DEREK P. CHEW, MBBS
Department of Cardiovascular Medicine,
The Cleveland Clinic

DAVID J. MOLITERNO, MD*
Department of Cardiovascular Medicine,
The Cleveland Clinic

GP IIb/IIIa inhibitors in coronary artery disease management: What the latest trials tell us

ABSTRACT

Recent clinical trials have refined our understanding of how the glycoprotein (GP) IIb/IIIa inhibitors should best be used. These trials examined whether there are clinical differences between agents, whether empiric use of GP IIb/IIIa inhibitors in acute coronary syndromes is justified, and whether these drugs might allow for early invasive management in acute coronary syndromes.

KEY POINTS

The TARGET study found abciximab more effective than tirofiban in patients undergoing percutaneous revascularization, but we cannot exclude the possibility that the bolus dose of tirofiban used was suboptimal.

Trials of GP IIb/IIIa inhibitors as empiric therapy in acute coronary syndromes (PRISM, PRISM PLUS, PURSUIT, PARAGON A) found these drugs to be only modestly beneficial; however, subgroup analyses indicated that patients with elevated troponin levels and those who underwent early revascularization derived particular benefit.

In a trial in which all patients presenting with acute coronary syndromes received tirofiban (TACTICS–TIMI-18), a strategy of early invasive management was more beneficial than a conservative strategy.

The GUSTO IV ACS trial underscores the important contribution of invasive management in attaining the optimal benefits from GP IIb/IIIa inhibition.

*The author has indicated that he has received grant or research support from the Centocor, Eli Lilly, and Merck corporations.

RECENT TRIALS of glycoprotein (GP) IIb/IIIa inhibitors have improved our understanding of how best to use these powerful antiplatelet drugs in coronary artery disease.

Previous studies provided robust evidence that these drugs are beneficial in patients undergoing percutaneous revascularization, but several important questions remained:

- Do the available GP IIb/IIIa inhibitors differ in efficacy?
- Are GP IIb/IIIa inhibitors effective as empiric treatment in patients with acute coronary syndromes who do not necessarily undergo early revascularization?
- When patients presenting with acute coronary syndromes receive a GP IIb/IIIa inhibitor, is an early invasive strategy (with angiography and possibly percutaneous revascularization for all) more beneficial than a conservative strategy?

In this article, we review recent trials that addressed these questions and offer recommendations for the optimal use of GP IIb/IIIa inhibitors.

DO GLYCOPROTEIN IIb/IIIa INHIBITORS DIFFER IN EFFICACY?

Abciximab (ReoPro), the first GP IIb/IIIa inhibitor to be developed, is a monoclonal antibody against the GP IIb/IIIa receptor on platelets; the newer agents tirofiban (Aggrastat), eptifibatide (Integrilin), and lamifiban (not released) also bind to the GP IIb/IIIa receptor but are much smaller molecules (nonantibody peptides or peptidomimetics).

Glossary of studies discussed in this article

CAPTURE—c7E3 FAB Anti-platelet Therapy in Unstable Refractory Angina[18]

ESPRIT—Enhanced Suppression of the Platelet Glycoprotein IIb/IIIa Receptor Using Integrilin Therapy[8]

FRISC II—Fragmin During Instability in Coronary Artery Disease II[19]

GUSTO IV ACS—Global Utilization of Strategies for Occluded Coronary Arteries IV trial in Acute Coronary Syndromes

IMPACT-II—Integrilin to Manage Platelet Aggregation to Combat Coronary Thrombosis-II[7]

PARAGON A—Platelet IIb/IIIa Antagonism for the Reduction of Acute Coronary Syndrome Events in a Global Organization Network A[16]

PRISM—Platelet Receptor Inhibition in Ischemic Syndrome Management

PRISM-PLUS—Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms[14]

PURSUIT—Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy[15]

RESTORE—Randomized Efficacy Study of Tirofiban for Outcomes and REstenosis[6]

TACTICS–TIMI-18—Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy–Thrombolysis in Myocardial Infarction-18[20]

TARGET—Do Tirofiban and ReoPro Give Similar Efficacy Outcomes Trial[13]

In percutaneous coronary revascularization, abciximab was more effective than tirofiban

Is one of them better than the others, or is there a pure class effect?

Trials with abciximab

Initial studies[1–5] demonstrated that abciximab confers a consistent and sustained benefit in patients undergoing balloon angioplasty, atherectomy, or stenting, reducing the 30-day rates of death, MI, or need for urgent target-vessel revascularization by 35% to 50%. Also observed was a reduced incidence of death at 12 months, particularly in patients at high risk, such as those with diabetes or acute coronary syndromes.

Trials with small-molecule inhibitors

Similar trials also found small-molecule GP IIb/IIIa inhibitors to be beneficial, but less consistently and, perhaps, to a lesser degree than abciximab.

The RESTORE trial[6] compared the use of tirofiban vs placebo in patients with unstable angina undergoing percutaneous revascularization. At 30 days, the rate of death, MI, and urgent target-vessel revascularization was lower in the tirofiban group by 24% (P = .052).

IMPACT II,[7] a similar trial, compared eptifibatide vs placebo. At 30 days, the rate of death, MI, urgent target-vessel revascularization, and stenting was lower in the eptifibatide group by 19% (P = .063).

Why were the risk reductions less impressive with the small-molecule drugs than with abciximab? There are several theories:

- The doses studied may have been too low. For example, the IMPACT II trial used an eptifibatide dosage of 135 µg/kg followed by an infusion of either 0.5 or 0.75 µg/kg/minute for 20 to 24 hours. Ultimately, the ESPRIT trial[8] used a nearly three times higher dose of eptifibatide (two 180-µg/kg bolus doses 2 minutes apart, followed by a 2-µg/kg/minute infusion for 18–24 hours) and demonstrated a greater benefit: at 30 days the reduction in death, MI, and urgent target-vessel revascularization was 37% (P = .034). Other studies[9–11] also suggested that it is important to achieve very high levels of platelet aggregation inhibition (> 95%) at the time of angioplasty.
- Small-molecule GP IIb/IIIa inhibitors, unlike abciximab, lack activity against the vitronectin and Mac-1 receptors.[12] It is possible that these separate receptors on platelets and white blood cells are also involved with ischemic events following angioplasty.
- The patient populations may have been different in the various trials, or the patients may have received different ancillary therapies.

The TARGET study: Testing abciximab vs tirofiban in percutaneous revascularization

The TARGET study[13] directly compared abciximab and tirofiban in patients undergoing coronary stenting. In a double-blind protocol, 4,809 patients received aspirin, heparin, clopidogrel, and either tirofiban in the same dosage used in the RESTORE study (a 10-µg/kg bolus, followed by a 0.15-µg/kg/minute infusion for 18 to 24 hours) or abciximab in the standard dosage (a 0.25-mg/kg bolus, followed by a 0.125-mg/kg/hour infusion for 12 hours).

At 30 days, a component of the primary composite end point (death, MI, or urgent target-vessel revascularization) had occurred in 6.0% of the abciximab group compared with 7.6% of the tirofiban group—a 26% greater incidence with tirofiban ($P = .037$; FIGURE 1). A similar difference was seen for each element of the composite end point considered individually.

Nearly all subgroups had a pattern consistent with the overall trial results: abciximab was associated with superior outcomes in the elderly, women, diabetic patients, and those not receiving pretreatment with clopidogrel. Interestingly, patients with unstable angina had a particularly marked reduction in ischemic events when treated with abciximab.

The incidence of major bleeding was similar in both treatment groups, but abciximab was associated with an approximately 2.0% higher incidence of thrombocytopenia and minor bleeding.

Comment. The TARGET study demonstrated that abciximab is more effective than tirofiban in patients undergoing percutaneous revascularization—at the dose of tirofiban tested. Abciximab may have greater biologic activity than tirofiban: the magnitude of difference in outcomes was greater in patients presenting with acute coronary syndromes, and the rate of bleeding was slightly higher with abciximab than with tirofiban.

The majority of the end point events (MIs) occurred during study drug infusion, so increasing the duration of therapy would likely not be helpful. Whether higher doses of tirofiban would be more effective or whether different receptor-binding characteristics inherent to the agents account for the disparity in efficacy requires further investigation.

ARE THESE DRUGS EFFECTIVE AS ACUTE EMPIRIC THERAPY?

Randomized trials seem to indicate that GP IIb/IIIa inhibitors confer less benefit as empiric therapy for acute coronary syndromes than when they are used during percutaneous revascularization.

The PRISM and PRISM PLUS studies.[6,14] Patients with non–ST-segment-elevation acute coronary syndromes received either tirofiban or placebo. At 30 days, the death rate was lower in the tirofiban group by 18% and the rate of MI was lower by 27%.

The PURSUIT study.[15] Patients (N = 10,948) received either eptifibatide or placebo. At 30 days, the death rate in the eptifibatide group was lower by 10%; at 6 months, the rate of MI was lower by 8%.

The PARAGON A study,[16] however, found little or no benefit from lamifiban,

given in two dosages. Subgroup analysis suggested that it is important to individualize the dose by renal function, ie, reduce the dose in patients with higher serum creatinine levels, as the small-molecule drugs are excreted via the kidneys. This hypothesis was subsequently tested prospectively in PARAGON B, but lamifiban in individualized dosages was still not superior to placebo.

The drugs may be more beneficial in troponin-positive patients

The benefit of GP IIb/IIIa drugs in these trials overall was moderate. However, subgroup analyses indicated that patients who were troponin-positive derived substantial benefit from these drugs.

In the PRISM and PARAGON B trials,[17] at 30 days, troponin-positive patients who received a GP IIb/IIIa inhibitor had a death rate that was lower by 67% ($P < .001$) and a rate of MI that was lower by 42% ($P = .018$) vs placebo.

Similarly, the CAPTURE study,[18] a hybrid acute coronary syndrome and percutaneous coronary intervention trial, found a 70% reduction ($P = .002$) in the 30-day rate of death or MI in troponin-positive patients randomized to receive abciximab.

These findings strongly support the use of GP IIb/IIIa inhibitors in patients presenting with evidence of myonecrosis.

Troponin levels should guide treatment in acute coronary syndromes

Efficacy in acute coronary syndromes with percutaneous revascularization

Subgroup analysis also revealed another group who derived greater benefit from GP IIb/IIIa inhibitors as empiric therapy in acute coronary syndromes: patients who underwent percutaneous revascularization while receiving the therapy. (We should note, however, that this group overlapped with the group that was troponin-positive.)

In the PRISM PLUS study,[14] among the patients who underwent percutaneous revascularization, the 30-day rate of death or MI was lower in the tirofiban group than in the placebo group by 42%. In contrast, the reduction among patients who did not undergo percutaneous revascularization was 23%. In the PURSUIT study, the relative risk reduction in this subgroup was 31%; in PARAGON B it was 35%.[15]

INVASIVE OR CONSERVATIVE MANAGEMENT FOR ACUTE CORONARY SYNDROMES

A long-standing debate in treating acute coronary syndromes has been whether to adopt an early invasive strategy (ie, to perform angiography in all patients, followed by revascularization in target vessels with identified lesions) or to take a more conservative approach.

Initial studies did not find an early invasive strategy to be more effective or safer than a conservative strategy; however, these studies did not use GP IIb/IIIa inhibitors, since they were unavailable at the time. For example, the FRISC II study[19] used low-molecular-weight heparin.

Observations from the PURSUIT trial suggest that percutaneous revascularization within a few hours of starting a GP IIb/IIIa inhibitor is associated with a greater reduction in events compared with later revascularization. This suggests that in patients with coronary instability the greatest benefit can be expected when percutaneous revascularization is performed early, emulating the "dose-and-dilate" design of the percutaneous revascularization trials.

TACTICS–TIMI-18: Invasive strategy beneficial in patients receiving tirofiban

The TACTICS–TIMI-18 study[20] randomized 2,220 patients with acute coronary syndromes to receive invasive management (angiography within 48 hours) or conservative management (drug therapy, with invasive testing prompted by recurrent ischemia).

Patients were enrolled only if they had chest pain for more than 20 minutes plus one of the following: ST-segment depression, positive troponin, or a history of coronary disease. All patients received tirofiban, aspirin, and heparin. The study used a composite 6-month end point of death, MI, or rehospitalization for an acute coronary syndrome.

During the index hospitalization, 60% of the invasive-treatment group and 36% of the conservative treatment group underwent coronary revascularization; by 6 months, the numbers had risen slightly to 61% of the patients in the invasive treatment group and 44% of patients in the conservative treatment

group. The reduction in composite end point events in the invasive treatment group was 22% (P = .025). These benefits also were observed for each component of the composite end point.

Subgroup analysis showed a similar benefit in women, diabetic patients, and patients over age 65. Interestingly, no benefit was observed in patients without ST-segment changes at baseline.

On the other hand, 54% of patients presented with a troponin level above 0.01 ng/mL, and in these patients the risk reduction in the primary composite end point with aggressive treatment was more striking at 41% (P < .001), thus confirming the value of troponin in guiding the management of patients presenting with acute coronary syndromes (FIGURE 2).

Similarly, patients at increased risk as defined by a TIMI risk score of 5, 6, or 7 experienced a 36% reduction in the 6-month composite ischemic end point with aggressive management, whereas patients at low risk (TIMI risk score 0–2) gained no benefit from invasive management.

TIMI major bleeding (≥ 5 mL blood loss) was not significantly increased in the invasive treatment group, whereas the overall length of stay was greater in patients treated conservatively (P < .001).

Hence, modern antithrombotic therapies enable the safe and effective application of early invasive investigation and management, and the combination improves outcomes.

GUSTO IV ACS: No benefit from abciximab without revascularization

The GUSTO IV ACS study assessed the benefit of aggressive medical management in 7,800 patients who had ischemic chest pain for more than 5 minutes and either ST-segment depression (> 0.5 mm) or a positive baseline troponin.

All patients received aspirin and heparin (either unfractionated or low-molecular-weight heparin). In addition, they were randomized to receive abciximab for 24 hours, abciximab for 48 hours, or placebo. Revascularization within the first 60 hours was discouraged, and only 5% of patients underwent revascularization within 30 days.

TACTICS–TIMI-18 subgroup analysis: The role of troponin T

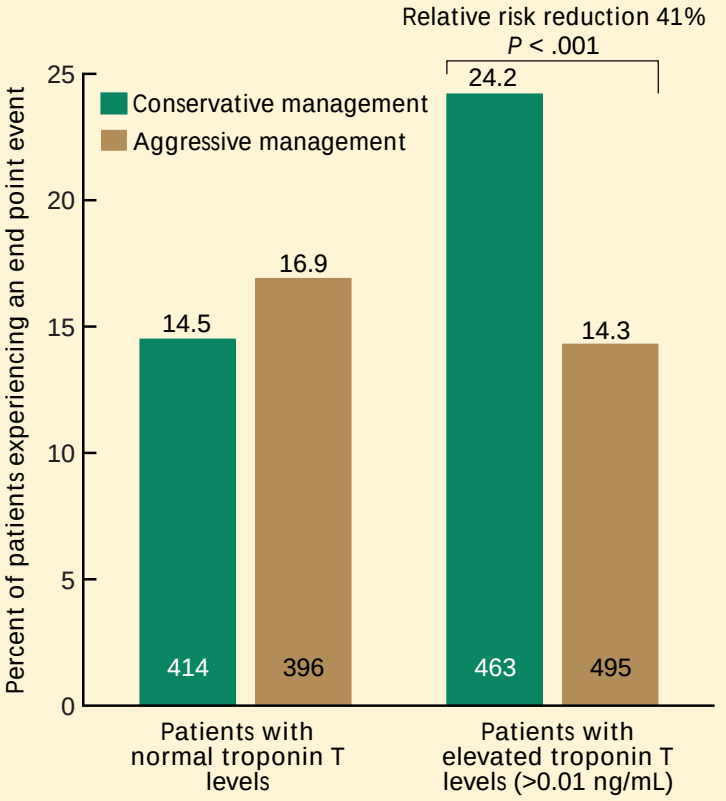

FIGURE 2. Subgroup analysis in TACTICS–TIMI-18 showed that when troponin T levels were 0.01 ng/mL or lower, there was no significant difference in rates of end point events when comparing conservative vs aggressive management for acute coronary syndrome. However, in the 54% of patients who presented with a troponin level above 0.01 ng/mL, a relative risk reduction in end point events of 41% (P < .001) occurred with aggressive treatment. This confirms the value of troponin in guiding the management of this patient subgroup.

Unexpectedly, prolonged administration of abciximab was not associated with any reduction in death or MI at 30 days, the primary end point. In fact, a post hoc analysis also suggested an *increase* in deaths in the abciximab treatment groups. Furthermore, in contrast to the other trials of GP IIb/IIIa inhibitors, no benefit was seen in patients with baseline troponin elevation. Bleeding events occurred more often in patients receiving abciximab.

Comment. While its results were incongruous with those of previous trials, the GUSTO IV ACS study underscores the important contribution of invasive management in attaining the optimal benefits from GP IIb/IIIa inhibition. In patients undergoing coronary intervention, the data on the efficacy of abciximab are compelling. In contrast, no benefit has been demonstrated in acute coronary syndromes when revascularization is performed less often. Hence, the benefit of GP IIb/IIIa inhibition in acute coronary syndromes appears to be coupled with early invasive management.

The greater rate of adverse events in the abciximab groups raises the question of whether GP IIb/IIIa inhibitors have clinically relevant partial-agonist or prothrombotic effects. In clinical trials, oral GP IIb/IIIa inhibitors were associated with increased mortality.[21] Heightened GP IIb/IIIa receptor activation and P-selectin expression induced by receptor antagonists has been demonstrated with "suboptimal" dosing.[22] Whether these agents induce platelet activation, particularly at lower levels of receptor occupancy, resulting in clinically relevant ischemic events, remains speculative.[23] The mechanisms underlying the association between prolonged use of GP IIb/IIIa inhibitors and adverse events require further research.

GUSTO IV ACS: optimal benefit from invasive approach plus GP inhibitors

WHAT THESE STUDIES TELL US

On the basis of our analysis of the current data, we draw the following conclusions:

- GP IIb/IIIa inhibitors remain an important component of percutaneous revascularization. Started in the catheterization laboratory, abciximab reduces the incidence of ischemic events compared with the small-molecule antagonist tirofiban, particularly in patients presenting with acute coronary syndromes.

On the other hand, if a patient is started on a small-molecule GP IIb/IIIa inhibitor empirically and then undergoes percutaneous revascularization hours or days later, should he or she be switched to abciximab? No controlled data support the safety and efficacy of doing this, so we cannot recommend it. Additionally, there are good data to support continuing the small-molecule drug, not only through percutaneous revascularization, but also early in the hospital course.

- In patients presenting with acute coronary syndromes, empiric treatment with a GP IIb/IIIa inhibitor (tirofiban) improves the safety and efficacy of an invasive approach (with angiography within 4 to 48 hours and revascularization as appropriate).
- Prolonged use of abciximab without revascularization cannot be recommended; randomized data suggest no benefit and, possibly, an increase in adverse events. Use of small-molecule IIb/IIIa inhibitors (tirofiban and eptifibatide) is recommended for patients with acute coronary syndromes, especially those who are troponin-positive or undergoing percutaneous revascularization—hopefully early.

REFERENCES

1. **The EPIC Investigation.** 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.
2. **The EPILOG Investigators.** Platelet glycoprotein IIb/IIIa receptor blockade and low-dose heparin during percutaneous coronary revascularization. N Engl J Med 1997; 336:1689–1696.
3. **Lincoff AM, Califf RM, Moliterno DJ, et al.** Complementary clinical benefits of coronary-artery stenting and blockade of platelet glycoprotein IIb/IIIa receptors. Evaluation of Platelet IIb/IIIa Inhibition in Stenting Investigators. N Engl J Med 1999; 341:319–327.
4. **Neumann FJ, Blasini R, Schmitt C, et al.** Effect of glycoprotein IIb/IIIa receptor blockade on recovery of coronary flow and left ventricular function after the placement of coronary-artery stents in acute myocardial infarction. Circulation 1998; 98:2695–2701.
5. **Schomig A, Kastrati A, Dirschinger J, et al.** Coronary stenting plus platelet glycoprotein IIb/IIIa blockade compared with tissue plasminogen activator in acute myocardial infarction. Stent versus Thrombolysis for Occluded Coronary Arteries in Patients with Acute Myocardial Infarction Study Investigators. N Engl J Med 2000; 343:385–391.
6. **The RESTORE Investigators.** Effects of platelet glycoprotein IIb/IIIa blockade with tirofiban on adverse cardiac events in patients with unstable angina or acute myocardial infarction undergoing coronary angioplasty. Randomized Efficacy Study of Tirofiban for Outcomes and REstenosis. Circulation 1997; 96:1445–1453.
7. **Integrilin to Minimise Platelet Aggregation and Coronary Thrombosis-II.** Randomised placebo-controlled trial of effect of eptifibatide on complications of percutaneous coronary intervention: IMPACT-II. Lancet 1997; 349:1422–1428.
8. Novel dosing regimen of eptifibatide in planned coronary stent implantation (ESPRIT): a randomised, placebo-controlled trial. Lancet 2000; 356:2037–2044.
9. **Scarborough RM, Kleiman NS, Phillips DR.** Platelet glycoprotein IIb/IIIa antagonists. What are the relevant issues concerning their pharmacology and clinical use? Circulation 1999; 100:437–444.
10. **Phillips DR, Teng W, Arfsten A, et al.** Effect of Ca2+ on GP IIb-IIIa interactions with integrilin: enhanced GP IIb-IIIa binding and inhibition of platelet aggregation by reductions in the concentration of ionized calcium in plasma anticoagulated with citrate. Circulation 1997; 96:1488–1494.

11. **Steinhubl S, Talley D, Kereiakes D, et al.** A prospective multicentre study to determine the optimal level of platelet inhibition with GP IIb/IIIa inhibitors in patients undergoing coronary intervention-the GOLD study. J Am Coll Cardiol 2000; 35:44A.
12. **Coller BS.** Potential non-glycoprotein IIb/IIIa effects of abciximab. Am Heart J 1999; 138 suppl:S1–S5.
13. **Topol EJ, Moliterno DJ, Herrmann HC, et al for the TARGET Investigators.** Comparison of two platelet glycoprotein IIb/IIIa inhibitors, tirofiban and abciximab, for the prevention of ischemic events with percutaneous coronary revascularization. N Engl J Med 2001; 344:1888–1894.
14. **PRISM-PLUS Study Investigators.** Inhibition of the platelet glycoprotein IIb/IIIa receptor with tirofiban in unstable angina and non-Q-wave myocardial infarction. Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS). N Engl J Med 1998; 338:1488–1497.
15. **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.
16. **The PARAGON Investigators.** International, randomized, controlled trial of lamifiban (a platelet glycoprotein IIb/IIIa inhibitor), heparin, or both in unstable angina. Platelet IIb/IIIa Antagonism for the Reduction of Acute Coronary Syndrome Events in a Global Organization Network. Circulation 1998; 97:2386–2395.
17. **Heeschen C, Hamm CW, Goldmann B, Deu A, Langenbrink L, White HD.** Troponin concentrations for stratification of patients with acute coronary syndromes in relation to therapeutic efficacy of tirofiban. PRISM Study Investigators. Platelet Receptor Inhibition in Ischemic Syndrome Management. Lancet 1999; 354:1757–1762.
18. **Hamm CW, Heeschen C, Goldmann B, et al.** Benefit of abciximab in patients with refractory unstable angina in relation to serum troponin T levels. c7E3 Fab Antiplatelet Therapy in Unstable Refractory Angina (CAPTURE) Study Investigators. N Engl J Med 1999; 340:1623–1629.
19. **Fragmin and Fast Revascularisation During Instability in Coronary Artery Disease Investigators.** Long-term low-molecular-mass heparin in unstable coronary-artery disease: FRISC II prospective randomised multicentre study. Lancet 1999; 354:701–707.
20. **Cannon CP, Weintraub WS, Demopoulos LA, et al for the TACTICS-Thrombolysis in Myocardial Infarction 18 Investigators.** Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with the glycoprotein IIb/IIIa inhibitor tirofiban. N Engl J Med 2001; 344:1879–1887.
21. **Chew D, Bhatt D, Topol E.** Increased mortality with oral platelet glycoprotein IIb/IIIa antagonists: a pooled analysis of the large scale oral glycoprotein IIb/IIIa trials [abstract]. J Am Coll Cardiol 2000; 35:393A.
22. **Holmes M, Sobel BE, Cannon CP, Schneider DJ.** Increased platelet reactivity in patients given orbofiban after an acute coronary syndrome. An OPUS-TIMI 16 substudy. Am J Cardiol 2000; 85:491–493.
23. **Peter K, Schwarz M, Ylanne J, et al.** Induction of fibrinogen binding and platelet aggregation as a potential intrinsic property of various glycoprotein IIb/IIIa inhibitors. Blood 1998; 92:3240–3249.

ADDRESS: *David J. Moliterno, MD, Department of Cardiovascular Medicine, F25, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195; e-mail molited@ccf.org.*