Platelet Glycoprotein IIb/IIIa Inhibition and Percutaneous Coronary Intervention in the Elderly

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Introduction

The introduction of balloon angioplasty in the early 1980s and stents in the mid-1990s has revolutionized mechanical reperfusion therapy in patients with stenotic coronary arteries.[1,2] In fact, percutaneous coronary interventions (PCI) are one of most frequently performed procedures, with more than 1.3 million performed worldwide in 1999.[3] However, an important limitation of PCI is the risk of inducing platelet aggregation. As a result of the disruption of the culprit plaque and injury to the coronary vessel during the procedure, the periprocedural risk of reocclusion of the vessel and myocardial infarction (MI) is high, and there is a 20–40% incidence of restenosis at 6–12 months after the index procedure.[3]

In an attempt to reduce the risk of these complications, several new strategies have been explored. Glycoprotein IIb / IIIa receptor inhibitors (GPIs), for example, have been enthusiastically tested in over 25,000 patients undergoing PCI over the last decade (Table 1). Gp IIb / IIIa receptors are found in great abundance on the surface of platelets and blocking these receptors obstructs the final common pathway leading to platelet aggregation.

In the following review, the efficacy and safety issues associated with these agents will be evaluated with particular emphasis on the elderly (as defined in the trials). Specifically, this appraisal is based on large-scale, phase III, randomized clinical trials and meta-analyses evaluating intravenous agents (abciximab, eptifibatide and tirofiban) in the setting of PCI, and xemilofiban, an oral agent that has been aimed at extending the benefits of intravenous agents after PCI. In the second part of this article (to be published in the July / August issue of *Geriatrics & Aging*) intravenous and oral GPIs will also be reviewed in the context of medical management of elderly patients suffering from non-ST-segment elevation acute coronary syndromes.

Intravenous GPIs

Abciximab

Based on the results of the groundbreaking trial, EPIC, abciximab (ReoPro™) was the first GPI to be approved for use in the United States in 1994, and in Canada in 1996, as an adjunct therapy to PCI (Table 2). In the EPIC trial, high-risk patients who were scheduled to undergo PCI were randomized to abciximab bolus, abciximab bolus plus infusion or placebo bolus plus infusion (Table 3). Patients who received abciximab bolus plus infusion benefited from a 35% relative reduction in death, MI or unplanned revascularization at 30 days compared to those who received the placebo (8.3% versus 12.8%, p=0.008), and these benefits were homogeneous across all age groups (Figure 1, page 34).[4] In the long-term evaluation of abciximab's efficacy, similar benefits were maintained at six months, and one and three years.[5,6] However, abciximab therapy was also associated with an increase in bleeding events and transfusions (Table 4, page 36).

Table 1
Glossary of Major Clinical Trials of GPIs used in PCI

EPIC	**E**valuation of Gp IIb/IIIa platelet receptor antagonist c7E3 in **P**reventing **I**schemic **C**omplications
EPILOG	**E**valuation in **P**TCA to **I**mprove **L**ong-term **O**utcome with abciximab **G**p IIb/IIIa blockade
CAPTURE	**c**7E3 Fab **A**nti**P**latelet **T**herapy in **U**nstable **RE**fractory angina
EPISTENT	**E**valuation of **P**latelet Gp IIb/IIIa **I**nhibitor for **Stent**ing
IMPACT-II	**I**ntegrilin to **M**inimize **P**latelet **A**ggregation and **C**oronary **T**hrombosis-II
ESPRIT	**E**nhanced **S**uppression of **P**latelet **R**eceptor GP IIb/IIIa using **I**ntegrilin **T**herapy
RESTORE	**R**andomized **E**fficacy **S**tudy of **T**irofiban for **O**utcomes and **R**estenosis
TARGET	Do **T**irofiban **A**nd **R**eoPro **G**ive similar **E**fficacy outcomes **T**rial?
EXCITE	**E**valuation of **X**emilofiban in **C**ontrolling **T**hrombotic **E**vents

Table 2
Characteristics of intravenous GPIs used in Percutaneous Coronary Intervention

Characteristic	Abciximab	Eptifibatide	Tirofiban
Type	antibody	cyclic heptapeptide	peptidomimetic
Molecular Weight (Da)	47 600	832	495
Binding to Receptor	irreversible	competitive	competitive
Plasma Half-life (hours)	10–30 min	2.5	2
FDA and Health Canada approved indications	PCI Refractory UA when PCI is planned within 24 hours	PCI ACS (UA and non-Q wave MI)	ACS (UA and non-Q wave MI)
FDA and Health Canada approved dose	PCI: 0.25mg/kg bolus, 0.125 µg/kg/min (10 µg/min) infusion for 12h UA:0.25 mg/kg bolus, 10 µg/min infusion for 18–24 h before PCI and continued 1 h after PCI	PCI: 135 µg/kg bolus, 0.5 µg/kg/min infusion for 20–24 h ACS: 180 µg/kg/min bolus, 2.0 µg/kg/min infusion for 72–96 h	ACS: 0.4 µg/kg/min for 30min, then 0.1 µg/kg/min for 48–108 h

ACS, acute coronary syndromes; FDA, Food and Drug Administration; MI, myocardial infarction; PCI, percutaneous coronary intervention; UA, unstable angina.

To address these concerns further, a pilot trial modified the heparin regimen and vascular access sheath removal time, as these factors were suspected contributors to the excess bleeding complications seen in the EPIC trial.[7] Subsequently, the EPILOG investigators tested these modifications in 2,792 patients undergoing PCI (Table 3).[8] The design of EPILOG also allowed for the effects of abciximab to be evaluated in patients of all risk profiles. Both the standard- and low-dose heparin regimens, in conjunction with abciximab, resulted in a significantly lower incidence of the primary composite endpoint (death, MI or urgent revascularization) at 30 days (placebo, 11.7%, versus abciximab plus standard-dose heparin, 5.4%, p<0.001, 54% relative risk reduction; versus abciximab plus low-dose heparin, 5.2%, p<0.001, 55% relative risk reduction), and these benefits were realized in younger and older patients (Figure 1). As expected, more bleeding complications occurred when the standard-dose of heparin was administered (Table 4).[8] Similar to the EPIC trial, the benefits of abciximab therapy continued over one year after initial treatment, regardless of age (data not presented).[9]

The second approved indication for use of abciximab is in patients with refractory unstable angina (UA) who are scheduled for PCI within 24 hours. The CAPTURE investigators revealed that patients of all ages who received abciximab experienced fewer adverse events within 30 days of randomization compared to placebo (11.3% versus 15.9%, p=0.012, 29% relative risk reduction) (Table 3).[10] In particular, the incidence of MI before and during PCI was significantly reduced in those patients who received abciximab. Major and minor bleeding events were rare, but occurred more often in patients receiving abciximab than in those receiving placebo (Table 4).

In the mid-1990s, the use of stents during PCI procedures was introduced and quickly became established in routine clinical care. In comparison to balloon angioplasty, stents provide structural integrity to the target vessel and significantly decrease the rate of restenosis.[2] However, stent implantation can activate the expression of Gp IIb / IIIa receptors on the platelet surface and predispose the coronary artery to restenosis.[11] The EPISTENT trial was designed to test the combined effect of stents and Gp IIb / IIIa inhibition in comparison with balloon angioplasty (Table 3).[12] Overall, the incidence of the death, MI or urgent revascularization at 30 days was significantly reduced in patients receiving abciximab in conjunction with stent (5.3% versus 10.8%, p<0.001, 51% relative risk reduction) when compared to those receiving stent and placebo, and also in those receiving balloon angioplasty and abciximab (6.9% versus 10.8%, p=0.007, 36% relative risk reduction) compared to those receiving stent and placebo. In the long-term (i.e., one year), patients randomized to stent and abciximab continued to experience fewer events (composite endpoint) than those receiving stent and placebo, while the frequency of composite endpoint was similar between those receiving balloon angioplasty and abciximab and those receiving stent and placebo.[13] Regardless of age, the use of abciximab with stent

Table 3
Summary of trials testing intravenous and oral GPIs in the setting of PCI

Study (Enrolment period)	No. of Patients	Inclusion Criteria	Study Treatment Arms	Primary Efficacy Endpoint
ABCIXIMAB				
EPIC (1991–1992)	2099	Patients <80 years old who are scheduled for PCI due to high risk for abrupt vessel closure but not at high risk for bleeding.	Randomly assigned to: a) abciximab bolus + 12 h abciximab infusion (708) b) abciximab bolus + 12h placebo infusion (695) c) placebo bolus + 12 h placebo infusion (696) Abciximab dose: 0.25mg/kg bolus + 10 µg/min infusion for 12 h. All received aspirin and heparin.	Death, non-fatal MI, revascularization (CABG or repeat PCI), rescue stent or IABP use within 30 days.
EPILOG (1995)	2792	Patients >21 years old who are scheduled for elective or urgent PCI with target lesion of ≥ 60% stenosis.	Randomly assigned to: a) abciximab + low-dose weight-adjusted heparin (935) b) abciximab + standard-dose weight-adjusted heparin (918) c) placebo + standard-dose weight-adjusted heparin (939) Abciximab dose: 0.25mg/kg bolus + 10 µg/min infusion for 12 h. All received aspirin and heparin.	Death, (re)-MI, urgent revascularization (CABG, re-PCI) at 30 days.
CAPTURE (1993–1995)	1265	Patients with refractory unstable angina scheduled for PCI.	Randomly assigned to: a) abciximab bolus + 12 h abciximab infusion (630) b) placebo bolus + 12 h placebo infusion (635) Abciximab dose: 0.25mg/kg bolus + 10 µg/min infusion for 12 h. All received aspirin and heparin.	Death, MI, urgent revascularization (re-PCI, CABG, stent or IABP), within 30 days.
EPISTENT (1996–1997)	2399	Patients scheduled to undergo elective or urgent PCI.	Randomly assigned: a) abciximab + stent (794) b) abciximab + balloon angioplasty (796) c) placebo + stent (809) Abciximab dose: 0.25mg/kg bolus + 10 µg/min infusion for 12 h. All received aspirin and heparin.	Death, MI or urgent revascularization at 30 days.

Table 3 cont.
Summary of trials testing intravenous and oral GPIs in the setting of PCI

EPTIFIBATIDE				
IMPACT-II (1993–1994)	4010	Patients scheduled for elective, urgent or emergent PCI.	Randomly assigned to: a) eptifibatide 135 µg/kg bolus + 0.5 µg/kg/min eptifibatide infusion for 20-24 h (1349) b) eptifibatide 135 µg/kg bolus + 0.75 µg/kg/min eptifibatide infusion for 20-24 h (1333) c) placebo (1328) All patients received aspirin and heparin.	Death, MI, urgent or emergent CABG or stent placement at 30 days.
ESPRIT (1999–2000)	2064	Patients scheduled for stent placement.	All patients received aspirin and heparin and a thienopyridine. Randomly assigned to: a) eptifibatide 180 µg/kg bolus + 2.0 µg/kg/minute eptifibatide infusion 18–24 h + 180 µg/kg bolus 10 mins after first bolus (1040) b) placebo (1024)	Death, MI, urgent target vessel revascularization or rescue at 30 days.
TIROFIBAN				
RESTORE (1995)	2141	ACS patients scheduled for PCI.	Randomly assigned to: a) tirofiban10 µg/kg over 3 minutes + 0.15 µg/kg/min infusion for 36 h (1071) b) placebo (1070) All patients received aspirin and heparin.	Death, MI or revascularization (CABG or re-PCI (including stent)) at 2, 7, 30 and 180 days.
COMBINATION				
TARGET (1999–2000)	5308	Patients with NSTE-ACS (with >70% stenosis) scheduled for stent placement.	Randomly assigned to: a) tirofiban 10 µg/kg bolus + 15 µg/kg/min for 18-24 h. (2398) b) abciximab 0.25 mg/kg bolus + 0.125 µg/kg/min for 12 h. (2411) All patients received aspirin and heparin and, if possible, clopidogrel.	Death, non-fatal MI, urgent target vessel revascularization within 30 days.
ORAL GPI				
XEMILOFIBAN				
EXCITE (1997–1998)	7232	Patients who were eligible for PCI (esp., high-risk).	Randomly assigned to: a) 20 mg single oral dose xemilofiban before PCI + 20 mg three times daily after PCI for 182 days (2418) b) 20 mg single oral dose xemilofiban before PCI + 10 mg three times daily after PCI for 182 days (2400) c) placebo before + after PCI for 182 days(2414)	Event-free survival (from death, non-fatal MI, urgent revascularization) at 182 days.

CABG, coronary artery bypass surgery; IABP, intra-aortic balloon pump; MI, myocardial infarction; PCI, percutaneous coronary intervention.

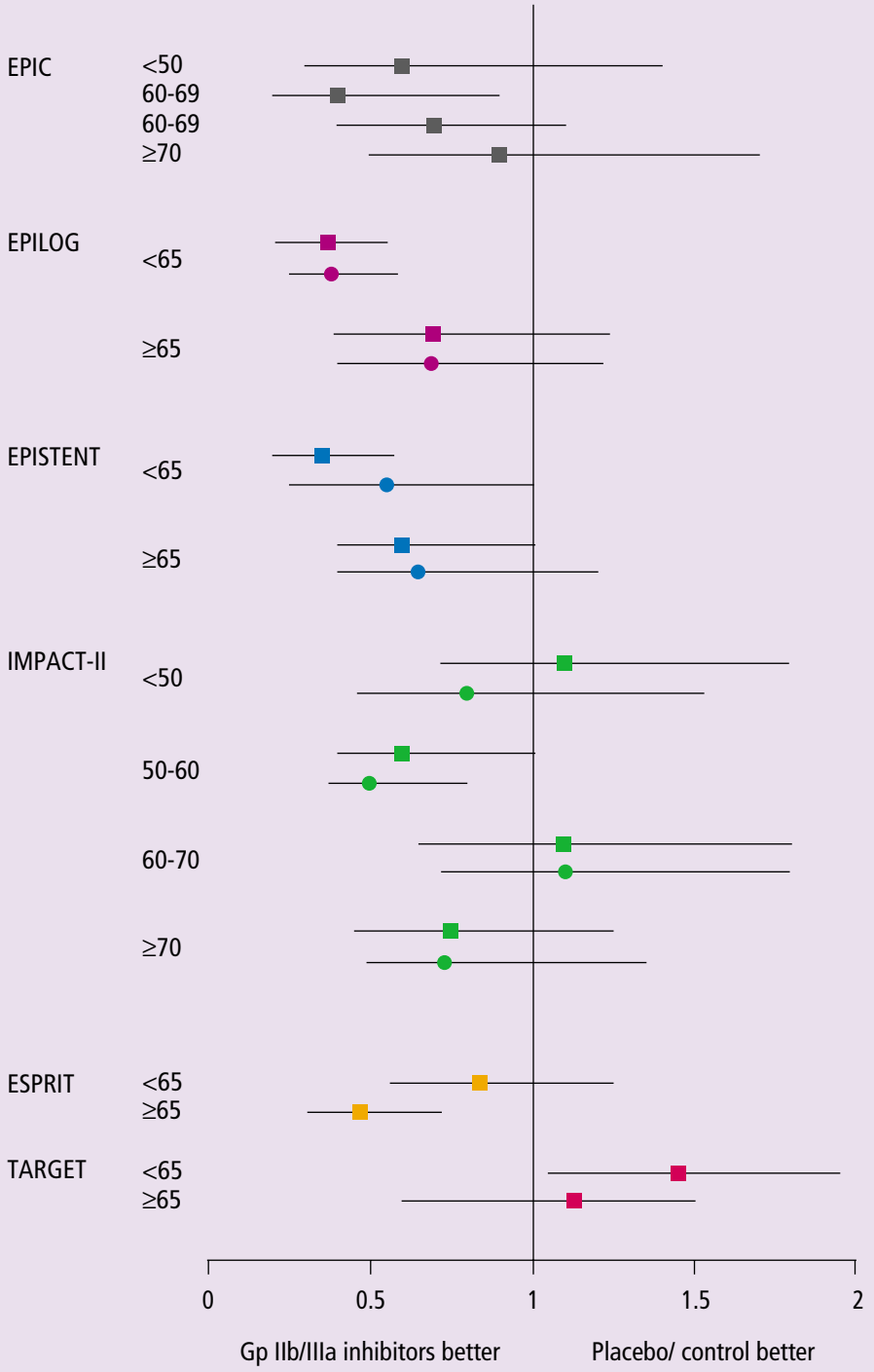


Figure 1. Age subgroup analysis of primary composite endpoints of trials evaluating intravenous Gp IIb/IIIa inhibitors in PCI setting.
(No age subgroup analysis reported for CAPTURE.)

EPILOG ■ low-dose heparin versus placebo,
● standard-dose heparin versus placebo;

EPISTENT ■ stent + placebo versus stent + abciximab,
● stent + placebo versus balloon angioplasty + abciximab;

IMPACT-II ■ low-dose eptifibatide versus placebo,
● high-dose eptifibatide versus placebo.

or balloon angioplasty resulted in fewer adverse events at 30 days (Figure 1).[12] Bleeding complications were not significantly different among treatment groups (Table 4).

Eptifibatide

Eptifibatide (Integrilin™) is a cyclic peptide and is based on the lysine-glycine-aspartic acid (KGD) sequence found in barbourin, a snake venom protein (Table 2).[14] Compared to abciximab, eptifibatide is smaller in molecular size and binds to the receptor with lower affinity, which translates into a shorter biological / plasma half-life. Despite these differences, eptifibatide also blocks the final common pathway of platelet aggregation, and therefore, it was hypothesized that eptifibatide would also significantly reduce the incidence of adverse cardiac events in PCI patients. The IMPACT-II trial demonstrated that low-dose infusion eptifibatide therapy reduced the incidence of death, MI or urgent revascularization by 19% (11.4% placebo versus 9.2% low-dose infusion eptifibatide, p=0.063) at 30 days; however, the high-dose infusion was not associated with a statistically significant reduction (9.9%, p=0.22) (Table 3).[15] In a subgroup analysis based on age, the point estimates and corresponding 95% confidence intervals were scattered for both dose regimens. Thus, conclusions should be made cautiously (Figure 1).

While the results of IMPACT-II were less impressive than those of the abciximab-PCI trials, it may be explained by the sub-optimal inhibition of Gp IIb / IIIa receptors with eptifibatide. The ESPRIT trial improved upon IMPACT-II by ensuring that complete (>80%) inhibition was achieved and by incorporating the use of stents (Table 3).[16] Patients who were scheduled for stent placement were randomized to receive either eptifibatide or placebo. Within 48 hours of the intervention, there was a 37% relative reduction (10.5% placebo versus 6.6% eptifibatide, p=0.0015) in the composite endpoint of death, MI, urgent revascu-

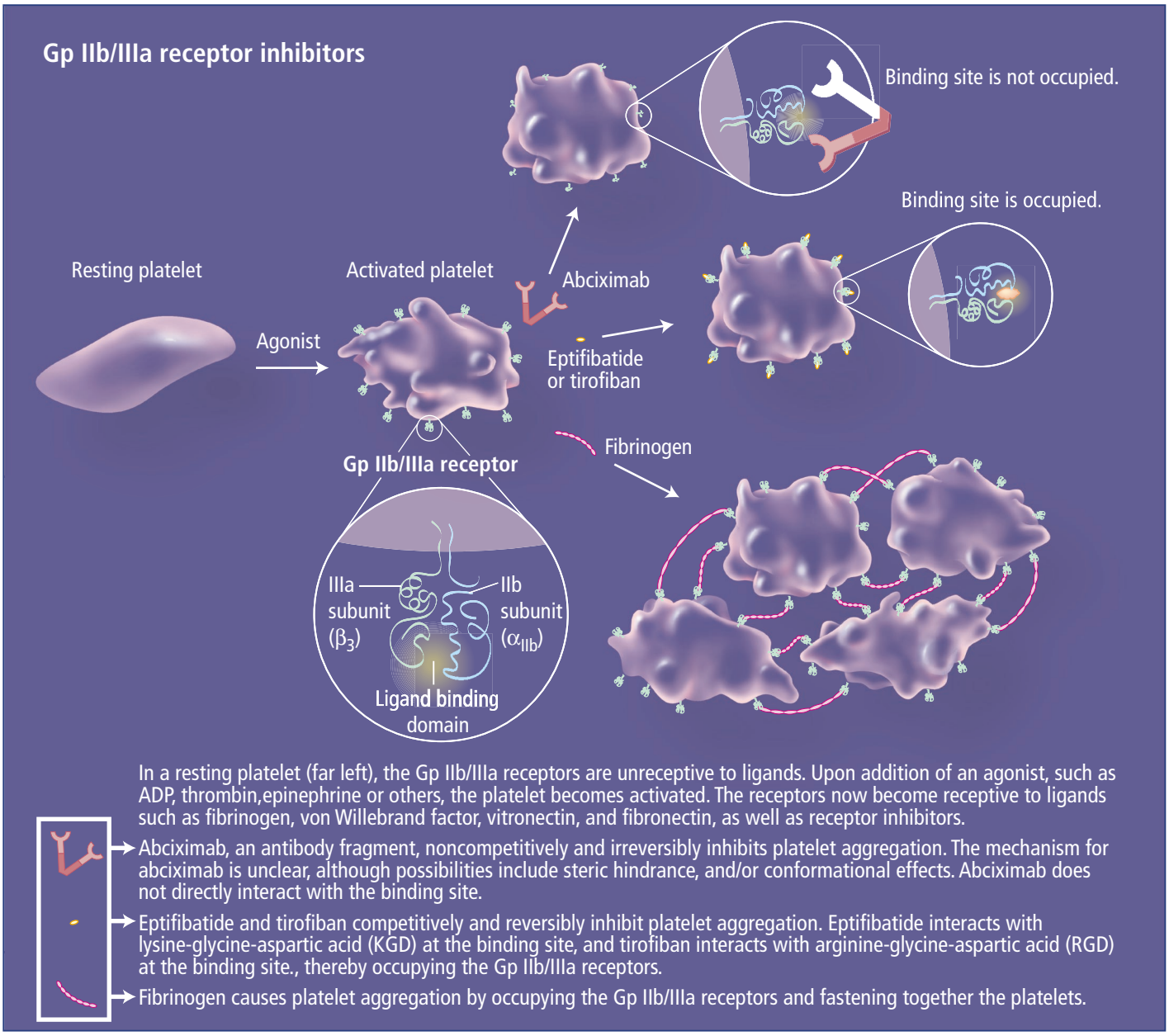
larization or thrombotic bailout GPI therapy, and benefits continued when re-evaluated at one year after randomization.[17] The benefits of eptifibatide therapy were experienced in patients of all ages, especially in those who were 65 years or older (Figure 1).

Tirofiban

Similar to eptifibatide, tirofiban (Aggrastat™) is a short-acting, small-molecule GPI and its design is based on a specific amino acid sequence (Table 2). The RESTORE trial compared the effects of tirofiban to placebo as adjunctive therapy to patients scheduled for PCI (Table 3).[18] Overall, the patients who received tirofiban realized significant reductions in adverse cardiac events early after PCI at two days (8.7% placebo versus 5.4% tirofiban, p=0.005, 38% relative risk reduction) and at seven days (10.4% placebo versus 7.6% tirofiban, p=0.022, 27% relative risk reduction). However, these benefits were not sustained at 30 days (12.2% placebo versus 10.3% tirofiban, p=0.16, 16% relative risk reduction) or six months (27.1% placebo versus 24.1% tirofiban, p=0.11, 11% relative risk reduction).[19] No subgroup analysis for age was reported.

Direct Comparison of GPIs in the Setting of PCI in the Elderly

Despite the overwhelming positive evidence of these agents compared to placebo, only one large-scale clinical trial has directly compared two GPIs in the setting of PCI. The TARGET investigators originally designed a non-inferiority trial to compare the efficacy of abciximab and tirofiban in PCI patients (Table 3).[20] However, their study revealed that tirofiban provided significantly less protection against adverse cardiac events (death, MI or urgent revascularization) at 30 days than did abciximab (7.6% tirofiban



versus 6.0% abciximab, p=0.038, 21% relative risk reduction). In the subgroup analysis, abciximab therapy continued to result in a lower incidence of the primary composite endpoint at 30 days in patients younger and older than 65 years.

Overview of Intravenous GPIs with PCI in the Elderly

Overall, patients undergoing PCI with GPIs benefit from a significant reduction in the composite endpoint of death, non-fatal MI or revascularization at 30 days (odds ratio (OR) 0.65, 95% confidence interval (CI) (0.54, 0.79), p<0.001) and 6 months (OR 0.87 95%CI (0.80, 0.95), p<0.003).[21] These benefits persisted when patients were evaluated for the composite endpoint of death or non-fatal MI (30-day OR 0.64, 95% CI (0.51, 0.80) p<0.001), but not for death alone (30-day OR 0.77, 95% CI (0.53, 1.10), p>0.05). No subgroup analyses on age have been reported but it seems that, overall, the older population also benefits from these agents as they did in the individual trials.

Oral GPIs and PCI in Elderly Patients

The success of the intravenous GPIs prompted the hypothesis that oral GPIs could extend the benefits of intravenous agents and may play a role in secondary prevention. However, the EXCITE trial revealed that oral xemilofiban did not significantly reduce clinical events when administered before and after PCI (for 182 days) (Table 3).[22] The next generation of oral agents may be more successful with the resolution of the challenges of inter-patient variation in inhibition levels (due to differences in bioavailability or genetics), establishment of titrated doses and development of longer half-lives with higher binding

Table 4
Bleeding Complications, Intracranial Hemorrhage and Stroke at 30 days in Patients Enrolled in Trials of Intravenous and Oral GPIs in the Setting of PCI

Trial	Study Drug (no. of patients)	Major bleeding (%)	Minor bleeding (%)	Intracranial hemorrhage (%)	Stroke (%)
EPIC	Placebo (696)	7	–	0.3	–
	Abciximab bolus (695)	11	–	0.1	–
	Abciximab bolus + infusion (708)	14*	–	0.4	–
EPILOG	Placebo + standard-dose heparin (939)	3.1	3.7	0	–
	Low-dose heparin + abciximab (935)	2.0	4.0	0.2	–
	Standard dose heparin + abciximab (918)	3.5	7.4**	0.3	–
CAPTURE	Placebo (635)	1.9	2.0	–	0.5
	Abciximab (630)	3.8†	4.8‡	–	0.2
EPISTENT	Stent + placebo (809)	2.2	1.7	0	0.1
	Stent + abciximab (794)	1.5	2.9	0	0.4
	Balloon angioplasty + abciximab (796)	1.4	2.9	0	0.3
IMPACT-II	Placebo (1328)	4.8	–	–	0.6
	Low-dose eptifibatide (1349)	5.1	–	–	0.5
	High-dose eptifibatide (1333)	5.2	–	–	0.7
ESPRIT	Placebo (1040)	0.4	1.7	0.1	0
	Eptifibatide (1024)	1.0§	2.8	0.2	0.1
RESTORE	Placebo (1070)	2.1	–	0.3	–
	Tirofiban (1071)	2.4	–	0.1	–
TARGET	Tirofiban (2398)	0.9	2.8	–	–
	Abciximab (2411)	0.7	4.3¶	–	–
EXCITE	Placebo (2414)	1.4	–	<0.1	–
	Low-dose xemilofiban (2400)	3.3*	–	0.1	–
	High-dose xemilofiban (2418)	4.3*	–	0.2	–

Bleeding complications defined by Thrombolysis In Myocardial Infarction (TIMI) study group.[34] In the EPILOG trial, intracranial hemorrhage frequencies also include stroke. *p=0.001 for comparison with placebo; **p<0.001 for comparison with placebo; †p=0.043 for comparison with placebo; ‡p=0.008 for comparison with placebo; §p=0.027 for comparison with placebo; ¶p<0.001 for comparison with tirofiban. Bleeding events in the EXCITE trial defined according to trial protocol. *p<0.001 for comparison to placebo (moderate or severe bleeding at 30 days).

affinities to increase the level of stable inhibition.[23,24]

Contraindications and Adverse Effects

While GPIs reduce ischemic complications, it comes at the cost of delayed hemostasis. As such, patients with active bleeding, major surgery within the past three months, stroke within the past six months, and a history of recent trauma are not recommended recipients of this therapy.[24] Other contraindications include uncontrolled hypertension (≥180 mmHg systole and / or ≥110mmHg diastole), severe anemia and thrombocytopenia.[25]

In the early trials evaluating Gp IIb / IIIa inhibition in PCI, increases in the risk of bleeding complications and transfusions were attributed to the use of these agents (Table 4). While advanced age is a significant predictor of bleeding complications, particularly at the vascular access site, subsequent studies have reduced the incidence of these complications by modifying heparin regimens (to use lose-dose, weight-adjusted heparin), decreasing sheath removal time, and avoiding emergency coronary artery bypass surgery for failed angioplasty.[26-28]

Because the underlying pharmacology of abciximab differs from that of small molecule GPIs, differences in safety endpoints have also been suspected. It appears that abciximab was associated with an increase in major bleeding complications at 30 days, while tirofiban and eptifibatide were not.[29] Also, a recent pooled analysis of the risk of thrombocytopenia with the use of intravenous GPIs in PCI and medical management of non-ST-segment elevation acute coronary syndromes revealed that the use of abciximab and heparin lead to an increase in the incidence of mild and severe thrombocytopenia compared to placebo and heparin.[30] Conversely, eptifibatide and tirofiban used alone or in combination with heparin did not result in higher incidences of thrombocytopenia compared to heparin alone.

GP IIb / IIIa inhibition therapy has been also a suspected contributor to excess intracranial hemorrhage and stroke. Despite these suspicions, the incidence of intracranial hemorrhage (ICH) was rare, and its use with or without heparin was not associated with an excess incidence of ICH.[31] Similarly, the administration of abciximab in addition to aspirin and heparin did not increase the risk of stroke in PCI patients.[32]

Conclusion

While advanced age is a major, well-known predictor of adverse cardiac events, the majority of the trials only compare the primary composite clinical endpoint in patients younger than 65 years relative to those over the age of 65 years. Efforts should be made to report more in-depth age-specific analyses, particularly on safety endpoints. Future investigations should specifically address optimal strategies for this rapidly expanding proportion of the population.

In general, the intravenous GPIs have significantly improved the short- and long-term prognosis of patients undergoing PCI, and are accompanied by a minor risk of bleeding complications. Older ischemic heart disease patients experience more acute cardiac events than do their younger counterparts, and the increased number of comorbidities and more severe cardiovascular history also contributes to their higher risk profile. Despite this, older patients do derive similar relative, and hence, greater absolute benefit from intravenous Gp IIb / IIIa therapy in the setting of PCI compared to their younger counterparts.[33] ◆

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