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Changes in glycoprotein IIb/IIIa inhibitor excess dosing with site-specific safety feedback in the CRUSADE initiative

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Abstract

Background—Glycoprotein (GP) IIb/IIIa inhibitors can improve outcomes in patients with non-ST-segment elevation acute coronary syndromes (NSTEMI ACS) but raise the risk of bleeding, particularly if dosed in excess. The impact of GP IIb/IIIa dosing feedback on safety and major bleeding is unknown.

Methods—GP IIb/IIIa dosing feedback was added to the CRUSADE quarterly site reports in the first quarter (Q1) of 2006. We describe GP IIb/IIIa use and dosing among 25,641 NSTEMI ACS patients from Q4 2005–Q4 2006.

Results—11,846 patients received GP IIb/IIIa inhibitors, including 4031 women and 2609 elderly patients (age ≥75 years). Among GP IIb/IIIa-treated patients, unadjusted rates of excess GP IIb/IIIa dosing declined overall (26.4–22.4%, $P_{\text{trend}}=0.01$) and among the elderly (65.6–52.1%, $P_{\text{trend}}<0.001$). After adjustment, declines in excess dosing remained significant only for the elderly, though over half of GP IIb/IIIa-treated elderly patients continued to receive excess dosing at the end of the study period (64.1–51.3%, $P_{\text{trend}}<0.001$). There were concurrent declines in unadjusted major bleeding rates overall (9.6–8.0%, $P_{\text{trend}}=0.02$), but declines among women (14.4–11.5%, $P_{\text{trend}}=0.08$) and the elderly (17.1–11.0%, $P_{\text{trend}}=0.05$) did not reach statistical significance. After adjustment for baseline characteristics and excess dosing, declines in major bleeding rates were no longer significant overall or for any subgroup.

Conclusion—Within 9 months of initiating a safety feedback program, we observed early decreases in excess GP IIb/IIIa dosing among the elderly but minimal changes in excess dosing overall. Further work is needed to promote safe and effective medication use in vulnerable patients who are most at risk of harm.

Glycoprotein (GP) IIb/IIIa inhibitors are beneficial in high-risk, invasively managed patients with non-ST-segment elevation (NSTEMI) acute coronary syndromes (ACS).^{1,2} However, their use increases bleeding, particularly in those already at risk for complications or when dosed in excess. Frequent excess GP IIb/IIIa inhibitor dosing and associated bleeding among NSTEMI ACS patients was previously demonstrated in the CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines) quality improvement (QI) initiative.³ Excess dosing was especially high among women, the elderly, and patients with renal insufficiency.

3-4 Studies have shown that major bleeding among NSTEMI ACS patients is associated with increased short- and long-term morbidity and mortality.⁵⁻⁸ Therefore, the 2007 ACC/AHA guideline update added a class IB recommendation for dose adjustment of antiplatelet medications and anticoagulants based on weight and renal function.¹ The 2008 ACC/AHA Performance Measures for Quality Care of Myocardial Infarction (MI) added test measures for excess dosing of antiplatelet and anticoagulant medications and the establishment of tracking systems for identifying dosing errors.⁹

Herein, we report trends in rates of GP IIb/IIIa inhibitor excess dosing, major bleeding, and mortality overall and in key subgroups within the first 3 quarters after initiation of site-specific GP IIb/IIIa dosing feedback in a national QI initiative.

Methods

CRUSADE QI initiative

The CRUSADE QI initiative collected data on high-risk NSTEMI ACS patients admitted to participating U.S. hospitals from November 2001–January 2007.^{10,11} Patient eligibility required ischemic symptoms lasting ≥ 10 minutes combined with positive cardiac markers (troponin or creatine kinase-MB) or ischemic ST-segment electrocardiographic changes (ST-segment depression or transient ST-segment elevation) within 24 hours of hospital admission. CRUSADE hospitals participated voluntarily and were diverse in size, teaching status, capacity, and region. Participating hospitals collected data through retrospective chart review using standardized data collection tools. Data elements included baseline demographics, clinical presentation, comorbidities, use of medications within the first 24 hours of hospitalization, use and timing of invasive cardiac procedures, laboratory results, interventions, in-hospital outcomes, and discharge medications. The institutional review board of each hospital approved participation in CRUSADE. Individual informed consent was not required as data were anonymous.

Quarterly site reports included site-specific information on guideline adherence and outcomes, with comparison data benchmarked to like hospitals, best performing hospitals, and overall national averages. Site-specific safety feedback on GP IIb/IIIa overdosing was added to the quarterly site reports in Q1 2006. These reports included rates of bleeding overall and among subgroups. To encourage sites to further review safety errors, patient-level data indicating case ID numbers were provided for those excessively dosed. During this time, participating sites were also provided with educational materials on dosing of GP IIb/IIIa inhibitors and tools—such as creatinine clearance (CrCl) and dosing calculators and standing order sets—to support proper dosing.

Definitions

Excess dosing of small molecule GP IIb/IIIa inhibitors (tirofiban and eptifibatide) was defined as an initial dose exceeding the FDA-approved manufacturer recommendations and published practice guidelines, including failure to appropriately reduce doses for low CrCl. CrCl was estimated with the Cockcroft-Gault formula.¹² For eptifibatide, full dose infusion was defined as 2 mcg/kg/min, with reduced dose of 1 mcg/kg/min specified for CrCl < 50 mL/min.¹³ For tirofiban, full dose infusion was defined as 0.1 mcg/kg/min, with reduced dose of 0.05 mcg/kg/min required for CrCl < 30 mL/min.¹⁴ Initial dosing was recorded on the case report form with check boxes for full dose, reduced dose, or other dose (specified).

Baseline and nadir hematocrit, episodes of intracranial hemorrhage, clinical bleeding events, and in-hospital transfusions were recorded on the data collection form. Major bleeding included any of the following: intracranial hemorrhage, retroperitoneal bleed, hematocrit

drop from baseline to nadir $\geq 12\%$, transfusion when baseline hematocrit was $\geq 28\%$, or transfusion when baseline hematocrit was $< 28\%$ with witnessed bleed.

Study population

CRUSADE sites eligible for this analysis contributed 5 quarters of consecutive data between Q4 2005 and Q4 2006 (October 1, 2005–December 31, 2006). This time interval was selected because it represented the quarter prior to and the 3 quarters immediately following Q1 2006, during which safety feedback was initiated. Q4 2006 was the last full quarter of data collection in CRUSADE.

For analyses exploring GP IIb/IIIa use, the population included 37,910 patients. Patients from hospitals without consecutive quarterly reporting ($n=7138$) and patients with contraindications to GP IIb/IIIa inhibitors ($n=5131$) were excluded, leaving a population of 25,641 patients eligible for GP IIb/IIIa treatment at 185 qualifying CRUSADE sites.

For the analyses exploring excess GP IIb/IIIa dosing, patients who did not receive GP IIb/IIIa inhibitors ($n=12,072$) and those missing dosing information ($n=1723$) were excluded, leaving a population of 11,846 patients receiving GP IIb/IIIa treatment at 184 sites. GP IIb/IIIa therapy initiated at any time during the hospitalization, including in the catheterization lab, was included.

Non-coronary artery bypass grafting (CABG)-related major bleeding was analyzed in GP IIb/IIIa-treated patients with dosing information. Patients were excluded if they were transferred out of the participating site ($n=1456$) or underwent CABG ($n=1041$), due to incomplete follow-up and issues of transfusion with CABG, leaving 9349 patients.

Among those who received GP IIb/IIIa inhibitors, most received eptifibatide (11,757 [99.3%]); only 87 (0.7%) received tirofiban, and 53 (0.5%) received abciximab. The total population exceeds 100% due to the possibility of a patient receiving more than 1 drug.

Statistical analysis

Baseline demographics, medical history, presentation features, and hospital characteristics are presented for patients who were and were not treated with GP IIb/IIIa inhibitors. Patients treated with GP IIb/IIIa inhibitors were further stratified by those who did and did not receive excess doses. Median and interquartile ranges are presented for continuous variables, and percentages are used for categorical variables. Continuous variables were compared using Wilcoxon rank-sum tests, and categorical variables were compared using chi-square tests.

The unadjusted rates of GP IIb/IIIa use, excess dosing of GP IIb/IIIa inhibitors among recipients, non-CABG-related major bleeding among GP IIb/IIIa recipients, and in-hospital mortality among eligible patients and among recipients were determined for the overall cohort and among women and the elderly. Adjusted rates were determined for the overall cohort and among women and the elderly by using the standard statistical methods for comparing *observed* rates to *expected* rates based on an internal standard.¹⁵ The predicted probabilities (i.e., *expected*) were calculated based on logistic generalized estimating equations (GEE) modeling procedure with an exchangeable working correlation matrix to account for within-hospital clustering because patients at the same hospital may be more likely to have similar responses relative to patients at other hospitals (e.g., within-center correlation for response). This method produced estimates similar to those from ordinary logistic regression, but variances were adjusted for the correlation of outcomes within a hospital.¹⁶ For each quarter, the predicted probabilities were summed over patient and interpreted as the expected rate. The observed dichotomous outcomes (e.g., GP IIb/IIIa

inhibitor use, excess dosing of GP IIb/IIIa inhibitors, non-CABG-related major bleeding, and in-hospital mortality) were summed similarly, and the ratios of sums were called the OE ratios or standardized adjusted rates.

The following clinically plausible variables were included in the model for rates of GP IIb/IIIa use, excess dosing, and non-CABG-related major bleeding: age, sex, body mass index, race, family history of coronary artery disease (CAD), hypertension, diabetes, current/recent smoker, hypercholesterolemia, prior MI, prior percutaneous coronary intervention (PCI), prior CABG, prior congestive heart failure (CHF), prior stroke, renal insufficiency, systolic blood pressure and heart rate at admission, electrocardiogram (ECG) findings, positive cardiac markers, and signs of CHF at presentation. For non-CABG-related major bleeding analyses, GP IIb/IIIa excess dosing was also included in the model. For in-hospital mortality, the model included excess dosing as well as the variables included in the previously developed CRUSADE in-hospital mortality model: age, body mass index, diabetes, hypercholesterolemia, prior PCI, prior CHF, prior stroke, renal insufficiency, systolic blood pressure and heart rate at admission, ECG findings, troponin ratio (x upper limit of normal [ULN]), and signs of CHF at presentation.¹⁷

P values for the temporal trends of GP IIb/IIIa use, excess dosing of GP IIb/IIIa inhibitors, non-CABG-related major bleeding, and in-hospital mortality were obtained by modeling time as an ordinal independent variable using a logistic GEE modeling procedure. A *P* value of <0.05 was considered statistically significant for all tests, and all tests of statistical significance were 2-tailed. All analyses were performed using SAS software version 9.2 (SAS Institute, Cary, NC).

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Results

GP IIb/IIIa inhibitor use

Of the 25,641 patients without contraindication to GP IIb/IIIa inhibitors (eligible), 13,569 received GP IIb/IIIa inhibitors and 12,072 did not. Between Q4 2005 and Q4 2006, declines in use of GP IIb/IIIa inhibitors were not statistically significant overall (53.2–51.2%, $P_{\text{trend}}=0.05$). However, use of GP IIb/IIIa inhibitors did decline among the elderly (37.7–33.6%, $P_{\text{trend}}=0.03$).

During index hospitalization, 43.8% of GP IIb/IIIa inhibitor-eligible patients underwent PCI only, 8.4% underwent CABG only, and 0.6% underwent both PCI and CABG. Baseline demographics, medical history, presentation, and hospital characteristics of eligible patients treated or not treated with GP IIb/IIIa inhibitors are shown in Table I. Compared with patients not given GP IIb/IIIa inhibitors, treated patients were more likely to be younger and male and were less likely to have comorbid conditions. At hospital presentation, treated patients were more likely to have positive cardiac markers and ECG changes, but less likely to have signs of CHF; they also had better creatinine clearance. They were more often treated in full-service hospitals without academic affiliation.

Excess dosing

Dosing information was available for 11,846 patients who received GP IIb/IIIa inhibitors, including 4031 women and 2609 elderly patients. During index hospitalization, 60.4% of GP IIb/IIIa inhibitor-treated patients underwent PCI only, 7.6% underwent CABG only, and 0.7% underwent both PCI and CABG.

Baseline demographics, medical history, presentation features, and hospital characteristics of patients treated with or without excess dose GP IIb/IIIa inhibitors are shown in Table I. Compared with GP IIb/IIIa-treated patients who received a recommended dose, those who received excess dose were more often elderly and female and had more comorbid conditions. At hospital presentation, they were more likely to have signs of CHF, faster heart rates, ischemic ECG changes, lower hematocrit, and lower estimated CrCl. Those who received excess dose were more often treated in smaller hospitals without academic affiliation.

In a previous analysis of CRUSADE data, the unadjusted excess dosing rate for GP IIb/IIIa inhibitors from Q1 2004 to Q3 2004 was 26.8%.³ In the current study, excess dosing occurred in almost 1 in 4 patients overall (2881/11,846 [24.3%]), including 41.8% of women (1684/4031) and 59.6% of the elderly (1554/2609). From Q4 2005 to Q4 2006, the unadjusted excess dosing rate declined significantly from 26.4% to 22.4% overall (relative reduction 15.2%; $P_{\text{trend}}=0.01$) and from 65.6% to 52.1% among the elderly (relative reduction 20.6%; $P_{\text{trend}} < 0.001$). The decrease in excess dosing among women was non-significant (44.6–38.8%; $P_{\text{trend}}=0.07$). After adjustment, the decline remained significant in the elderly (64.1–51.3%; relative reduction 20.0%; $P_{\text{trend}} < 0.001$), but there was no significant decline overall (24.0–21.6%; $P_{\text{trend}}=0.16$) or for women (42.6–38.5%; $P_{\text{trend}}=0.18$) (Table II).

Major bleeding

Among GP IIb/IIIa inhibitor-treated patients with dosing information, unadjusted non-CABG-related major bleeding also declined from Q4 2005–Q4 2006 overall (9.6–8.0%; relative reduction 16.7%; $P_{\text{trend}}=0.02$). There were non-significant declines in major bleeding rates among women (14.4–11.5%, $P_{\text{trend}}=0.08$) and among the elderly (17.1–11.0%, $P_{\text{trend}}=0.05$). (Table III).

However, after adjusting for baseline characteristics and excess dosing, trends in bleeding rates were no longer significant overall (9.1–8.2%, $P_{\text{trend}}=0.20$), among women (13.9–11.7%, $P_{\text{trend}}=0.23$), or among the elderly (16.1–12.0%, $P_{\text{trend}}=0.20$) (Table III). Declines in bleeding remained significant after adjusting for excess GP IIb/IIIa dosing only (9.4–8.1%, $P_{\text{trend}}=0.04$) but not after adjusting for baseline patient characteristics only (9.1–8.2%, $P_{\text{trend}}=0.17$), suggesting that the significant improvements in unadjusted bleeding were primarily related to the case-mix of patients treated with GP IIb/IIIa inhibitors.

Mortality

Among patients eligible to receive GP IIb/IIIa inhibitors, adjusted in-hospital mortality rates remained stable overall (2.7–2.3%, $P_{\text{trend}}=0.10$) and for women (3.2–2.7%, $P_{\text{trend}}=0.05$) but declined significantly among the elderly (6.3–4.2%, $P_{\text{trend}}=0.02$). Similarly, among GP IIb/IIIa-treated patients with dosing information, adjusted in-hospital mortality rates remained stable overall (1.8–1.8%; $P_{\text{trend}}=0.53$) and among women (2.4–2.2%; $P_{\text{trend}}=0.21$) but declined significantly among the elderly (5.6–2.7%, $P_{\text{trend}}=0.006$) (Table IV).

Discussion

Traditionally, QI initiatives have worked to improve patient outcomes by increasing the use of effective therapies.^{18–22} To our knowledge, this is the first QI initiative of this size focused on optimizing the proper dosing of effective therapies through systematic feedback. Within only 9 months of the initiation of safety feedback, we observed a 20.0% relative decline (12.8% absolute decline) in the excess dosing rate of GP IIb/IIIa inhibitors among the elderly, with non-significant declines overall and in women. At the end of the study period, however, high rates of excess dosing persisted, so much work remains to be done.

The expected benefit from improved dosing should primarily be decreased bleeding. Previous analysis has demonstrated 2-fold higher bleeding with excess GP IIb/IIIa dosing and association of bleeding with in-hospital mortality and longer lengths of stay.³ Other studies have demonstrated correlation between bleeding and longer-term mortality rates.^{5–7,23,24} In the current study, unadjusted major bleeding among patients receiving GP IIb/IIIa inhibitors declined (Table III). After adjusting for case-mix and dosing, however, the trend toward decreased bleeding was no longer significant.

Focusing on drug safety should not result in under-use of effective therapies in high-risk populations. Risk factors that predict bleeding, including advanced age, female sex, and renal insufficiency,²⁵ may also identify high-risk NSTEMI ACS patients with potential to benefit from potent therapies including GP IIb/IIIa inhibitors.^{26–29} Therefore, balancing the risks and benefits of therapy will remain challenging. In the current study, as in previous reports,²⁶ patients treated with GP IIb/IIIa inhibitors tended to have lower-risk features than those who were not treated (Table I). Although site feedback was focused on dosing and not patient selection, there was a 10.9% relative decline over the observation period in the rate of GP IIb/IIIa inhibitor use in the elderly (37.7–33.6%, $P_{\text{trend}}=0.03$) compared with a 3.8% relative decline overall (53.2–51.2%, $P_{\text{trend}}=0.05$). Without long-term follow-up, unavailable through this registry, the net benefit of changes in dosing and patient selection is difficult to ascertain and warrants close attention in future safety initiatives. To explore whether there was any signal suggesting harm from changes in patient selection for GP IIb/IIIa treatment, we did evaluate in-hospital mortality over the study period and found no increased mortality in either GP IIb/IIIa-eligible or -treated patients over the study period (Table IV).

Given the observational nature of the study and reliance on historical comparisons rather than experimental controls, changes in GP IIb/IIIa dosing cannot be attributed to specific feedback interventions. Previous analysis of CRUSADE data has shown improvements in guideline adherence over time³⁰ with associated improvements in clinical outcomes,¹⁹ so changes in dosing of GP IIb/IIIa inhibitors may reflect general upward trends independent of feedback. In particular, awareness of the scope and consequences of improper dosing of antiplatelet and antithrombotic medications was growing over the study period, outside of structured feedback and educational activities provided through CRUSADE.

Our study has other limitations that are important to consider. The follow-up length, truncated by the end of data collection in CRUSADE, may not have been long enough to fully capture the effects of feedback, and there were no means to directly assess the response to feedback or the use of dosing tools at individual sites. However, with QI infrastructure already in place at participating CRUSADE hospitals, it is reasonable that some improvements could have been seen within the data collection period. The current rate of GP IIb/IIIa inhibitor excess dosing in the NSTEMI population from the ACTION Registry–Get With the Guidelines program using similar safety feedback was 9.5% (Q4 2009), compared with 22.4% in Q4 2006 in CRUSADE. While CRUSADE hospitals include a wide cross-

section of U.S. institutions, hospitals participated voluntarily and thus represented a subset interested in quality improvement. We limited our analysis to major bleeding, and effects on rates of minor bleeding were not available. Our analysis is also based on initial GP IIb/IIIa inhibitor dose, so later dose adjustments were not considered. Many other NSTEMI ACS treatments can also alter the risk of bleeding; analysis of these was beyond the scope of the study. Additionally, no long-term patient outcomes were available, so effects beyond the initial hospitalization could not be assessed.

In conclusion, performance improvement plays an important role in the culture of safety in medicine. Following the initiation of site-specific dosing feedback, we observed early decreases in excess dosing among the elderly. Despite this, high rates of dosing excess persisted at the end of the study period, underscoring the need for sustained efforts and more effective solutions than feedback alone to promote the safe use of medications like GP IIb/IIIa inhibitors. Therefore, much work remains to identify and implement methods to improve systems of care and promote the safe use of proven therapies without limiting their effective use in groups most likely to benefit.³¹

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Table 1

Baseline demographics and clinical and hospital characteristics by GP IIb/IIIa inhibitor treatment and dosing status among eligible patients

	GP IIb/IIIa treatment status			Dosing status among treated*		
	Untreated N=12,072	Treated N=13,569	P value	Excess dose N=2881	No excess N=8965	P value
Patient characteristics						
Age (yrs) [†]	70 (58, 80)	62 (53, 73)	<0.001	75 (68, 81)	59 (51, 67)	<0.001
Age ≥75 yrs	39.9	21.6	<0.001	53.9	11.8	<0.001
Weight (kg) [†]	80 (68, 96)	85 (73, 99)	<0.001	77 (66, 90)	88 (76, 101)	<0.001
Female sex	43.6	33.6	<0.001	58.5	26.2	<0.001
Non-white race	18.6	16.4	<0.001	15.0	16.7	0.03
Hypertension	75.4	67.5	<0.001	80.9	63.4	<0.001
Diabetes	35.8	29.4	<0.001	38.6	26.7	<0.001
Current/recent smoker	24.4	34.9	<0.001	16.9	40.4	<0.001
Prior MI	31.4	25.7	<0.001	29.5	24.6	<0.001
Prior revascularization	36.4	33.0	<0.001	38.4	31.3	<0.001
Prior CHF	20.3	8.5	<0.001	16.4	6.0	<0.001
Prior stroke	10.6	6.3	<0.001	11.0	4.9	<0.001
Renal insufficiency [‡]	14.9	7.3	<0.001	14.1	4.6	<0.001
Signs at presentation						
Signs of CHF	26.5	13.0	<0.001	22.5	9.9	<0.001
Heart rate (bpm) [†]	84 (71, 101)	80 (68, 93)	<0.001	81 (69, 98)	79 (68, 92)	<0.001
Systolic BP (mm Hg) [†]	144 (124, 164)	145 (127, 165)	<0.001	146 (126, 167)	145 (127, 164)	0.18
ST depression (%)	26.0	27.5	0.009	30.3	26.8	<0.001
Positive cardiac markers (%)	91.3	94.8	<0.001	95.2	94.9	0.56
HCT baseline (%) [†]	40 (36, 44)	42 (39, 45)	<0.001	39 (36, 43)	43 (40, 46)	<0.001
CrCl (mL/min) ^{†§}	49 (33, 71)	65 (46, 84)	<0.001	39 (32, 45)	73 (60, 89)	<0.001
Hospital characteristics						

	GP IIb/IIIa treatment status			Dosing status among treated*		
	Untreated N=12,072	Treated N=13,569	P value	Excess dose N=2881	No excess N=8965	P value
Region (%)			<0.001			0.12
West	9.5	8.9		7.3	8.5	
Northeast	21.4	20.3		21.4	21.0	
Midwest	42.1	38.5		38.3	38.9	
South	26.9	32.3		33.0	31.6	
Revascularization services (%)			<0.001			0.08
None	4.8	3.3		3.7	3.4	
Catheterization only	12.3	7.5		8.8	8.0	
PCI, no surgery	5.2	5.7		6.8	5.8	
Surgery	77.7	83.5		80.7	82.7	
Academic affiliation (%)¶	35.1	33.3	0.002	31.6	33.8	0.03
Number of beds‡	357 (260, 556)	357 (270, 561)	<0.001	352 (264, 500)	357 (274, 561)	0.008

BP, blood pressure; HCT, hematocrit.

* 1723 patients with missing dose information were excluded.

‡ Median (25th, 75th percentiles).

§ Renal insufficiency defined as Cr >2.0 mg/dL, CrCl <30 mL/min, or need for renal dialysis.

¶ Cockcroft-Gault equation; dialysis patients excluded.

‡ Academic affiliation reflects listing in Council of Teaching Hospitals.

Table II

Unadjusted and adjusted* excess dosing rates of GP IIb/IIIa inhibitors over time

	Q4 2005	Q1 2006	Q2 2006	Q3 2006	Q4 2006	P value
Unadjusted						
All patients (%)	26.4	25.0	22.3	25.1	22.4	0.01
Women (%)	44.6	43.6	38.0	43.4	38.8	0.07
Elderly (%)	65.6	61.0	56.3	60.6	52.1	<0.001
Adjusted						
All patients (%)	24.0	23.4	22.1	24.3	21.6	0.16
Women (%)	42.6	42.8	38.9	42.5	38.5	0.18
Elderly (%)	64.1	60.6	56.2	59.9	51.3	<0.001

P values are for trends over time.

* Adjusted for age, sex, body mass index, race, family history of CAD, hypertension, diabetes, current/recent smoker, hypercholesterolemia, prior MI, prior PCI, prior CABG, prior CHF, prior stroke, renal insufficiency, systolic blood pressure and heart rate at admission, ECG findings, positive cardiac markers, and signs of CHF at presentation.

Table III

Unadjusted and adjusted* non-CABG-related major bleeding rates over time

	Q4 2005	Q1 2006	Q2 2006	Q3 2006	Q4 2006	P value
Unadjusted						
All patients (%)	9.6	10.7	8.5	8.9	8.0	0.02
Women (%)	14.4	16.4	12.8	14.7	11.5	0.08
Elderly (%)	17.1	18.2	14.6	16.1	11.0	0.05
Adjusted						
All patients (%)	9.1	10.2	8.8	9.1	8.2	0.20
Women (%)	13.9	15.8	13.2	15.0	11.7	0.23
Elderly (%)	16.1	17.4	15.2	16.4	12.0	0.20

P values for time trends.

* Adjusted for: excess dosing, age, sex, body mass index, race, family history of CAD, hypertension, diabetes, current/recent smoker, hypercholesterolemia, prior MI, prior PCI, prior CABG, prior CHF, prior stroke, renal insufficiency, systolic blood pressure and heart rate at admission, ECG findings, positive cardiac markers, and signs of CHF at presentation.

Table IV

Adjusted* in-hospital mortality rates among patients eligible for or treated with GP IIb/IIIa inhibitors over time

	Q4 2005	Q1 2006	Q2 2006	Q3 2006	Q4 2006	P value
GP IIb/IIIa eligible						
All patients (%)	2.7	2.7	2.3	2.5	2.3	0.10
Women (%)	3.2	3.5	3.0	2.3	2.7	0.05
Elderly (%)	6.3	5.5	4.8	5.2	4.2	0.02
GP IIb/IIIa treated						
All patients (%)	1.8	1.8	1.7	1.4	1.8	0.53
Women (%)	2.4	2.8	1.7	1.3	2.2	0.21
Elderly (%)	5.6	5.1	4.0	3.7	2.7	0.006

P values for time trends.

* Model includes age, blood pressure at admission, signs of CHF, renal insufficiency, heart rate at admission, hypercholesterolemia, prior stroke, troponin ratio (xULN), prior CHF, body mass index, diabetes, ECG findings, prior PCI, and excess GP IIb/IIIa dosing.