotrafiban arm was stopped after enrollment of 34 patients on recommendation by the DSMB due to excess major bleeding within that group. About two thirds of patients were enrolled as cardiovascular patients (unstable angina 31.5%, MI 31.0%). The remaining patients were enrolled as cerebrovascular patients (recent TIA 13.5%,

### TABLE 1. Patient Characteristics for All Randomized Patients

<table>
<thead>
<tr>
<th></th>
<th>Lotrafiban Group</th>
<th>Placebo Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, y (interquartile range)</td>
<td>62 (53–72)</td>
<td>63 (56–71)</td>
</tr>
<tr>
<td>Female, %</td>
<td>29.6</td>
<td>25.3</td>
</tr>
<tr>
<td>Median weight, kg (interquartile range)</td>
<td>82 (71–93)</td>
<td>81 (70–93)</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>66.2</td>
<td>62.5</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>19.2</td>
<td>19.8</td>
</tr>
<tr>
<td>Hyperlipidemia, %</td>
<td>63.7</td>
<td>59.4</td>
</tr>
<tr>
<td>Current smoker, %</td>
<td>19.6</td>
<td>27.5</td>
</tr>
<tr>
<td>Peripheral vascular disease, %</td>
<td>10.1</td>
<td>8.3</td>
</tr>
<tr>
<td>Prior stroke, %</td>
<td>30.4</td>
<td>36.5</td>
</tr>
<tr>
<td>Prior TIA, %</td>
<td>21.4</td>
<td>15.6</td>
</tr>
<tr>
<td>Prior MI, %</td>
<td>51.8</td>
<td>52.1</td>
</tr>
<tr>
<td>Prior CABG, %</td>
<td>12.1</td>
<td>14.6</td>
</tr>
<tr>
<td>Prior percutaneous intervention, %</td>
<td>41.1</td>
<td>42.7</td>
</tr>
<tr>
<td>Prior congestive heart failure, %</td>
<td>9.0</td>
<td>11.5</td>
</tr>
<tr>
<td>Prior carotid endarterectomy, %</td>
<td>3.9</td>
<td>2.1</td>
</tr>
</tbody>
</table>

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### TABLE 2. Percent Inhibition of ADP-Induced Platelet Aggregation

<table>
<thead>
<tr>
<th>Lotrafiban, mg</th>
<th>5</th>
<th>20</th>
<th>50</th>
<th>100</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline, % (interquartile range)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before dosing</td>
<td>(n=16)</td>
<td>(n=14)</td>
<td>(n=15)</td>
<td>(n=8)</td>
<td>(n=16)</td>
</tr>
<tr>
<td>24 (20–32)</td>
<td>22 (18–40)</td>
<td>28 (22–32)</td>
<td>27 (22–50)</td>
<td>26 (20–32)</td>
<td></td>
</tr>
<tr>
<td>1.5 h after dosing</td>
<td>(n=16)</td>
<td>(n=15)</td>
<td>(n=14)</td>
<td>(n=7)</td>
<td>(n=15)</td>
</tr>
<tr>
<td>26 (21–36)</td>
<td>43 (25–54)</td>
<td>56 (41–69)</td>
<td>83 (48–99)</td>
<td>31 (23–36)</td>
<td></td>
</tr>
<tr>
<td>3 h after dosing</td>
<td>(n=16)</td>
<td>(n=15)</td>
<td>(n=14)</td>
<td>(n=7)</td>
<td>(n=15)</td>
</tr>
<tr>
<td>28 (23–36)</td>
<td>52 (27–69)</td>
<td>50 (45–64)</td>
<td>88 (74–96)</td>
<td>27 (19–34)</td>
<td></td>
</tr>
<tr>
<td>6 h after dosing</td>
<td>(n=14)</td>
<td>(n=15)</td>
<td>(n=14)</td>
<td>(n=6)</td>
<td>(n=15)</td>
</tr>
<tr>
<td>24 (19–38)</td>
<td>44 (22–54)</td>
<td>49 (35–62)</td>
<td>69 (47–85)</td>
<td>28 (19–34)</td>
<td></td>
</tr>
<tr>
<td>Week 2, % (interquartile range)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before dosing</td>
<td>(n=13)</td>
<td>(n=12)</td>
<td>(n=12)</td>
<td>(n=5)</td>
<td>(n=14)</td>
</tr>
<tr>
<td>26 (20–28)</td>
<td>32 (24–50)</td>
<td>46 (40–63)</td>
<td>80 (34–85)</td>
<td>26 (20–27)</td>
<td></td>
</tr>
<tr>
<td>1.5 h after dosing</td>
<td>(n=15)</td>
<td>(n=13)</td>
<td>(n=12)</td>
<td>(n=5)</td>
<td>(n=14)</td>
</tr>
<tr>
<td>29 (20–35)</td>
<td>40 (33–55)</td>
<td>68 (42–92)</td>
<td>97 (84–99)</td>
<td>23 (17–28)</td>
<td></td>
</tr>
<tr>
<td>3 h after dosing</td>
<td>(n=16)</td>
<td>(n=13)</td>
<td>(n=13)</td>
<td>(n=6)</td>
<td>(n=15)</td>
</tr>
<tr>
<td>26 (19–36)</td>
<td>47 (35–81)</td>
<td>83 (76–89)</td>
<td>98 (82–100)</td>
<td>27 (24–31)</td>
<td></td>
</tr>
<tr>
<td>6 h after dosing</td>
<td>(n=16)</td>
<td>(n=13)</td>
<td>(n=13)</td>
<td>(n=6)</td>
<td>(n=15)</td>
</tr>
<tr>
<td>24 (22–33)</td>
<td>46 (36–62)</td>
<td>70 (66–87)</td>
<td>92 (77–95)</td>
<td>29 (21–37)</td>
<td></td>
</tr>
</tbody>
</table>
stroke 23.9%). Baseline characteristics were similar for the lotrafiban and placebo patients.

Pharmacodynamics
Lotrafiban produced dose-dependent inhibition of ADP-induced platelet aggregation (Table 2). Figure 2A shows median inhibition before the week 2 morning dose (ie, the trough effect at steady-state). Figure 2B shows the median peak inhibition of aggregation as measured after the week 2 morning dose. The effects of the 5-mg dose were similar to those of placebo, whereas the 100-mg dose inhibited aggregation by nearly 100% in all tested patients.

Bleeding and Tolerability
There was a dose-dependent increase in minor bleeding (trend testing for any bleeding, comparison of the 5-, 20-, and 50-mg lotrafiban groups versus placebo, \( P=0.001 \)); the placebo and the 5-mg groups had similar rates of both minor and major bleeding (Table 3). Major bleeding and packed red blood cell transfusion were infrequent in all treatment arms (trend testing for major bleeding, comparison of the 5-, 20-, and 50-mg lotrafiban groups versus placebo, \( P=0.46 \)) except the 100-mg arm. Minor bleeding was most often bruising or mucosal bleeding (38.7% and 17.8% for lotrafiban versus 28.4% and 9.5% for placebo, respectively). There also was greater gastrointestinal bleeding among lotrafiban-treated patients versus placebo recipients (12.3% versus 3.2%), although most of this was hemorhoidal and minor. No intracranial hemorrhages occurred.

Except for the 100-mg dose, lotrafiban was well tolerated. Only 1.8%, 0%, and 7.7% in the 5-, 20-, and 50-mg groups, respectively, responded at any time on the questionnaire that they had bleeding that was causing concern or inconvenience and that they would not take the drug chronically even if proved to be clinically beneficial. The incidence of this response in the placebo group was 3.2%. Early withdrawal, for any reason, from study drug occurred in 13.4% (5 mg), 14.1% (20 mg), 27.9% (50 mg), and 21.1% (placebo) of patients. Withdrawal rates for either major or minor bleeding were 3.6% (5 mg), 2.0% (20 mg), 9.6% (50 mg), and 2.1% (placebo).

Thrombocytopenia
Five lotrafiban-treated patients developed thrombocytopenia (\(<100,000\text{ platelets/\mu L}\) (1.4%, 95% CI 0.2% to 2.7%), as did 1 placebo-treated patient (1.1%, 95% CI 0% to 3.1%), all within 10 days of initiation of therapy (Table 4). Four cases of thrombocytopenia occurred in the 50-mg lotrafiban arm (3.9%, 95% CI 0.2% to 7.7%), and 1 occurred in the 100-mg group. Three patients in the lotrafiban group, versus none in the placebo group, had a nadir platelet count of \(<20,000/\mu L\) (0.9%, 95% CI 0% to 1.8%). Platelet counts recovered in all patients several days after the study drug was stopped except in the patient administered 100 mg lotrafiban. Her platelet count did not return to normal for \(\approx 16\) days, during which she had detectable blood levels of lotrafiban.

Efficacy
The composite end point of death, MI, or readmission for cardiac or neurological events occurred in 10.0% of the combined lotrafiban patients (excluding the 100-mg group) versus 13.8% of the placebo patients (\( P=0.29 \)) (Table 5). The difference in the clinical composite was mainly due to a difference in revascularization procedures performed at the discretion of the investigators.

Discussion
Other trials that have examined the safety and efficacy of the oral platelet GP IIb/IIIa inhibitors have been limited to patients with ACSs or undergoing PCI. The current study is
the first trial of a GP IIb/IIIa inhibitor to enroll patients with either coronary or cerebral atherosclerosis. In this population, we noted dose-dependent effects on the inhibition of platelet aggregation and on bleeding risk. We identified both a dosage of lotrafiban that was indistinguishable from placebo (5 mg BID) and a dosage with an unacceptable bleeding profile (100 mg BID). Most reported bleeding was minor, consisting of either mucocutaneous bleeding or surface bruising.

According to a customized, nurse-administered questionnaire, lotrafiban was well tolerated at the 5-, 20-, and 50-mg doses. Enrollment into the 100-mg arm was stopped early due to excess major bleeding on recommendation of the DSMB. The incidence of thrombocytopenia (which tended to occur early during treatment) was low and within the range expected on the basis of reports of similar agents. Estimation of the true rate of thrombocytopenia will require much larger cohorts.

Similar to other oral and intravenous platelet GP IIb/IIIa inhibitors, lotrafiban provided dose-dependent inhibition of ADP-induced platelet aggregation. The threshold level that confers clinical benefit for patients with ACSs or undergoing PCI has been assumed to be 80% inhibition of ADP-induced platelet aggregation (with intravenous GP IIb/IIIa inhibitors), but the optimal level of platelet inhibition to safely provide maximum clinical benefit is unknown.21 This is especially true for chronic, oral administration of these agents, for which patients will likely be less tolerant of even minor bleeding.4 Also unsettled is whether a constant inhibition is more effective or better tolerated than “pulse therapy,” in which periods of moderate to high inhibition are punctuated by recovery periods. In the latter situation, background aspirin therapy may be especially important to provide a low, constant level of platelet inhibition.

An early trial of xemilofiban, another oral GP IIb/IIIa inhibitor, administered with aspirin after PCI, showed a dose-related increase in mild bleeding and a low overall rate of moderate or severe bleeding.23 As in APLAUD, the need for blood transfusion was unusual. In a trial of sibrafiban, an oral peptidomimetic GP IIb/IIIa inhibitor, versus aspirin in ACS, the mean peak platelet inhibition in response to 20 μmol/L ADP ranged from 47% to 97% on day 28 across the 7 doses that were evaluated.24 Patients with once-daily dosing had more bleeding than those with twice-daily therapy, which correlated with higher peak levels of inhibition. Similarly, intolerable bleeding occurred among the present patients who received 100 mg lotrafiban BID, a dosage that resulted in close to 100% inhibition of platelet aggregation.

All patients in APLAUD received lotrafiban or placebo in addition to aspirin. We do not know whether the addition of aspirin (which provides constant and at least low-level platelet inhibition) to chronic GP IIb/IIIa inhibition increases bleeding risk. Our results and those of Kereiakes et al23 suggest that the combination of an appropriate dose of an oral GP IIb/IIIa antagonist and aspirin can be used with an acceptable bleeding incidence. Furthermore, continued aspirin use ensures that patients have a fixed cyclooxygenase 1–mediated antiplatelet effect during the trough period of GP IIb/IIIa inhibition.

Major bleeding was infrequent overall, but minor bleeding occurred in a dose-dependent manner and was more likely to cause early drug termination than was major bleeding. In the sibrafiban trial, drug was stopped in 51%

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**TABLE 4. Thrombocytopenia**

<table>
<thead>
<tr>
<th>Age, y</th>
<th>Sex</th>
<th>Stratum</th>
<th>Dose, mg</th>
<th>Day</th>
<th>Nadir/μL</th>
<th>Complications</th>
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<tbody>
<tr>
<td>60</td>
<td>M</td>
<td>Cardiovascular</td>
<td>Placebo</td>
<td>8</td>
<td>91 000</td>
<td>None</td>
</tr>
<tr>
<td>55</td>
<td>M</td>
<td>Cardiovascular</td>
<td>50</td>
<td>9</td>
<td>2000</td>
<td>Platelet transfusion</td>
</tr>
<tr>
<td>46</td>
<td>M</td>
<td>Cardiovascular</td>
<td>50</td>
<td>4</td>
<td>63 000</td>
<td>None</td>
</tr>
<tr>
<td>53</td>
<td>M</td>
<td>Cardiovascular</td>
<td>50</td>
<td>7</td>
<td>80 000</td>
<td>Bruising</td>
</tr>
<tr>
<td>52</td>
<td>M</td>
<td>Cardiovascular</td>
<td>50</td>
<td>4</td>
<td>6000</td>
<td>Hospitalized, petechiae</td>
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<tr>
<td>82</td>
<td>F</td>
<td>Cardiovascular</td>
<td>100</td>
<td>8</td>
<td>1000</td>
<td>Gastrointestinal bleed, MI, platelet/red blood cell transfusions, recovery &gt;2 wk</td>
</tr>
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</table>

**TABLE 5. Efficacy Events for All Randomized Patients**

<table>
<thead>
<tr>
<th>Lotrafiban, mg</th>
<th>5 (n=116)</th>
<th>20 (n=98)</th>
<th>50 (n=107)</th>
<th>100 (n=34)</th>
<th>Placebo (n=96)</th>
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<tbody>
<tr>
<td>Death, %</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1.0</td>
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<td>MI, %</td>
<td>0.9</td>
<td>0.9</td>
<td>0.9</td>
<td>5.9</td>
<td>1.1</td>
</tr>
<tr>
<td>Percutaneous intervention, %</td>
<td>4.3</td>
<td>2.0</td>
<td>1.9</td>
<td>0</td>
<td>8.4</td>
</tr>
<tr>
<td>CABG, %</td>
<td>0</td>
<td>3.1</td>
<td>0.9</td>
<td>0</td>
<td>0</td>
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<td>Ischemic stroke, %</td>
<td>0.9</td>
<td>1.0</td>
<td>0</td>
<td>0</td>
<td>1.1</td>
</tr>
<tr>
<td>Carotid endarterectomy, %</td>
<td>0.9</td>
<td>2.0</td>
<td>0.9</td>
<td>0</td>
<td>1.1</td>
</tr>
<tr>
<td>Composite, %</td>
<td>10.3</td>
<td>9.2</td>
<td>10.3</td>
<td>14.7</td>
<td>13.8</td>
</tr>
</tbody>
</table>

*Death, MI, or readmission for cardiac or neurological events.
of patients who had either major or minor bleeding. In APLAUD, the rate of minor bleeding was 34.7% even among patients who received placebo plus aspirin, which suggests that bleeding rates are higher than expected with increased ascertainment efforts. Likewise, Kereiakes et al reported mild and insignificant bleeding in >33% of the placebo-plus-aspirin patients. There also was a tolerability dose-response, yet even with the 50-mg dose, <10% of patients found the bleeding to be intolerable versus ≈3% in the placebo group. A large outcomes trial will be required to determine actual bleeding rates and tolerability among a broader population. The larger trial also will provide an estimate of benefit, so the clinical community can consider appropriate risk–benefit tradeoffs.

The incidence of thrombocytopenia with lotrafiban was within the anticipated 1.0%, which is comparable with reports for other oral agents. Thrombocytopenia also occurs with intravenous GP IIb/IIIa inhibitors. Much less is known about the incidence and clinical course of thrombocytopenia with oral GP IIb/IIIa inhibition, because the relevant experience is limited to dose-finding studies of several hundred patients. Kereiakes et al reported 2 cases (0.5%) of thrombocytopenia (100,000 platelets/μL) among patients receiving xemilofiban, observed on days 10 and 16 of therapy.

Frequent platelet count sampling, as was done in APLAUD, suggests that thrombocytopenia occurs within the first 10 days of therapy, may be profound (<20,000 platelets/μL), and is reversible after the drug is stopped. These patients have serious reductions in platelet count days after therapy has begun; thus, the mechanism of thrombocytopenia with oral glycoprotein IIb/IIIa antagonists may differ from that with intravenous delivery, where declines in platelet count occur much sooner.

Four patients in the 50-mg twice-daily dosing group developed thrombocytopenia. Whether this occurs more often with higher doses cannot be determined from this study or those of other agents to date. One elderly patient with diminished renal function who was randomized to the 100-mg twice-daily dosage group in APLAUD had prolonged thrombocytopenia, during which time she had measurable plasma levels of lotrafiban. This event highlights the need to better understand both the mechanisms responsible for thrombocytopenia and the ways to expedite the clearance of oral agents when adverse consequences arise.

We had insufficient statistical power to make inferences about the efficacy of lotrafiban. Overall event rates were low during the 12-week observation period, likely reflecting the lower risk of this population enrolled in a phase II trial of a new antiplatelet agent. A large efficacy trial of GP IIb/IIIa inhibition begun days to weeks after an acute ischemic event likely will need to continue for many months to years as a secondary prevention strategy, because event rates depend on accumulated benefit over time rather than on a cluster of events around the acute episode.

Lotrafiban provides dose-dependent platelet inhibition across a spectrum of vascular disease. These levels of platelet inhibition correlate with bleeding risk and drug tolerance. The long-term administration of lotrafiban with aspirin for patients with atherosclerosis who are at risk for future ischemic events appears attractive and is worthy of study in large, definitive trials.

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References


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for the Anti-Platelet Useful Dose (APLAUD) Study Investigators

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