

Review

Oral Platelet Glycoprotein IIb/IIIa Receptor Inhibitors—Part I

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Summary: With the central importance of antiplatelet therapy in patients with coronary artery disease and the numerous positive trials with glycoprotein (GP) IIb/IIIa inhibitors given intravenously, it was hoped that one could extend the benefit of IIb/IIIa inhibition to long-term treatment. Although the hypothesis that prolonged oral IIb/IIIa inhibition was appealing, many issues have been identified in the initial Phase II trials that would limit the usefulness of these compounds. Variability of the level of platelet inhibition was one major culprit that distinguished the oral compounds from intravenous ones. The problems that arose were that increased bleeding has been seen when levels of platelet inhibition are high (e.g., >90%) and that, conversely, efficacy would likely be limited when levels of platelet inhibition were low. If further development of this class of drugs is undertaken, formal dosing studies would have to establish an oral dosing strategy that achieves appropriately high (80–95% inhibition) and steady levels of inhibition.

Key words: platelets, acute coronary syndromes, myocardial infarction, unstable angina, antiplatelet therapy, prognosis, angioplasty

Introduction

The importance of antiplatelet therapy in patients with coronary artery disease comes from the broad experience with aspirin, which has dramatic effects in reducing both mortality and nonfatal events in patients across the spectrum

of acute coronary syndromes.^{1–8} In addition, the thienopyridines (clopidogrel and ticlopidine) have also been shown to be beneficial in reducing recurrent cardiac events or death, compared with aspirin alone in coronary stenting^{9–12} in symptomatic patients with atherosclerosis,^{1,13} and those with unstable angina or non-ST-segment elevation myocardial infarction (UA/NSTEMI).^{14,15}

With the numerous positive trials with glycoprotein (GP) IIb/IIIa inhibitors given intravenously,¹⁶ it was hoped that one could extend the benefit of IIb/IIIa inhibition to long-term treatment. This class of drugs was designed to target the final common pathway of platelet aggregation, which is the final step in which platelets form a platelet plug in the thrombus. Glycoprotein IIb/IIIa receptor antagonists block the binding of fibrinogen to specific membrane GP IIb/IIIa integrin receptors, thus preventing platelet aggregation induced by various platelet agonists. Whereas platelet activation is produced by a wide variety of stimuli, the final common step to platelet aggregation is fibrinogen binding. Therefore, no matter what physiologic stimuli are present, blockade of the GP IIb/IIIa receptor can prevent formation and/or propagation of a platelet thrombus.

Glycoprotein IIb/IIIa Receptor

The platelet GP IIb/IIIa receptor is a member of the integrin receptor superfamily of complexes that mediate cell–protein and cell–cell interactions.¹⁷ The GP IIb/IIIa receptor is a calcium-dependent heterodimer, composed of two different subunits (α_{IIb} and β_3), both of which span the platelet membrane. The GP IIIa subunit contains a four-amino acid sequence which is crucial for binding of fibrinogen and other ligands.¹⁷ The first three amino acids are arginine-glycine-aspartic acid (RGD) while the fourth amino acid may vary. Low-molecular-weight peptide and nonpeptide GP IIb/IIIa inhibitors have been developed to bind to the RGD sequence of the receptor, thereby interfering with the binding of fibrinogen to the GP IIb/IIIa receptor.

Numerous trials have recently shown that when high levels of IIb/IIIa receptor blockers are administered, targeting a level of inhibition of 80 to 90% of receptors, clinical events are improved in patients undergoing percutaneous coronary intervention and in acute coronary syndromes.^{16,18–21}

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Rationale for Long-Term Glycoprotein IIb/IIIa Inhibition

The rationale for long-term platelet inhibition comes from both biological and clinical observations. From the biological standpoint, platelet function tests show that platelets remain activated long after a patient is stabilized clinically. Active thrombus has been observed by coronary angiography even 1 month following acute coronary syndromes,²² indicating the long period of time that is needed for complete antithrombotic treatment of a culprit lesion. Similarly, in the Thrombolysis In Myocardial Infarction (TIMI) 12 trial of an oral IIb/IIIa inhibitor in patients stabilized after an acute coronary syndrome, we observed high levels of activated platelets in patients at baseline but also 1 month later, despite oral IIb/IIIa treatment.²³ Thus, there is an active, prothrombotic “milieu” in patients following acute coronary syndromes, which could potentially benefit from more aggressive antithrombotic therapy than just aspirin.

The clinical observation is that the benefit of intravenous GP IIb/IIIa inhibitors is achieved only during the infusion. Because of the potent platelet inhibition, the benefits are maintained but no added benefit is observed after the infusions are stopped. For example, in the Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) trial in UA/NSTEMI, eptifibatid reduced death or MI by an absolute 1.7% at 72 h; the reduction was similar (1.5%) at 30 days.²¹ Similarly, in the Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) trial, tirofiban plus heparin reduced the rate of death or MI by an absolute 3.4% at 7 days, and 3.2% at 30 days.²⁰ Although these benefits were sustained to long-term follow-up, there was no added benefit beyond the time of the initial infusion. Thus, it was recognized that for this class of drugs to have longer-term benefit, they would need to be administered for the long term.

Types of Glycoprotein IIb/IIIa Inhibitors

There are three broad categories of IIb/IIIa inhibitors: (1) the monoclonal antibody fragment to the IIb/IIIa receptor, abciximab (ReoPro[™]); (2) the intravenous peptide and nonpeptide small molecule inhibitors, such as eptifibatid (Integrilin[™]) and tirofiban (Aggrastat[™]); and (3) the oral IIb/IIIa inhibitors, such as xemilofiban, orbofiban, sibrafiban, and roxifiban.

Abciximab, a monoclonal antibody fragment, binds very tightly to the GP IIb/IIIa receptor.²⁴ Thus, the antiplatelet effect lasts much longer than the infusion period—a potential benefit on improving efficacy. On the other hand, if bleeding occurred, stopping the drug will not reverse the antiplatelet effect immediately; transfusion of platelets, however, will allow the antibody fragments to redistribute among all the platelets, thereby reducing the level of platelet inhibition. Abciximab also binds to other integrins on the platelet receptor, such as the vitronectin receptor,¹⁷ but the clinical significance of this cross reactivity is not yet established.

The peptide and peptidomimetic inhibitors (e.g., tirofiban and eptifibatid) are competitive inhibitors of the IIb/IIIa receptor.^{25,26} Thus, the level of platelet inhibition is directly related to the drug level in the blood. Since both inhibitors have short half lives when the drug infusion is stopped,^{25,27} the antiplatelet activity reverses after a few hours, which is a potential benefit for avoiding bleeding complications. On the other hand, for prolonged antiplatelet effect, the drug needs to be given intravenously for a longer period of time. The inhibitors developed to date have been specifically targeted to the GP IIb/IIIa receptor and not to cross react other integrins. Accordingly, the amount of drug in the bloodstream is very different. With the short-acting agents, the ratio of drug molecules to IIb/IIIa receptors is > 250, whereas for the “tight-binding” agents (abciximab and roxifiban) the ratio is approximately 2 to 5. (Fig. 1).

Oral Glycoprotein IIb/IIIa Inhibition

The third group of GP IIb/IIIa inhibitors are the oral agents. These agents are also competitive inhibitors and are usually pro-drugs, which are absorbed and then converted to active compounds in the blood.^{28–31} The oral agents all have longer half lives, such that they can be given once, twice, or three times daily in order to achieve relatively steady levels of IIb/IIIa inhibition. With oral dosing, long-term therapy is possible. As with the intravenous compounds, two major groups of drugs exist in the oral class: those with competitive inhibition and short “off time” from the receptor, where a high drug level is critical to achieving high levels of platelet inhibition (e.g., sibrafiban, orbofiban, xemilofiban, lotrafiban), and those which have “tight” binding to the platelet (similar to abciximab) with the majority of the drug circulating bound to platelets (e.g., roxifiban) (Fig. 1).

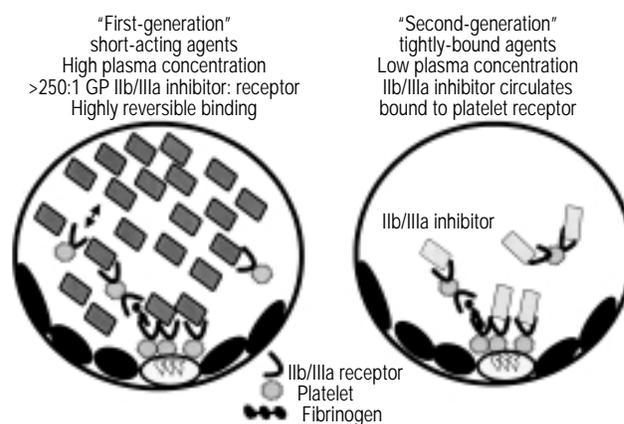


FIG. 1 Differentiation of the two classes of oral IIb/IIIa inhibitors. The first generation agents generally have competitive binding, with short “off times” from the receptor. Thus, to achieve high levels of platelet inhibition, high levels of the drug and a high drug:receptor ratio are needed. In contrast, the “second generation” agents, such as roxifiban, have tight binding to the receptor, thus the majority of drug circulates bind to the receptor and there is a low drug:receptor ratio. GP = glycoprotein.

TABLE I Oral IIb/III Inhibitors that have undergone or are undergoing clinical testing

Oral agent	Company	Trials	Phase	Study population	Drug half-life
Xemilofiban	G.D. Searle	ORBIT EXCITE	II III	Coronary intervention	4.1 h
Sibrafiban	Roche Genentech	TIMI 12 SYMPHONY	II III	Post acute coronary syndrome	11 h
Orbofiban	G.D. Searle	SOAR OPUS-TIMI 16	II III	Acute coronary syndromes	10 h
Lotrafiban	Smith Kline Beecham	APLAUD BRAVO	II III	Acute coronary syndromes, TIA, post-ischemic stroke	4–8 h
Klerval	RPR	TIMI 15	II	Acute coronary syndromes, CAD	4–5 h
Lefradifiban	Boehringer Ingelheim	FROST	II	Acute coronary syndrome	8–12 h
Chromofiban	Cor	N/A	I	Acute coronary syndrome	12–24 h
Roxifiban	DuPont	ROCKET PURPOSE	II III	Acute coronary syndrome, peripheral arterial disease	24 h

Abbreviations: TIA = transient ischemic attack, CAD = coronary artery disease, N/A = not applicable, ORBIT = Oral glycoprotein IIb/IIIa Receptor Blockade to Inhibit Thrombosis, SOAR = Safety of Orbofiban in Acute coronary Research, APLAUD = Anti-PLAtelet Useful Dose, BRAVO = Blockade for the GP IIb/IIIa Receptor to Avoid Vascular Occlusion, FROST = Fibrinogen Receptor Occupancy Study, ROCKET = Roxifiban Outcomes Cardiovascular Clinical Event Trial, PURPOSE = Peripheral arterial disease Utilization of Roxifiban to Prevent Outcomes of iSchemic Events. Other trial acronyms as in Figures 2 and 4.

Pharmacokinetics and Pharmacodynamics

A number of orally active platelet GP IIb/IIIa inhibitors have been studied in clinical trials (Table I). These agents produce inhibition of ex vivo platelet aggregation in response to various agonists such as adenosine diphosphate (ADP), collagen, or thrombin receptor activation peptide (TRAP) that correlate closely with plasma level of active metabolite. In addition,

the dose/concentration response is maintained without evidence for tolerance or tachyphylaxis over time.²⁹ The pharmacokinetic and pharmacodynamic response to most oral GP IIb/IIIa inhibitors can be illustrated by comparing and contrasting the responses of short (xemilofiban, half life 4.1 h) and moderate (sibrafiban and orbofiban; half lives approximately 10–11 h) and longer acting agents (roxifiban and chromofiban, half lives approximately 24 h) (Fig. 2).

Scoreboard—comparing oral IIb/IIIa inhibitors

	“Second generation”	“First generation”		
	Roxifiban	Orbofiban	Sibrafiban	Xemilofiban
Trial	ROCKET	OPUS-TIMI 16	SYMPHONY	EXCITE
IIb/IIa selective binding	+++	+++	+++	+++
“Off rate”	Tightly bound	Competitive	Competitive	Competitive
Drug: receptor ratio	7 min	>250	>250	>250
Peak of onset	2–5	4–6 h	4–6 h	2–3 h
Half-life	3–6 h	8–10 h	11 h	4–5 h
Excretion	24 h	Renal	Renal	Renal
Dosing	Plt. dissociation	Renal	Renal	Renal
Low peak/trough	q.d.	b.i.d.	b.i.d.	t.i.d.
Inpatient variability	+++	++	++	+
Interpatient variability	+	++	++	++
Platelets < 50,000	++	++	++	++
	<0.5%	0.6%	0.6%	0.5%

FIG. 2 A profile of the pharmacokinetic and pharmacodynamic differences between the “first” and “second” generation oral IIb/IIIa inhibitors. q.d. = daily, b.i.d. = twice a day, t.i.d. = three times a day, plt = platelet. ROCKET = Roxifiban Outcomes Cardiovascular Clinical Event Trial, OPUS-TIMI 16 = Orbofiban in Patients with Unstable coronary Syndromes-Thrombolysis in Myocardial Infarction 16, SYMPHONY = Sibrafiban versus aspirin to Yield Maximum Protection from ischemic Heart events post acute cOronary sYndromes, EXCITE = Evaluation of oral Xemilofiban In Controlling Thrombotic Events.

Xemilofiban

The first experience with oral GP IIb/IIIa inhibition was with xemilofiban.^{28, 32, 33} High degrees of platelet inhibition could be achieved with this oral IIb/IIIa inhibitor. It had a relatively short half life and thus is given three times daily. The Oral Glycoprotein IIb/IIIa Receptor Blockade to Inhibit Thrombosis (ORBIT) trial was a randomized dose-ranging trial of xemilofiban in patients undergoing percutaneous intervention.³⁴ Peak inhibition of platelet aggregation was similar following the same dose of xemilofiban administered on Days 14 and 28 of the trial. The time to peak blood level following the same dose of xemilofiban was reduced from 4 h following the first dose of drug to 2 h with steady-state dosing during chronic therapy.³⁴ Most bleeding events were observed during the first 2 weeks of therapy on a three-times daily dosing regimen.³⁴

The Thrombolysis In Myocardial Infarction 12 Trial

The TIMI 12 trial was a Phase II, double-blind, dose-ranging trial designed to evaluate the pharmacokinetics (PK), pharmacodynamics (PD), safety, and tolerability of sibrافiban in 329 patients post acute coronary syndromes.²⁹ In the PK/PD cohort of TIMI 12, 106 patients were randomized to receive one of seven dosing regimens of sibrافiban, 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 sibrافiban (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 μ M ADP-induced platelet aggregation on Day 28 across the seven doses. Twice daily dosing provided more sustained platelet inhibition (mean inhibition 36–86% on Day 28), while platelet inhibition returned to baseline levels by 24 h with once-daily dosing.²⁹ Although in the initial experience major hemorrhage was rare with either sibrافiban (1.5%) or aspirin (1.9%), protocol-defined “minor” bleeding, usually mucocutaneous bleeding, occurred in up to 32% of patients in the various sibrافiban groups, compared with none in the aspirin-treated patients. In a multivariate model, minor bleeding was related to total daily dose ($p = 0.002$), once-versus twice-daily dosing ($p < 0.0001$), renal function ($p < 0.0001$), and presentation with unstable angina ($p < 0.01$).²⁹

Thus, the oral IIb/IIIa antagonist sibrافiban achieved effective, chronic platelet inhibition with a clear dose-response, but at the expense of a relatively high incidence of minor bleeding. The mucocutaneous bleeds appeared to be related to plasma drug concentrations, the degree of platelet inhibition, and other patient factors (weight, renal function). The question then arose whether a high degree of platelet inhibition could be tolerated for long-term treatment.

“Peak-to-Trough-Ratios”

In TIMI 12, it was also observed that the rate of minor bleeding was approximately double with once-daily dosing

compared with a similar total daily dose of twice-daily dosing (e.g., 15 mg once daily vs. 7 mg twice daily) (Fig. 3). This may indicate that the higher peak drug concentrations and degree of platelet inhibition (sometimes 100%) may be related to the bleeding episodes observed. The timing of the bleeding appeared to occur approximately 6 h after study drug ingestion, which correlates with the peak blood level. Thus, these data suggested that using dosing regimens that avoid high peaks may decrease the risk of bleeding. However, it also showed that high levels of inhibition would not be well tolerated in long-term treatment.

Variability

In addition, interpatient variability has been observed in drug level and degree of platelet inhibition (Fig. 4). In contrast, the 24–72 h infusions of intravenous (IV) IIb/IIIa inhibitors have doses selected to achieve 80–95% inhibition—and very steady levels of inhibition are achieved. This is one of the major differences in the pharmacokinetics between the IV and oral IIb/IIIa inhibitors, and it may be an explanation for differences in clinical outcomes observed today. This variability might lead to too low a level of inhibition at the trough level or too high a level of inhibition in some patients at peak times.

One potential strategy for dosing oral IIb/IIIa antagonists 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

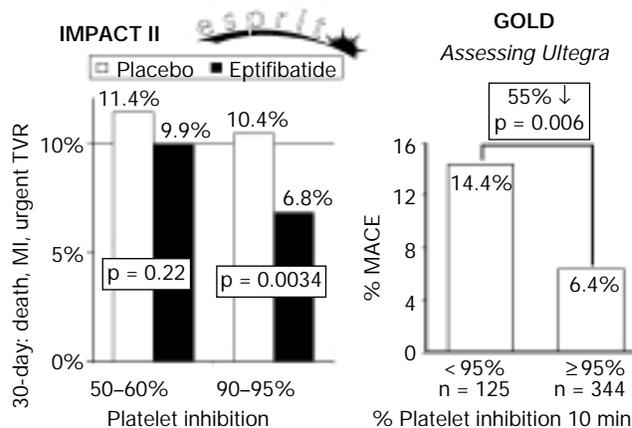


FIG. 3 Major adverse cardiac event (MACE) rates in two separate trials of eptifibatide, the first with a low level and the second with a higher level of platelet inhibition. A greater benefit was seen in improvement of cardiac outcomes with the higher level of platelet inhibition. Similarly, in the Assessing Ultegra (AU - GOLD) study, lower rates of MACE were noted in patients who had > 95% platelet inhibition 10 min after start of administration of a IIb/IIIa inhibitor. MI = myocardial infarction, TVR = target vessel revascularization. IMPACT II = Integrilin (eptifibatide) to Minimize Platelet Aggregation and Coronary Thrombosis II, ESPRIT = Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrilin Therapy. Data from Refs. No. 19, 40, and 44.

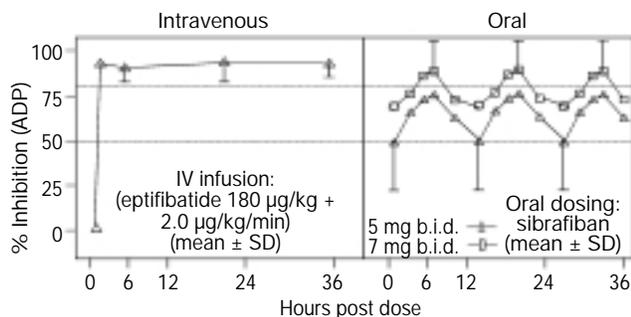


FIG. 4 The level of inhibition of 20 μ M adenosine diphosphate (ADP)-induced platelet aggregation using an intravenous (IV) IIB/IIIA inhibitor, eptifibatide, or an oral agent, sibrافiban, in the TIMI 12 trial. A greater degree of variability, as well as peaks and troughs corresponding to the dosing interval of the oral agent, are seen with the oral agent. b.i.d. = twice a day, SD = standard deviation. Adapted from Refs. No. 29 and 41 with permission.

reduce bleeding complications. This could potentially be accomplished with a bedside assay for platelet inhibition.³⁵

Thrombocytopenia

Thrombocytopenia is another key area of tolerability. To date, thrombocytopenia (platelet count falling to $< 50,000$ cells/ mm^3) has been relatively rare, occurring in 0.5–1.0% of patients for most agents tested.^{18, 20, 21, 36–38} Data from larger trials suggest that with oral therapy thrombocytopenia generally occurs early, with very low rates during long-term follow-up.³⁹

Degree of Platelet Inhibition and Efficacy

Previous animal and clinical studies have suggested that the maximum benefit of GP IIB/IIIA inhibition occurs when the degree of platelet inhibition is $> 80\%$.^{37, 38} In support of this, three sets of clinical observations support the need for 80–95% inhibition in order to obtain optimal clinical outcomes.

The Integrilin (eptifibatide) to Minimize Platelet Aggregation and Coronary Thrombosis-II (IMPACT-II) study showed a strong trend toward the reduction of recurrent ischemic events after coronary angioplasty at a dose of eptifibatide that achieved only 50–60% inhibition (Fig. 3).⁴⁰ In contrast, a greater benefit was observed with a higher dose of eptifibatide (that targeted 85–90% platelet inhibition) in the Enhanced Suppression of the Platelet IIB/IIIA Receptor with Integrilin Therapy (ESPRIT) trial.⁴¹ Thus, it appears that greater benefit, at least in the acute setting, is achieved with doses that achieve 80–95% inhibition of 20 μ M ADP-induced platelet aggregation. However, it is not truly a “threshold” below which there is no benefit, since a modest benefit was seen in the IMPACT II trial.

Similarly, the superiority of abciximab over tirofiban in reducing early clinical events has been most likely attributed to the low level of platelet inhibition (65–70%) achieved by tirofiban at the dose used in the Do Tirofiban and ReoPro Give

Similar Efficacy Trial (TARGET).^{42, 43} Finally, there are two sets of observational data relating percent inhibition and outcome. The AU-Assessing Ultegra (GOLD) found that after 10 min post bolus, a level of platelet inhibition of $> 95\%$ was associated with a lower rate of major cardiac events compared with a lower level of platelet inhibition (Fig. 3).⁴⁴ An analysis of the The Fibrinogen Receptor Occupancy Study (FROST) found that there was a lower event rate in patients who achieved high levels of inhibition and, it was interesting to note, a higher event rate than placebo in patients with a level of inhibition $< 50\%$.⁴⁵ Thus, it now appears that optimal outcomes are achieved when the level of inhibition is high.

However, for long-term therapy, a high level of blockade will need to be balanced with the potential of increased bleeding, and thus a slightly lower level of inhibition was targeted in the large phase III trials.

Degree of Platelet Inhibition and Bleeding

As observed in TIMI 12, increasing the degree of platelet inhibition may produce a higher incidence of minor bleeding events (Fig. 5).²⁹ A similar finding was recently reported with intravenous IIB/IIIA inhibitors, where the rate of major bleeding was much higher in patients with $> 90\%$ inhibition of platelet aggregation on the bedside Rapid Platelet Function Assay (RPFA).⁴⁶ This suggested that a lower degree of platelet inhibition may be better tolerated during chronic, oral therapy. In the oral large IIB/IIIA inhibitor trials,^{47–50} the higher doses of the agents studied have significantly higher rates of bleeding, as summarized in a recent meta-analysis by Newby *et al.*⁵¹ Thus, this potent class of drugs clearly would need to be very carefully titrated to optimize the outcomes. In addition, the high level of inhibition may preclude very long-term treatment, since bleeding becomes such a problem over time.

Conclusion—Part I

Although the hypothesis that prolonged oral IIB/IIIA inhibition was appealing, many issues have been identified in the ini-

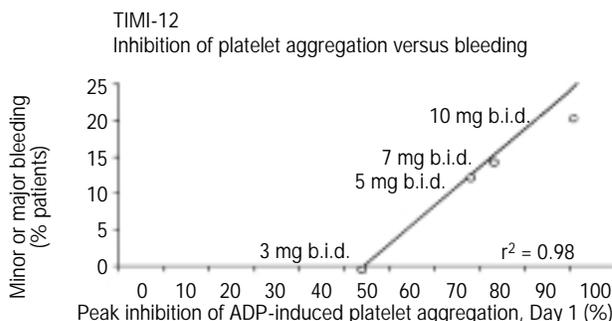


FIG. 5 Correlation of the rate of major or minor bleeding events with the dose of sibrافiban and the mean percent inhibition of platelet aggregation. b.i.d. = twice a day, ADP = adenosine diphosphate. Adapted from Ref. No. 29 with permission.

tial Phase II trials that would limit the usefulness of these compounds. Increased bleeding has been seen when levels of platelet inhibition are high (e.g. > 90%); conversely, efficacy may be limited, based on data from the IV IIb/IIIa inhibitors, when levels of platelet inhibition were low. The large Phase 3 trials, as will be reviewed in Part II, will show the clinical balance of efficacy and safety. If further development of this class of drugs is undertaken, formal dosing studies would have to establish an oral dosing strategy that achieves appropriately high (80–95% inhibition) and steady levels of inhibition.

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