

Bolus-Only Platelet Glycoprotein IIb/IIIa Inhibition During Percutaneous Coronary Intervention

Jonathan D. Marmur, MD, Shyam Poludasu, MD, Ajay Agarwal, MD, Pompeiu Vladutiu, MD, Alan Feit, MD, Reuven Lapin, PA, Erdal Cavusoglu, MD

ABSTRACT: Background. Platelet glycoprotein IIb/IIIa inhibitors (GPI) are traditionally administered as a bolus followed by an infusion. In the current era of routine stenting, we hypothesized that a bolus-only GPI strategy can be used during percutaneous coronary intervention (PCI) in order to reduce bleeding complications, while preserving the benefits of inhibition of platelet aggregation at the time of device deployment. **Methods.** We retrospectively analyzed consecutive patients ($n = 1,001$) who underwent PCI and received an unfractionated heparin (UFH) and bolus-only GPI regimen, from January 2003 to August 2004 in a single institution. All patients received clopidogrel and aspirin prior to PCI. Post-procedure myocardial infarction (MI) was defined using the TIMI definitions, and bleeding complications were defined by the criteria used in REPLACE-2. **Results.** The most frequently used GPI was eptifibatide (58.3%), followed by abciximab (37.3%) and tirofiban (4.3%). The composite outcome of in-hospital death (0.1%), MI (4.3%), repeat revascularization (0) and major plus minor bleeding (2.6%) was 7%. These rates are lower than those that have been reported in the UFH group with planned GPI, and the bivalirudin with provisional GPI arms of the REPLACE-2 trial. After adjustment for baseline and procedural risk factors, the abciximab bolus-only group had a higher rate of major bleeding compared to the eptifibatide bolus-only group (adjusted odds ratio 3.5; 95% confidence intervals 1.047 and 11.698; $p < 0.05$). **Conclusion.** A bolus-only GPI strategy appears to maintain the anti-ischemic benefits of GPI, with the added benefit of reduced bleeding complications and the potential for reduced cost and shortened length of hospital stay.

J INVASIVE CARDIOL 2006;18:521–526

Several large randomized clinical trials and meta-analyses have shown that inhibition of platelet aggregation with platelet glycoprotein IIb/IIIa inhibitors (GPI) improves outcomes in patients presenting with acute coronary syndromes and in those undergoing percutaneous coronary intervention (PCI).^{1–5} Platelet GPI inhibits the thrombotic cascade directly by blocking the final common pathway of platelet aggregation, and indirectly, by inhibiting the generation of thrombin.^{6,7} Traditionally, GPI are administered as an intravenous (IV) bolus, followed by a prolonged infusion (12–18 hours). Many patients undergoing PCI (both in the United States and worldwide) do not receive a GPI, in part owing to concerns about bleeding and cost. In the present era of oral

thienopyridines, where patients are preloaded with a high dose of clopidogrel (300–600 mg) in order to achieve an antiplatelet effect within 2–4 hours,^{8,9} the relevance of a prolonged GPI infusion may be questionable, particularly given the widespread use of stents that have virtually eliminated the problem of abrupt closure. The prolonged GPI infusion, as opposed to bolus-only administration, may contribute to increased bleeding complications, without an incremental anti-ischemic benefit. The avoidance of prolonged infusion of GPI has the potential to not only reduce vascular complications, but also to reduce the length of hospital stay and total cost of the procedure.

Based on these theoretical considerations, the full-time interventional cardiology faculty at State University of New York–University Hospital of Brooklyn (SUNY-UHB) adopted in 2003 a GPI bolus-only strategy during PCI, with the exception of patients with acute ST-segment elevation MI (STEMI). We now report a retrospective analysis of the first 1,001 consecutive patients who underwent PCI using a bolus-only GPI strategy.

Methods

This is a retrospective study of 1,001 consecutive patients who underwent PCI at SUNY-UHB at Brooklyn, from January 2003 to August 2004. The hospital's Institutional Review Board approved the study. Demographic, periprocedural and laboratory data were collected by reviewing charts and hospital records. The in-hospital events and the length of stay were also recorded. Patients with acute STEMI were excluded from the analysis.

All patients were treated with unfractionated heparin (UFH) plus a standard dose bolus of abciximab (0.25 mg/kg), or eptifibatide (180 μ g/kg $\times$ 2), or tirofiban (0.4 μ g/kg/minute over 30 minutes) at the beginning of the intervention. The choice of a specific GPI was left to the discretion of the operator. All patients were loaded with aspirin 325 mg and clopidogrel 300 mg p.o. immediately prior to the procedure. An initial IV bolus of UFH 40 units/kg, followed by supplemental boluses if required, was administered to achieve a target activated clotting time (ACT) of at least 200 seconds. The ACT was measured using the Hemochron® device (*ITC Technidyne Corp, Edison, New Jersey*). Coronary interventional procedures were performed according to standard techniques via a femoral approach. Femoral vascular closure devices — Angio-Seal (*St. Jude Medical, Minnetonka, Minnesota*) or Perclose (*Perclose Inc., Redwood City, California*) — were used unless contraindicated. Serial monitoring of cardiac biomarkers

From the State University of New York, SUNY Downstate Medical Center, Brooklyn, New York.

The authors report no conflicts of interest regarding the content herein.

Manuscript submitted May 17, 2006, provisional acceptance given June 21, 2006, manuscript accepted August 4, 2006.

Address for correspondence: Jonathan D. Marmur, MD, FACC, SUNY Health Sciences Center at Brooklyn, Cardiology, 450 Clarkson Avenue, Box 1257, Brooklyn, NY 11203. E-mail: jonathan@marmur.com

Table 1. Baseline characteristics.

Variable	Total (n = 1,001)	Abciximab (n = 374)	Eptifibatide (n = 584)	p-Value*
Demographics, biometrics				
Age (mean $\pm$ SD in years)	62 $\pm$ 11	62.3 $\pm$ 10.3	61.9 $\pm$ 11	0.79
Women, n (%)	590 (59)	202 (54)	294 (50)	0.28
Age > 75 years, n (%)	130 (13)	40 (11)	76 (13)	0.31
Race, n (%)				
Black	841 (84)	310 (83)	491 (84)	0.65
Hispanics	90 (9)	35 (9)	49 (8.5)	0.64
Caucasians	50 (5)	19 (5)	31 (5.5)	1.00
Other	20 (2)	10 (3)	13 (2)	0.67
Body mass index (mean $\pm$ SD, kg/m ²)	30 $\pm$ 6	30.2 $\pm$ 5.7	30.3 $\pm$ 6	0.98
Medical history	n (%)	n (%)	n (%)	
Hypertension	891 (89)	326 (87)	525 (90)	0.20
Diabetes mellitus	490 (49)	188 (50)	286 (49)	0.74
Smoking	330 (33)	128 (34)	192 (33)	0.67
Hyperlipidemia	320 (32)	152 (41)	146 (25)	
End stage renal disease	70 (7)	28 (7.5)	40 (7)	0.70
Documented history, or overt congestive heart failure	110 (11)	38 (10)	64 (11)	0.74
Previously documented coronary artery disease	631 (63)	185 (49.5)	427 (73)	< 0.001
Periprocedural medications**	n (%)	n (%)	n (%)	
Aspirin	991 (99)	373 (100)	581 (99.5)	1.00
Beta-blocker	831 (83)	314 (84)	484 (83)	0.72
ACE-inhibitor	721 (72)	280 (75)	410 (70)	0.12
Statins	861 (86)	326 (87)	496 (85)	0.34
Indication	n (%)	n (%)	n (%)	
NSTEMI	190 (19)	74 (20)	89 (15)	0.078
Unstable angina	370 (37)	142 (38)	221 (38)	1.00
Stable angina, positive stress test	441 (44)	158 (42)	274 (47)	0.163
Left ventricular ejection fraction (mean $\pm$ SD)	52 $\pm$ 12	51.8 $\pm$ 15.3	49.3 $\pm$ 16.9	0.031
CAD = coronary artery disease; ESRDE = endstage renal disease; CHF = congestive heart failure; ACE = angiotension-converting enzyme; NSTEMI = non-ST-segment elevation myocardial infarction. *Comparison between the abciximab and the eptifibatide groups. **Administered upon admission and continued through discharge from hospital.				

was performed every 8 hours for 24 hours after PCI in every patient.

Definitions

Periprocedural myocardial infarction (MI) was defined according to the Thrombolysis in Myocardial Infarction (TIMI) criteria.¹⁰ A new MI was defined by biochemical or electrocardiographic criteria: the MB isoform of creatinine kinase (CK-MB) at least three times the upper limit of the normal range in at least one blood sample, or the finding of abnormal Q-waves in two or more contiguous leads. For patients with recent MI who had an elevated CK-MB level before the procedure, a value of more than three times the upper limit of normal and at least 50% above the baseline value was required to meet the definition.

Bleeding was defined according to the Randomized Evaluation in the PCI Linking Angiomax to Reduced Clinical Events (REPLACE-2) criteria.¹¹ Major bleeding was defined

as either any intracranial, intraocular, or retroperitoneal or clinically overt bleeding with a drop of hemoglobin by 3 g/dl, or any drop of hemoglobin by 4 g/dl, or the transfusion of two or more units of packed red blood cells. Minor bleeding was defined as clinically overt bleeding not meeting the above criteria. We chose to define and compare our bleeding complications using the REPLACE-2 trial definitions and outcomes, as this trial has reported the lowest rates of bleeding in the context of modern PCI. Thrombocytopenia was defined as a fall in the platelet count below 100,000/ μ l, or a decrease by 25% below baseline values, in the event the initial platelet count was less than 100,000/ μ l.

Statistical analysis. Categorical variables are presented as percentages. Continuous variables are presented as mean $\pm$ standard deviation (SD). Categorical variables were compared using the Chi-square test. Continuous variables with normal distribution were compared using the independent samples t-test, and continuous variables without normal distribution were

Table 2. Procedural characteristics.

Variable	Total (n = 1,001)	Abciximab (n = 374)	Eptifibatide (n = 584)	p-Value*
Target coronary artery (n = 1,021)	n (%)	n (%)	n (%)	
Left anterior descending	408 (40)	213 (57)	176 (30)	< 0.001
Right coronary	312 (30.5)	86 (23)	214 (37)	< 0.001
Left circumflex	240 (23.5)	61 (16)	169 (29)	< 0.001
Bypass graft	30 (3)	13 (3.5)	16 (3)	0.56
Ramus intermedius	5 (0.5)	3 (1)	9 (1.5)	0.385
Left main	26 (2.5)	8 (2)	8 (1)	0.44
ACC/AHA lesion type (n = 1,131)	n (%)	n (%)	n (%)	
A	68 (6)	21 (6)	35 (6)	0.888
B1	848 (75)	293 (78)	447 (76.5)	0.529
B2	68 (6)	23 (6)	30 (5)	0.563
C	147 (13)	45 (12)	85 (14.5)	0.288
GPI administered	n (%)	n (%)	n (%)	
Tirofiban	43 (4.3)	0	0	N/A
Eptifibatide	584 (58.3)	0	584 (100)	N/A
Abciximab	374 (37.3)	374 (100)	0	N/A
ACT (mean in seconds $\pm$ SD)	281 $\pm$ 59	279 $\pm$ 62	284 $\pm$ 59	0.115
Stent usage during PCI, %	98	98.5	98	1.00
Multivessel intervention, n (%)	20 (2)	11 (3)	9 (1.5)	0.165
Successful PCI, %	99	99	99.5	1.00
Length of hospital stay (days $\pm$ SD)	1.89 $\pm$ 3.1	2.2 $\pm$ 4.6	1.7 $\pm$ 2	0.58

GPI = glycoprotein IIb/IIIa Inhibitor; ACT = activated clotting time; SD = standard deviation; N/A = not applicable.
 *Comparison between the abciximab and the eptifibatide groups.

compared using the Mann-Whitney test. Adjustment for baseline risk factors and procedural characteristics between the abciximab and eptifibatide groups was done using multivariate analysis, with in-hospital outcomes as dependable variables and the baseline and procedural as covariates. Logistic regression analysis was used to determine if the use of abciximab over eptifibatide is an independent risk factor for major bleeding complications. A *p*-value < 0.05 was considered significant. All statistical analyses are performed utilizing SPSS software, version 14.0 (SPSS, Inc., Chicago, Illinois).

Results

A total of 1,001 consecutive patients underwent PCI and received UFH plus a bolus-only GPI regimen during the study period. Baseline characteristics and procedural data are shown in Tables 1 and 2, respectively. Most of our patients were African-American and had a high prevalence of hypertension, diabetes and smoking. A majority (59%) was female, and 13% of patients were older than 75 years of age. The indication for coronary angiography was acute coronary syndrome (ACS) in 56% of cases, comprised of NSTEMI in 19%, and unstable angina in 37% of cases. A previously documented history of coronary artery disease (CAD) was present in approximately two-thirds of the patients (63%). The interventions targeted 1,021 coronary arteries and addressed 1,131 lesions. Twenty patients (2%) underwent multivessel PCI, and 110 patients (11%) underwent multilesion PCI of the same vessel. Abciximab and eptifibatide were predominantly used in our study. The

Table 3. In-hospital outcomes.

Variable	Total (n = 1,001)
Composite endpoint (%)	71 (7.1)
Death (%)	1 (0.1)*
Nonfatal MI (%)	n (%)
Any	43 (4.3)
CK-MB 3–5x	11 (1.1)
CK-MB 5–10x	12 (1.2)
CK-MB >10x	14 (1.4)
Bleeding (%)	n (%)
Major bleeding	14 (1.4)
Minor bleeding	12 (1.2)
Repeat revascularization (%)	0
Thrombocytopenia (%)	18 (1.8)
Vascular complications	n (%)
Pseudoaneurysm	3 (0.3)
Ischemic CVA	1 (0.1)
Thrombosis of aorto-femoral bypass	1 (0.1)

*One in-hospital death occurred in the tirofiban group.
 MI = myocardial infarction; CK-MB = creatinine kinase-MB fraction;
 CVA = cerebrovascular accident.

mean ACT was 281 $\pm$ 59 seconds. PCI was successful in 99% of cases, and the majority of lesions were stented (98%).

The incidence of in-hospital MI after PCI was 4.3% in our study (compared to 6.3% in the UFH with planned GPI arm and 7.2% in the bivalirudin with provisional GPI arm of the REPLACE-2 trial, respectively).¹² Major bleeding complications occurred in 1.4% of our patients (Table 3) (compared

Table 4. Comparison of in hospital outcomes between abciximab and eptifibatide subgroups.

Variable	Abciximab (n = 374)	Eptifibatide (n = 584)	p-Value*
Composite endpoint (%)	33 (8.8)	31 (5.3)	0.019
Death (%)	0	0	N/A
Nonfatal MI, n (%)			
Any	18 (4.8)	22 (3.77)	0.40
CK-MB 3–5x	4 (1.06)	6 (1.03)	0.75
CK-MB 5–10x	5 (1.33)	6 (1.03)	0.21
CK-MB > 10x	8 (2.1)	6 (1.03)	0.47
Bleeding, n (%)			
Major bleeding	9 (2.4)	4 (0.68)	0.016
Minor bleeding	6 (1.6)	5 (0.86)	0.379
Repeat revascularization (%)	0	0	N/A
Thrombocytopenia	14 (3.7)	3 (0.51)	0.004

MI = myocardial infarction; CK-MB = creatinine kinase-MB fraction.

Table 5. Hemorrhagic endpoints.

Variable	n (%)
Major bleeding	14 (1.4)
Intracranial bleeding	1 (0.1)
Retroperitoneal bleeding	0
Gastrointestinal bleeding	3 (0.3)
Genitourinary bleeding	0
Vascular Puncture site	2 (0.2)
Transfusion > 2 units	9 (0.9)
Minor bleeding	12 (1.2)
Vascular puncture site	9 (0.9)
Transfusion < 2 units	2 (0.2)
Bleeding from AV graft site during dialysis	1 (0.1)

to 2.8% in the bivalirudin arm and 4.5% in the UFH arm of the REPLACE-2 trial).¹² In comparison to those who received abciximab, those who received eptifibatide had a significantly lower incidence of major bleeding (2.4% versus 0.68%, respectively; $p = 0.016$) and thrombocytopenia (3.7% versus 0.51%, respectively; $p = 0.004$) after adjustment for baseline and procedural risk factors (Table 4). The adjusted odds ratio for major bleeding with abciximab over eptifibatide was 3.5, with 95% confidence intervals between 1.047 and 11.698. One patient died of unknown cause 3 days after PCI (an autopsy was not performed). One patient in the abciximab group had an acute ischemic stroke in the catheterization laboratory. One patient in the eptifibatide group developed acute thrombosis of a right aorto-femoral bypass graft and underwent surgical thrombectomy. Three patients (1 in the abciximab group and 2 in the eptifibatide group) developed pseudoaneurysms at the puncture site and were managed conservatively.

Discussion

Our retrospective study shows that a strategy of bolus-only GPI administration in patients undergoing PCI is effective in reducing bleeding complications, while maintaining an anti-ischemic benefit.

As earlier studies have shown that 70% of the platelet deposition at the site of balloon injury is GP IIb/IIIa integrin-dependent,¹³ the GPI bolus is necessary to obtain a rapid and complete blockade of the IIb/IIIa receptors before the intervention. The concept of a prolonged infusion of GPI after a bolus dose was derived from the EPIC trial,² a clinical trial of abciximab during high-risk balloon angioplasty published over a decade ago, in which insertion of a stent was considered an adverse event. Under these conditions (*i.e.*, balloon angioplasty with frequent residual stenosis and dissection), it is not surprising that an infusion of GPI was needed in order to preserve the benefits of the intervention. The GPI bolus-only arm in EPIC showed a nonsignificant reduction in the primary endpoints as compared to the placebo arm (11.5% versus 12.8%). Adverse events in the GPI bolus-only arm started to occur 6 hours after the index procedure and were mainly driven by acute closures, resulting in emergency percutaneous transluminal coronary angioplasty (3.6% in the bolus-only arm versus 0.8% in the bolus-plus-infusion arm). In the present era of routine thienopyridine administration and high-pressure stent implantation, the incidence of acute closure is low, on the order of less than 1%.^{14,15} It is in this context that we question the need for prolonged infusion of GPI after successful PCI.

Bivalirudin is a short-acting, reversible direct thrombin inhibitor, with a plasma half-life of 25 minutes, and was studied in the REPLACE-2 trial.¹¹ In this trial, a bolus of bivalirudin followed by a short infusion (which was terminated at the end of the procedure), with provisional GPI administration, was compared to a heparin with planned GPI strategy. GPI administration involved a bolus followed by a prolonged infusion (12–18 hours). The bivalirudin arm in this trial showed a significant reduction in bleeding complications, possibly related to the absence of a prolonged infusion post-PCI. However, there was a nonsignificant increase in post-PCI nonfatal MI, as compared to the heparin plus GPI arm. In an attempt to preserve the anti-ischemic benefits of GPI, as well as the lower bleeding rates associated with a postprocedural strategy devoid of an infusion (*e.g.*, the bivalirudin arm of REPLACE-2), we used a GPI bolus-only strategy during PCI.

Although initially studied in higher-risk ACS patients, the benefit of GPI has been demonstrated in a broad range of risk profiles (*e.g.*, EPIC,² EPILOG,¹⁶ EPISTENT,¹⁷ ESPRIT¹⁸). Even in the relatively low-risk REPLACE-2 population, it is notable that the MI rate was lower with GPI than it was with bivalirudin. In the REPLACE-2 study, this apparent benefit came at the cost of increased bleeding. It is our contention that this “cost” of higher bleeding rates is not inherent to the use of GPI, but rather can be eliminated by omitting the infusion portion of the standard GPI drug regimen. Using this

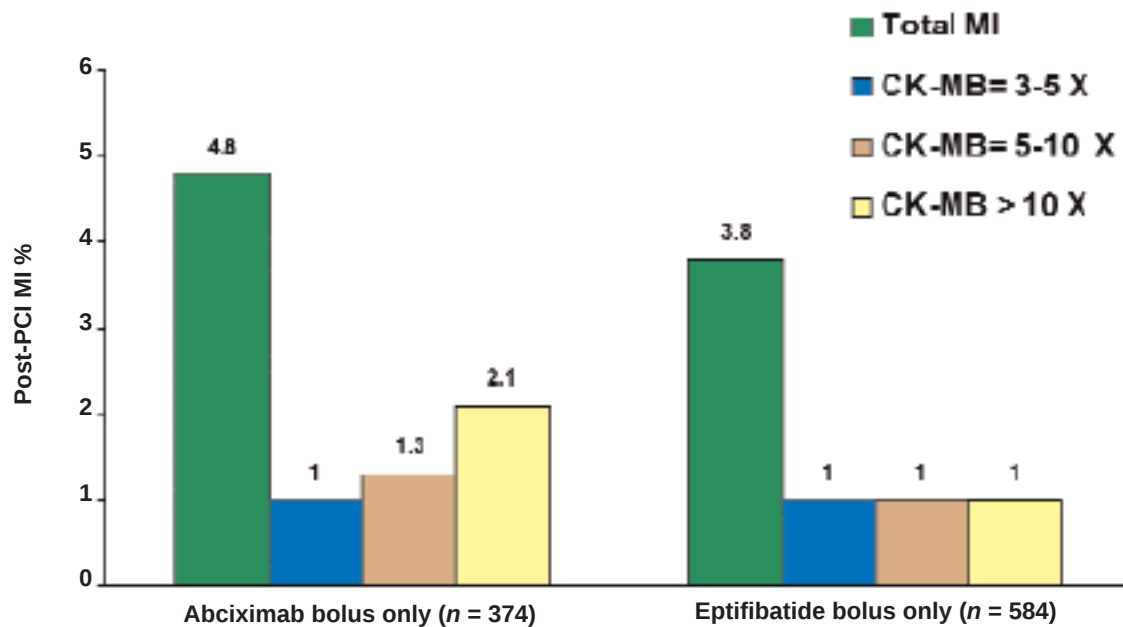


Figure 1. Incidence of post-PCI MI in the abciximab bolus-only group compared to the eptifibatide bolus-only group.

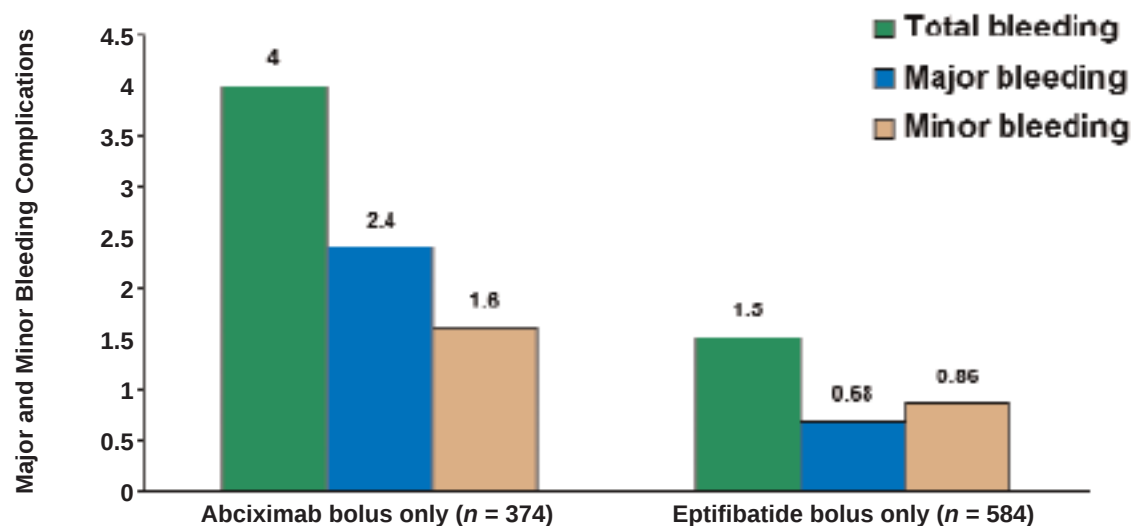


Figure 2. Incidence of bleeding complications in the abciximab bolus-only group compared to the eptifibatide bolus-only group.

strategy, patients may benefit from the “best of both worlds”: low MI rates and low bleeding rates with a GPI bolus-only regimen.

In our patient population, the in-hospital adverse outcome rates were lower than those reported in the REPLACE-2 trial. Lower bleeding rates may be due in part to the lower dose of heparin used (40 u/kg versus 65 u/kg) and possibly due to the experience of the full-time interventional cardiology staff at our institution. The lower post-PCI MI rates may be due in part to fewer multivessel PCIs (2% versus 15%). On the other hand, the risk profile of our study population was greater than that of the REPLACE-2 cohort (*e.g.*, diabetes 49% versus 27%, hypertension 89% versus 67%, smoking 33% versus 26.5%, history of heart failure 11% versus 7%).

Female gender and end-stage renal disease (ESRD) are known risk factors for vascular complications in patients undergoing PCI.^{19,20} In our study population, 59% were female patients and 7% of patients were on hemodialysis for ESRD. Similarly, higher body mass index (BMI) affects vascular complication rates as well.²¹ Approximately 7% of our patients had a BMI of more than 40 kg/m². Of note as well, 63% of our patients had a previously-documented history of CAD. The African-American population has been shown to have a higher prevalence of major risk factors for CAD.²² In our study, the higher prevalence of these major risk factors may be attributed to the predominantly African-American population (84%). While the procedural characteristics in our population are comparable to those of the REPLACE-2 cohort (with the exception of

fewer multivessel PCIs and fewer PCIs of coronary bypass grafts [3 versus 6%, respectively]), our patients underwent PCI more often for ACS and less often for stable angina, or positive stress test (56% versus 44%, respectively).

In our study, the comparison between patients who received abciximab and eptifibatide revealed no significant difference in the rates of death, nonfatal MI and minor bleeding. However, the composite endpoint of in-hospital outcomes showed a significant difference between these two groups ($p = 0.019$), which was driven mainly by the higher incidence of major bleeding in the abciximab group ($p = 0.016$) (Table 4). Thrombocytopenia was also significantly more common in the abciximab group. ($p = 0.004$).

Currently, more than one million PCIs are performed every year.¹² Thus, even modest cost savings on a per-patient basis have the potential to result in substantial savings to the healthcare system. At the very least, a strategy of bolus-only GPI administration may reduce the costs associated with drug acquisition; furthermore, there is the potential for greater cost savings through a reduction in the rate of bleeding, and by conversion of the procedure from an in-patient to an out-patient setting.

Limitations and Conclusion

Our study has all the inherent limitations of a retrospective study. Other major limitations are the absence of a control group and the lack of long-term follow-up data. We compared our results with the REPLACE-2 trial results despite other differences (e.g., lower dose of UFH, smaller number of multi-vessel PCIs and the uniform use of stents in our study), and we did not adjust for baseline differences in groups to exclude selection bias. Moreover, our study included a predominantly African-American population (84%), as compared to a 92% white population in the REPLACE-2 trial.

Despite these limitations, our study demonstrates the efficacy and safety of a bolus-only GPI strategy, and suggests that further large-scale investigations are warranted.

References

1. Fuster V, Badimon L, Badimon JJ, et al. The pathogenesis of coronary artery disease and the acute coronary syndromes. *N Engl J Med* 1992;326:242–250.
2. The EPIC Investigators. Use of a monoclonal antibody directed against the platelet glycoprotein IIb/IIIa receptor in high-risk coronary angioplasty. *N Engl J Med* 1994;330:956–961.
3. Platelet receptor inhibition in ischemic syndrome management in patients

- limited by Unstable Signs and Symptoms (PRISM-PLUS) Study Investigators. Inhibition of the platelet glycoprotein IIb/IIIa receptor with tirofiban in unstable angina and non-Q-wave myocardial infarction. *N Engl J Med* 1998;338:1488–1497.
4. The PURSUIT Trial Investigators. Inhibition of platelet glycoprotein IIb/IIIa with eptifibatide in patients with acute coronary syndromes. Platelet glycoprotein IIb/IIIa in unstable angina: Receptor suppression using integrilin therapy. *N Engl J Med* 1998;339:436–443.
5. Kong DF, Hasselblad V, Harrington RA, et al. Meta-analysis of survival with platelet glycoprotein IIb/IIIa antagonists for percutaneous coronary interventions. *Am J Cardiol* 2003;92:651–655.
6. Reverter JC, Beguin S, Kessels H, et al. Inhibition of platelet-mediated, tissue factor-induced thrombin generation by the mouse/human chimeric 7E3 antibody. *J Clin Invest* 1996;98:863–874.
7. Collier B. Anti-GPIIb/IIIa drugs: Current strategies and future directions. *Thromb Haemost* 2001;86:427–443.
8. Savcic M, Hauert J, Bachmann F, et al. Clopidogrel loading dose regimens: Kinetic profile of pharmacodynamic response in healthy subjects. *Semin Thromb Hemost* 1999;25(Suppl 2):15–19.
9. Müller I, Seyfarth M, Rudiger S, et al. Effect of a high loading dose of clopidogrel on platelet function in patients undergoing coronary stent placement. *Heart* 2001;85:92–93.
10. Bovill EG, Terrin ML, Stump DC, et al. Hemorrhagic events during therapy with recombinant tissue-type plasminogen activator, heparin, and aspirin for acute myocardial infarction. Results of the Thrombolysis in Myocardial Infarction (TIMI), Phase II Trial. *Ann Intern Med* 1991;115:256–265.
11. Lincoff AM, Bittl JA, Harrington RA, et al. Bivalirudin and provisional glycoprotein IIb/IIIa blockade compared with heparin and planned glycoprotein IIb/IIIa blockade during percutaneous coronary intervention: REPLACE-2 randomized trial. *JAMA* 2003;289:853–863.
12. Cohen DJ, Lincoff AM, Lavelle TA, et al. Economic evaluation of bivalirudin with provisional glycoprotein IIb/IIIa inhibition versus heparin with routine glycoprotein IIb/IIIa inhibition for percutaneous coronary intervention: results from the REPLACE-2 trial. *J Am Coll Cardiol* 2004;44:1792–1800.
13. Kaplan AV, Leung LLK, Leung WH, et al. Roles of thrombin and platelet membrane glycoprotein IIb/IIIa in platelet-subendothelial deposition after angioplasty in an *ex vivo* whole artery model. *Circulation* 1991;84:1279–1288.
14. Cutlip DE, Baim DS, Ho KK, et al. Stent thrombosis in the modern era: A pooled analysis of multicenter coronary stent clinical trials. *Circulation* 2001;103:1967–1971.
15. Leon MB, Baim DS, Popma JJ, et al. A clinical trial comparing three antithrombotic-drug regimens after coronary-artery stenting. Stent Anticoagulation Restenosis Study Investigators. *N Engl J Med* 1998;339:1665–1671.
16. EPILOG Investigators. Platelet glycoprotein IIb/IIIa blockade with abciximab with low-dose heparin during percutaneous coronary revascularization. *N Engl J Med* 1997;336:1689–1696.
17. EPISTENT Investigators. Randomised placebo-controlled and balloon-angioplasty-controlled trial to assess safety of coronary stenting with use of platelet glycoprotein IIb/IIIa blockade. *Lancet* 1998;352:87–92.
18. ESPRIT Investigators. Novel dosing regimen of eptifibatide in planned coronary stent implantation (ESPRIT): A randomised, placebo-controlled trial. *Lancet* 2000;356:2037–2044.
19. Chiu JH, Bhatt DL, Ziada KM, et al. Impact of female sex on outcome after percutaneous coronary intervention. *Am Heart J* 2004;148:998–1002.
20. Naidu SS, Selzer F, Jacobs A, et al. Renal insufficiency is an independent predictor of mortality after percutaneous coronary intervention. *Am J Cardiol* 2003;92:1160–1164.
21. Minutello RM, Chou ET, Hong MK, et al. Impact of body mass index on in-hospital outcomes following percutaneous coronary intervention. *Am J Cardiol* 2004;93:1229–1232.
22. Sharma S, Malarcher AM, Giles WH, et al. Racial, ethnic and socioeconomic disparities in the clustering of cardiovascular disease risk factors. *Ethn Dis* 2004;14:43–48.