

LONG-TERM TREATMENT WITH A PLATELET GLYCOPROTEIN-RECEPTOR ANTAGONIST AFTER PERCUTANEOUS CORONARY REVASCULARIZATION

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ABSTRACT

Background When administered intravenously at the time of percutaneous coronary revascularization, glycoprotein IIb/IIIa receptor antagonists decrease the incidence of death and nonfatal myocardial infarction and the need for urgent revascularization. We hypothesized that long-term administration of oral glycoprotein IIb/IIIa antagonists, which block the aggregation of platelets, might stabilize intravascular plaque and prevent additional ischemic cardiac events.

Methods We conducted a prospective, double-blind trial in which 7232 patients were randomly assigned to receive 20 mg of oral xemilofiban or placebo 30 to 90 minutes before undergoing percutaneous coronary revascularization, with maintenance doses of 10 or 20 mg of xemilofiban or placebo administered three times daily for up to 182 days. There were two primary composite end points: one was death, nonfatal myocardial infarction, or urgent revascularization at 182 days, and the other was death or nonfatal myocardial infarction at 182 days.

Results Death, myocardial infarction, or urgent revascularization occurred within 182 days in 324 patients who received placebo (Kaplan–Meier cumulative event rate, 13.5 percent), 332 who received 10 mg of xemilofiban (13.9 percent, $P=0.82$ for the comparison with placebo), and 306 who received 20 mg of xemilofiban (12.7 percent, $P=0.36$ for the comparison with placebo). The incidence of death or myocardial infarction was also similar in all three groups. Clinically significant hemorrhagic complications and thrombocytopenia were infrequent.

Conclusions The administration of the glycoprotein IIb/IIIa antagonist xemilofiban before percutaneous coronary revascularization and for up to six months thereafter does not significantly reduce the incidence of important clinical end points. (N Engl J Med 2000;342:1316–24.)

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THE activation and aggregation of platelets are thought to be responsible for the development of thrombi that lead to ischemic events after percutaneous transluminal coronary revascularization (PTCR).¹ The aggregation of platelets is mediated by the binding of fibrinogen to the platelet glycoprotein IIb/IIIa receptor.^{2,3} Numerous trials have demonstrated that the administration of intravenous glycoprotein IIb/IIIa receptor

antagonists immediately before and during the 24-to-48-hour period after PTCR reduces the incidence of death and myocardial infarction and the need for urgent revascularization.^{4–15} The reduction in ischemic events persisted for 30 days or more in some studies, but the benefit was derived from a reduction in early ischemic events rather than from continued prevention of new events. Since platelet activation persists for up to 1 month after the onset of acute coronary syndromes¹⁶ and since reocclusion may occur for up to 21 days after the implantation of a stent,¹⁷ long-term oral treatment with a glycoprotein-receptor antagonist may have clinical value.

Current oral antithrombotic regimens for PTCR have serious limitations. Although ticlopidine has been widely used with aspirin to prevent thrombosis after stent placement, the Food and Drug Administration has not approved the use of the drug for this indication.^{18–26} In addition, ticlopidine causes neutropenia and thrombotic thrombocytopenic purpura,^{27,28} and restenosis within the stent remains a problem.^{29–32}

The Evaluation of Oral Xemilofiban in Controlling Thrombotic Events (EXCITE) trial tested the hypothesis that long-term oral administration of a glycoprotein IIb/IIIa receptor antagonist would provide sustained protection from death, myocardial infarction, and the need for urgent revascularization.

METHODS

Study Design

Our phase 3 trial was a double-blind, randomized, placebo-controlled study conducted at 412 centers in North and South America, Europe, Israel, Australia, New Zealand, and South Africa. The protocol for the trial has been described in detail elsewhere.³³

Enrollment of Patients

Patients with angiographic evidence of clinically significant coronary artery disease necessitating PTCR were eligible for the study. Patients at high risk for ischemic events³⁴ were sought in order to maximize the event rate and thus increase the opportunity to

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demonstrate a therapeutic effect. Patients who had received abciximab before PTCR were not eligible for enrollment.

The main exclusion criteria were a history of bleeding disorders or active bleeding, thrombocytopenia (platelet count, <120,000 per cubic millimeter), coagulation-factor deficiency, uncontrolled hypertension, major trauma or surgery within the previous three months, thrombolytic treatment within six hours before revascularization, a serum creatinine level higher than 1.5 mg per deciliter (132.6 μ mol per liter), an inability to discontinue oral anticoagulant therapy, nonhemorrhagic stroke within the previous two months, a history of hemorrhagic stroke, or an inability to provide informed consent.

Study Protocol

We tested the efficacy of xemilofiban administered orally in a dose of 10 or 20 mg given three times daily for up to six months. These doses were selected to minimize the risk of excessive bleeding during the treatment period. The level of inhibition of adenosine diphosphate-induced platelet aggregation is 40 to 70 percent with the 10-mg regimen and 60 to 90 percent with the 20-mg regimen.³⁵ The protocol was approved by the institutional review board of each participating hospital, and all patients gave written informed consent before they were enrolled in the study.

After the diagnostic angiogram had been obtained and before PTCR was performed, patients were randomly assigned to one of three regimens: a single oral dose of 20 mg of xemilofiban administered before PTCR and a maintenance dose of 20 mg given three times daily after the procedure, a single oral dose of 20 mg of xemilofiban administered before the procedure and a maintenance dose of 10 mg given three times daily, or placebo administered both before and after the procedure. The random assignments were made by telephone with the use of an interactive voice-response computer system and were stratified according to the study center. Among patients in whom stents were implanted, those in the placebo group also received ticlopidine, in a dose of 250 mg administered orally twice daily for 14 to 28 days, and those in both xemilofiban groups received a placebo that was identical in appearance to ticlopidine (in order to maintain the blinding). The initial dose of ticlopidine or placebo was administered 30 to 90 minutes before the performance of PTCR, with maintenance treatment initiated 6 to 8 hours after the first dose. All patients received a daily dose of 80 to 325 mg of aspirin.

Patients were evaluated 10 to 21 days and 60 days after PTCR. Subsequent monitoring for cardiac events, safety, laboratory values, concurrent medications, and compliance was performed monthly by telephone or by site visits. Cardiac end points were reported throughout the 182-day study period, regardless of compliance. Adverse events, including bleeding, were reported only if they occurred while the patient was receiving the study drug. A follow-up visit was scheduled to detect cardiac events that occurred within 30 days after the study regimen had been terminated.

Study End Points

There were two primary end points. The first was event-free survival at 182 days, with an event defined as death, nonfatal myocardial infarction, or the need for urgent revascularization on the basis of evidence of ischemia, cardiac symptoms, or both. The second primary end point was event-free survival at 182 days, with an event defined as death or nonfatal myocardial infarction.

Secondary end points included event-free survival at 30 days and at 7 months for the two sets of events noted above, the cumulative incidence of bleeding events, and survival at 30 days, 6 months, and 7 months without the need for revascularization and without other events, including rehospitalization because of unstable angina or nonhemorrhagic stroke. We also evaluated the efficacy of treatment with xemilofiban according to whether the patient received a stent.

For patients who did not have a diagnosis of myocardial infarction at the time of enrollment, the criterion for a new myocardial infarction occurring within 24 hours after PTCR was a creatine

kinase MB level that was more than three times the upper limit of the normal range.³⁶ For patients undergoing PTCR within 24 hours after the onset of acute myocardial infarction, the criterion for the diagnosis of reinfarction within 24 hours after the procedure was defined as a creatine kinase MB level that was twice as high as the lowest elevated value before PTCR. For all patients, a myocardial infarction more than 24 hours after PTCR was defined by a creatine kinase level that was more than two times the upper limit of the normal range or the appearance of new Q waves of 0.04 second's duration with a depth of more than one quarter of the corresponding R-wave amplitude in two or more contiguous leads. When creatine kinase MB values were not available, values for total creatine kinase were used. Serum samples were collected at base line and 8, 16, and 24 hours after PTCR. Thereafter, cardiac enzymes were measured only when clinically indicated.

Urgent revascularization was defined as unanticipated revascularization (PTCR or coronary bypass surgery) performed because of unstable coronary symptoms (unstable angina or myocardial infarction) or evidence of acute, unprovoked ischemia.

Episodes of bleeding were considered moderate if they caused a drop in the hemoglobin level of at least 5 g per deciliter or a drop in the hematocrit of 15 percent or if a transfusion was required. All episodes of intracranial bleeding and bleeding that caused hemodynamic compromise and required intensive monitoring and intervention were considered severe. Episodes of mild bleeding were also recorded.

An independent clinical-events committee adjudicated all reported cardiac end points and episodes of moderate or severe bleeding. In addition, a central electrocardiographic laboratory reviewed all electrocardiograms obtained at base line and on withdrawal of the study drug. Another committee reviewed all cases of thrombocytopenia (defined as a platelet count of less than 80,000 per cubic millimeter) to determine whether they were caused by the study drug. Committee members were unaware of the treatment assignments.

Statistical Analysis

The trial was designed to have 90 percent power to detect a 25 percent reduction in the composite end point of death, nonfatal myocardial infarction, or urgent revascularization in pairwise comparisons of each xemilofiban treatment group with placebo, with a two-sided type I error of 0.025, assuming an event rate of 17.6 percent in the placebo group. Early in the trial and before unblinding, the type I error for each treatment comparison was partitioned between the two primary end points, with a type I error of 0.02 allocated to the first primary end point, and the remainder to the second primary end point.

Two interim analyses of efficacy (and more frequent reviews of safety) were conducted by an independent data and safety monitoring board with the use of symmetric O'Brien-Fleming type sequential monitoring boundaries. Analyses were prepared for the data and safety monitoring board by an independent data-analysis center. For the final analysis, the level of significance was 0.02 for the first primary end point and 0.01 for the second primary end point, with simulation used to account for repeated testing and the correlation between the test statistics for the two primary end points over the course of the trial.³⁷

Cumulative event rates for each end point were estimated with the use of the Kaplan-Meier method; for composite end points, the time from randomization to the first occurrence of any component of the end point was analyzed. Comparison of each xemilofiban group with the placebo group was performed with the use of a protocol-specified Wilcoxon test for cardiac events and a log-rank test for bleeding events. Hazard ratios and 95 percent confidence intervals were estimated with the use of a Cox model. Analyses of cardiac end points were performed on an intention-to-treat basis and included all patients according to the assigned treatment and all adjudicated cardiac end points during the designated follow-up period.

TABLE 1. BASE-LINE AND PROCEDURAL CHARACTERISTICS OF THE PATIENTS.

CHARACTERISTIC*	PLACEBO (N=2414)	XEMILOFIBAN, 10 mg (N=2400)	XEMILOFIBAN, 20 mg (N=2418)
Male sex (%)	79.4	76.5	78.5
White race (%)	88.8	88.2	89.9
Age (yr)			
Median	59	59	59
Interquartile range	52–67	51–67	51–67
Weight (kg)			
Median	81.7	81.0	81.2
Interquartile range	72.6–92.3	72.0–91.0	72.2–92.1
Diagnosis at entry (%)			
Unstable angina	44.7	44.7	44.5
Stable angina	42.6	42.8	42.4
Myocardial infarction	12.7	12.5	13.1
Prior CABG (%)	9.6	10.4	10.6
High-risk criteria (%)†			
Lesion type B1 (and age >65 yr), B2, or C	56.8	55.0	55.7
Diabetes mellitus	17.9	20.3	18.0
Ejection fraction <0.30	2.0	2.1	1.9
Multivessel disease	47.4	47.6	44.8
Lesion in saphenous-vein graft	3.8	4.8	4.7
Intervention (%)‡			
PTCR with stenting	71.9	70.1	71.4
PTCR without stenting	25.0	26.0	25.0
PTCR not performed	3.2	3.9	3.6
Rotational atherectomy	4.3	4.8	5.3
Use of abciximab	1.6	1.2	1.5
Heparin dose (units/kg of body weight)			
Median	118	119	118
Interquartile range	98–149	98–152	97–149
Maximal ACT (sec)			
Median	310	317‡	320‡
Interquartile range	265–356	268–377	270–374

*CABG denotes coronary-artery bypass grafting, PTCR percutaneous transluminal coronary revascularization, and ACT activated clotting time.

†The categories are not mutually exclusive.

‡P<0.001 for the comparison with the placebo group.

Other variables are reported as medians with interquartile ranges (25th and 75th percentiles), in the case of continuous variables, and as frequencies, in the case of categorical variables, with treatment-group comparisons performed with the use of the Wilcoxon test and the chi-square test, respectively. All reported P values are nominal and two-sided.

RESULTS

Between June 25, 1997, and April 24, 1998, a total of 7232 patients between the ages of 25 and 81 years were enrolled in the study. The average duration of follow-up was 205 days in the placebo group and the group that received 20 mg of xemilofiban and 204 days in the group that received 10 mg of xemilofiban.

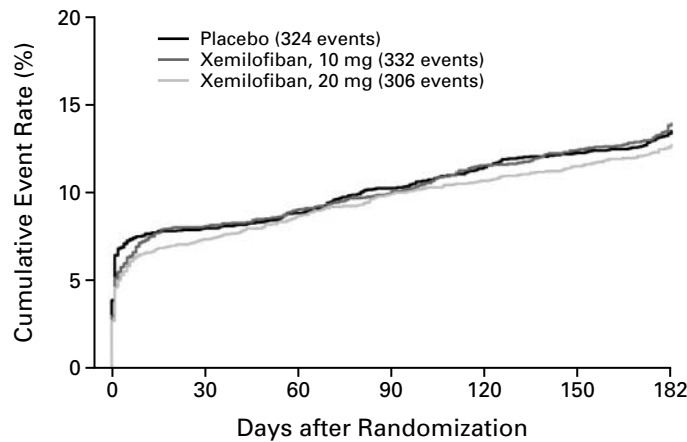
The base-line characteristics of the patients are shown in Table 1. There were no significant differences among the three groups. The characteristics of the index PTCR are also shown in Table 1. Stents

were implanted in 71 percent of patients, and rotational atherectomy was performed in 5 percent, with no significant differences among the groups. The median maximal activated clotting time was significantly longer in both xemilofiban groups than in the placebo group (P<0.001).

Death, nonfatal myocardial infarction, or urgent revascularization occurred within 182 days in 324 patients in the placebo group (Kaplan–Meier cumulative event rate, 13.5 percent), 332 patients in the 10-mg xemilofiban group (cumulative event rate, 13.9 percent; P=0.82 for the comparison with the placebo group; hazard ratio, 1.03; 98 percent confidence interval, 0.86 to 1.23), and 306 patients in the 20-mg xemilofiban group (cumulative event rate, 12.7 percent; P=0.36 for the comparison with the placebo group; hazard ratio, 0.94; 98 percent confidence interval, 0.78 to 1.13) (Fig. 1 and Table 2). Death or nonfatal myocardial infarction occurred within 182 days in 215 patients in the placebo group (cumulative event rate, 8.9 percent), 220 patients in the 10-mg xemilofiban group (cumulative event rate, 9.2 percent; P=0.87 for the comparison with the placebo group; hazard ratio, 1.02; 99 percent confidence interval, 0.80 to 1.31), and 199 patients in the 20-mg xemilofiban group (cumulative event rate, 8.2 percent; P=0.36 for the comparison with the placebo group; hazard ratio, 0.92; 99 percent confidence interval, 0.71 to 1.18). There were no significant differences among the three groups in either composite end point at 30 or 213 days (Table 2). Mortality rates were similar to or lower than those reported in prior studies³⁸; however, there were nominally more deaths in the 10-mg xemilofiban group than in the placebo group (Table 2).

Hazard ratios for the composite end point of death, nonfatal myocardial infarction, or urgent revascularization within 182 days are shown in Figure 2 for various subgroups of patients. None of the differences between subgroups were significant. Treatment effects were similar in the stent and no-stent groups. In addition, there were no significant or clinically meaningful differences in the treatment effect according to the timing of the initial dose of the study drug (i.e., whether it was administered within 60 minutes before the performance of PTCR or earlier) or the timing of the first maintenance dose.

Analyses of myocardial infarction at various intervals after PTCR were performed to determine whether there was a period during which xemilofiban conferred a benefit. Notably, myocardial infarctions that occurred within a day after randomization or after the index procedure were less frequent in patients treated with 10 or 20 mg of xemilofiban than in those who received placebo (P=0.02 for both comparisons) (Fig. 3). Subsequently, however, there were more infarctions in both xemilofiban groups, and by 30 days, there were no significant differences between the xemilofiban groups and the placebo group (Table 2).



No. AT RISK		2414	2220	2197	2163	2134	2110	1974
Placebo								
Xemilofiban, 10 mg		2400	2206	2183	2160	2120	2095	1944
Xemilofiban, 20 mg		2418	2242	2212	2178	2158	2132	2005

Figure 1. Kaplan–Meier Cumulative Event Rates for the Composite End Point of Death, Nonfatal Myocardial Infarction, or Urgent Revascularization.

The cumulative event rates in the two xemilofiban groups did not differ significantly from the rate in the placebo group.

TABLE 2. KAPLAN–MEIER CUMULATIVE EVENT RATES FOR CARDIAC END POINTS.

TIME AND EVENT	PLACEBO (N=2414)		XEMILOFIBAN, 10 mg (N=2400)			XEMILOFIBAN, 20 mg (N=2418)		
	NO. OF EVENTS	CUMULATIVE RATE	NO. OF EVENTS	CUMULATIVE RATE	P VALUE*	NO. OF EVENTS	CUMULATIVE RATE	P VALUE*
		%		%			%	
30 Days								
Death	8	0.3	20	0.8	0.02	14	0.6	0.20
Myocardial infarction	147	6.1	139	5.8	0.58	131	5.4	0.28
Urgent revascularization	71	2.9	86	3.6	0.23	64	2.6	0.49
Death or myocardial infarction	153	6.3	154	6.4	0.98	137	5.7	0.29
Death, myocardial infarction, or urgent revascularization	191	7.9	192	8.0	0.96	176	7.3	0.33
182 Days								
Death	24	1.0	40	1.7	0.04	27	1.1	0.68
Myocardial infarction	202	8.4	192	8.1	0.56	181	7.5	0.23
Urgent revascularization	166	6.9	184	7.7	0.30	158	6.6	0.59
Death or myocardial infarction†	215	8.9	220	9.2	0.87	199	8.2	0.36
Death, myocardial infarction, or urgent revascularization†	324	13.5	332	13.9	0.82	306	12.7	0.36
213 Days								
Death	25	1.0	44	1.9	0.02	30	1.3	0.55
Myocardial infarction	211	8.8	207	8.8	0.76	194	8.1	0.32
Urgent revascularization	171	7.2	189	8.0	0.29	165	7.0	0.66
Death or myocardial infarction	225	9.4	238	10.1	0.62	213	8.9	0.46
Death, myocardial infarction, or urgent revascularization	337	14.1	352	14.9	0.64	325	13.6	0.47

*P values are nominal and are for comparisons with the placebo group.

†This was a primary end point.

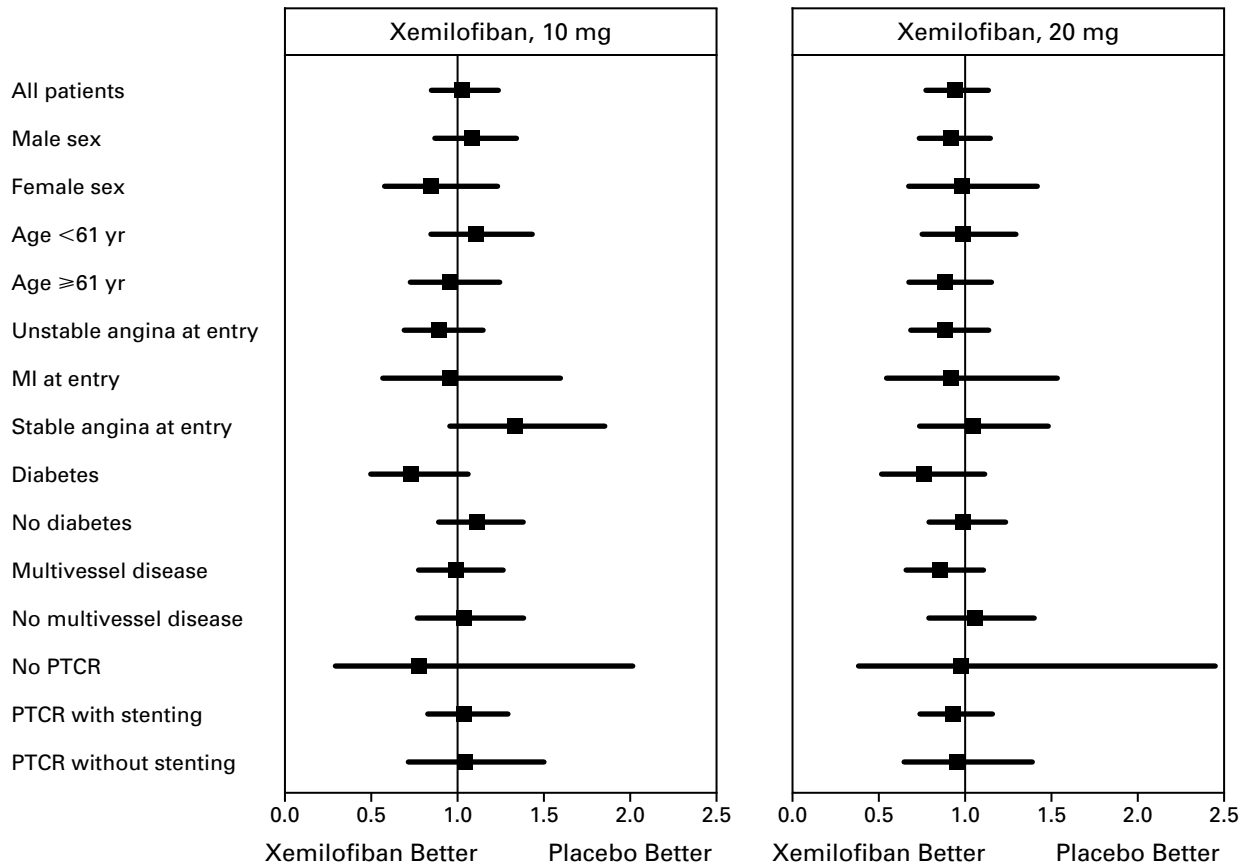


Figure 2. Hazard Ratios for the Composite End Point of Death, Myocardial Infarction, or Urgent Revascularization within 182 Days after Randomization. The horizontal lines indicate 98 percent confidence intervals. MI denotes myocardial infarction, and PTCR percutaneous transluminal coronary revascularization.

Overall, 67.0 percent of the patients receiving placebo completed the treatment regimen, as compared with 64.2 percent of the patients receiving 10 mg of xemilofiban ($P=0.04$) and 59.4 percent of those receiving 20 mg of xemilofiban ($P<0.001$). The proportions of patients who withdrew from the study because of cardiac events were similar in the placebo, 10-mg, and 20-mg groups (10.0, 10.8, and 9.6 percent, respectively). The proportions of patients who withdrew because of episodes of bleeding (Table 3) were significantly larger in the 10-mg and 20-mg xemilofiban groups (6.1 and 11.6 percent, respectively) than in the placebo group (1.5 percent), and these differences account for the lower overall rates of completion in the xemilofiban groups.

Although a majority of the patients taking xemilofiban had bleeding, moderate or severe episodes of bleeding were infrequent (Table 3). Bleeding episodes occurred throughout the treatment period rather than predominantly in the initial period after revascularization. Thrombocytopenia (a platelet count of less

than 80,000 per cubic millimeter) occurred in 0.5 percent of the patients receiving 10 or 20 mg of xemilofiban, generally in the first three or four weeks of treatment, and in 0.1 percent of the patients receiving placebo. Among the patients with thrombocytopenia, the nadir platelet count was generally less than 20,000 per cubic millimeter, and the count returned to a level of 80,000 per cubic millimeter or higher within three or four days after the study drug had been withdrawn. No deaths were attributable to thrombocytopenia.

DISCUSSION

The EXCITE trial tested the hypothesis that in patients treated with PTCR, long-term oral administration of xemilofiban, after an initial dose given before the procedure, would extend the clinical benefit of short-term glycoprotein IIb/IIIa receptor blockade previously demonstrated with abciximab, tirofiban, and eptifibatide.³⁹ Our finding that treatment with xemilofiban did not improve the long-term out-

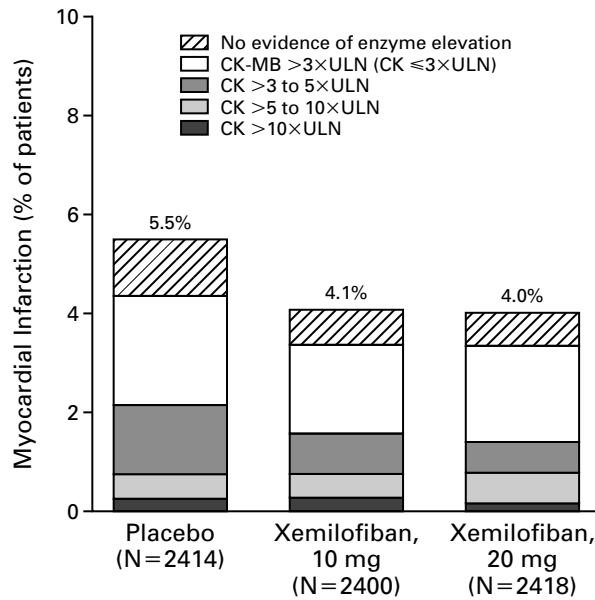


Figure 3. Myocardial Infarctions Occurring within One Day after Randomization or the Index Revascularization, According to the Creatine Kinase (CK) Level.

P=0.02 for the comparison between each xemilofiban group and the placebo group. ULN denotes the upper limit of the normal range.

come after PTCR has two possible explanations. First, this short-acting oral agent may not have had sufficient efficacy in the short term. Second, long-term use of the agent may not have had an incremental benefit. Pharmacokinetic studies have shown that 20 mg of xemilofiban provides 60 to 80 percent receptor blockade 60 to 90 minutes after oral administration.³⁵ Since we found no difference in outcomes according to the timing of the initial dose in relation to PTCR or the timing of the first maintenance dose, timing is an unlikely explanation for our results.

Although we did not perform systematic assays of platelet inhibition, it is possible to make inferences from other studies. Dangas et al.⁴⁰ have shown that intravenous administration of glycoprotein-receptor antagonists inhibits the generation of thrombin and prolongs the activated clotting time. In our study, the activated clotting time was significantly longer in the patients who received 10 or 20 mg of xemilofiban than in those who received placebo, suggesting that the biologic effects of xemilofiban are similar to those of other glycoprotein-receptor antagonists. More important, as with all previous trials of intravenous agents in patients undergoing PTCR, xemilofiban significantly decreased the rate of myocardial infarction in the first 24 hours after the procedure. In addition, the need for “bailout” use of abciximab was excep-

TABLE 3. EPISODES OF BLEEDING.

VARIABLE	PLACEBO (N=2414)		XEMILOFIBAN, 10 mg (N=2400)		P VALUE*	XEMILOFIBAN, 20 mg (N=2418)		P VALUE*
	NO. OF EVENTS	RATE %	NO. OF EVENTS	RATE %		NO. OF EVENTS	RATE %	
Any bleeding†								
Within 30 days	763	32.8	1071	46.3	<0.001	1324	57.1	<0.001
Within 182 days	919	41.1	1313	59.0	<0.001	1628	72.6	<0.001
Moderate or severe bleeding†								
Within 30 days	31	1.4	75	3.3	<0.001	96	4.3	<0.001
Within 182 days	39	1.8	106	5.1	<0.001	145	7.1	<0.001
Site or sign of moderate or severe bleeding								
Groin	10	0.4	20	0.8	0.06	31	1.3	0.001
Intracranial site	1	<0.1	3	0.1	0.31	5	0.2	0.10
Drop in hematocrit or hemoglobin level	16	0.7	37	1.5	0.004	48	2.0	<0.001
Melena	0	0	19	0.8	<0.001	28	1.2	<0.001
Other gastrointestinal site	4	0.2	10	0.4	0.11	33	1.4	<0.001
Intervention due to bleeding								
Transfusion	26	1.1	76	3.2	<0.001	108	4.5	<0.001
Dose adjustment	30	1.2	129	5.4	<0.001	285	11.8	<0.001
Withdrawal of study drug	36	1.5	146	6.1	<0.001	281	11.6	<0.001
Abnormal laboratory value‡								
Hemoglobin	492	21.4	637	28.0	<0.001	691	29.9	<0.001
Hematocrit	548	23.9	648	28.8	<0.001	727	31.6	<0.001
Platelet count	98	4.3	101	4.5	0.76	133	5.8	0.02

*P values are nominal and are for comparisons with the placebo group.

†Percentages are Kaplan–Meier cumulative event rates during receipt of the study drug.

‡Data are for patients who had a value below the lower limit of the normal range at any time after enrollment. Data were available for 2299 patients in the placebo group, 2275 patients in the group given 10 mg of xemilofiban, and 2311 patients in the group given 20 mg of xemilofiban.

tionally low, and the rate of bleeding events in the early period after PTCR was higher in the active-treatment groups than in the placebo group. These findings suggest that xemilofiban had short-term biologic and clinical efficacy.

The second explanation for these results is that continued treatment with xemilofiban did not confer long-lasting protection from death, myocardial infarction, or the need for urgent revascularization. The lack of a prolonged benefit was observed both in the entire cohort of patients and in subgroups defined according to the diagnosis at enrollment, stent use or nonuse, age, sex, and interval between the initial dose of the study drug and PTCR.

The lack of long-term efficacy is unlikely to be due to an insufficient dose of xemilofiban. Blood levels of xemilofiban were sufficiently high to exert the desired antagonist effect on platelet receptors, at least intermittently, since there was a dose-dependent increase in bleeding events over the entire study period. The steep dose responses characteristic of xemilofiban pharmacodynamics and pharmacokinetics may have caused large fluctuations in the inhibition of platelet aggregation in individual patients, with variable inhibition in the study population as a whole.³⁵

Lamifiban has been reported to prevent death and myocardial infarction only at intermediate plasma levels, not at lower or higher plasma levels, in patients with unstable angina.⁴¹ Studies of platelet activation raise the possibility, which has not yet been confirmed, that at low concentrations, platelet-receptor antagonists alter the steric conformation of the glycoprotein IIb/IIIa sites and, paradoxically, enhance the thrombogenicity of these sites.⁴² This may explain the higher mortality rates in the low-dose xemilofiban group. It therefore appears that lack of a long-term protective effect is the most likely explanation for the results of our trial.

Another unexpected finding was that event rates were lower than in previous trials. The rate of death, nonfatal myocardial infarction, or urgent revascularization at 30 days was 7.9 percent in our placebo group, as compared with 12.8 percent in the placebo group in the Evaluation of 7E3 for the Prevention of Ischemic Complications (EPIC) trial,⁴ 11.4 percent in the placebo group in the Integrelin to Minimize Platelet Aggregation and Prevent Coronary Thrombosis (IMPACT) II trial,¹¹ 11.7 percent in the placebo group in the Evaluation in PTCR to Improve Long-Term Outcome with Abciximab GP IIb/IIIa Blockade (EPILOG) study,⁷ and 10.8 percent in the stent group in the Evaluation of Platelet IIb/IIIa Inhibition in Stenting (EPISTENT) study.³⁸ Although the enzymatic criteria for diagnosing myocardial infarction were not uniform in these trials, a trend is suggested. During the period when the EXCITE trial was conducted, PTCR was evolving rapidly. Stent placement was becoming commonplace throughout

the world and was used in 71 percent of the patients in the trial. New stent designs that eliminated the need for bulky delivery devices and implantation under high pressure may have lessened the trauma to the vessel wall. Angioplasty without stent placement was reserved predominantly for patients in whom the results of angioplasty were "stent-like."²⁶ These improvements in interventional techniques may have diminished the importance of glycoprotein IIb/IIIa receptor blockade. In addition, heparin therapy was more aggressive in our trial than in studies of abciximab. The longer activated clotting time in our study may have decreased the frequency of thrombotic or embolic complications of PTCR.

Fifty-seven percent of the patients enrolled in our trial had a diagnosis of acute myocardial infarction or unstable angina at enrollment. The lack of treatment efficacy in this subgroup suggests that the overall lack of a benefit was not due to the unintentional enrollment of low-risk patients.

In conclusion, the administration of xemilofiban immediately before and for up to six months after PTCR does not decrease the combined end point of death, nonfatal myocardial infarction, or urgent revascularization. Although treatment with xemilofiban reduces the rate of myocardial infarction by 25 percent in the first 24 hours after PTCR, it does not reduce the mortality rate initially or at six months. The value of long-term treatment with oral glycoprotein-receptor blockers thus remains unproved.

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APPENDIX

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