

Report Card on the Pharmacologic Management of Coronary Artery Disease in the Catheterization Laboratory

A CME Certified Monograph

REPORT CARD

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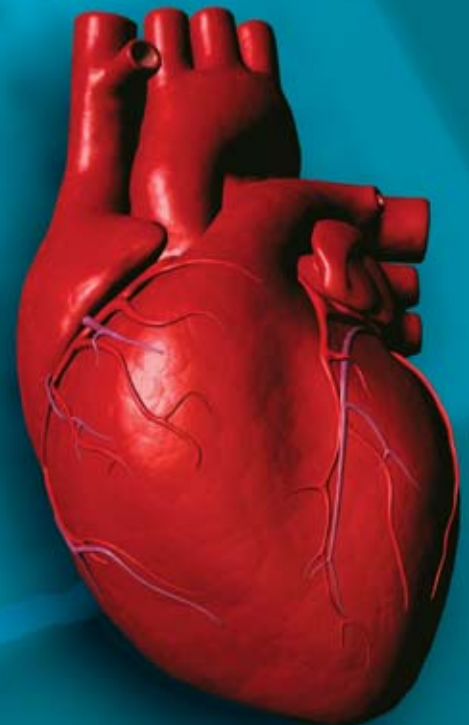


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Target Audience

This activity has been designed to meet the educational needs of interventional cardiologists and other healthcare professionals involved in the treatment of patients with acute coronary syndromes.

Statement of Need/Program Overview

The pace of advances in the field of interventional cardiology continues to accelerate. New pharmacologic and device therapies have improved the safety and efficacy of treatments for obstructive coronary artery disease (CAD). This monograph will discuss recent advances in antiplatelet therapy in coronary interventions with a focus on the role of glycoprotein IIb/IIIa (GP IIb/IIIa) inhibitors. The monograph will examine how clinicians can identify those PCI patients who will benefit the most from GP IIb/IIIa inhibition, as well as how to use this therapy in special high-risk populations (eg, diabetic and elderly patients). The most recent clinical data concerning safety and efficacy of various antiplatelet agents will be discussed, as will the concomitant use of these agents with drug-eluting stents. Data pertaining to management of underlying microcirculatory dysfunction and inflammation will be reviewed as well.

Educational Objectives

Upon completion of this activity, participants should be better able to:

- State the effect of GP IIb/IIIa inhibitors on coronary artery inflammation, microcirculation, and platelet function.
- Discuss the role of abciximab in a catheterization laboratory approach to acute myocardial infarction.
- Identify those patients undergoing drug-eluting stent placement who could benefit from the concomitant use of GP IIb/IIIa receptor inhibitors.
- Review the nuances involved in the care of high-risk patients (diabetes, chronic kidney disease).
- Discuss the future of new antiplatelet and antithrombotic therapies and their potential clinical implications.

Accreditation Statement

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The Postgraduate Institute for Medicine designates this educational activity for a maximum of 2 category 1 credits toward the AMA Physician's Recognition Award. Each physician should claim only those credits that he/she actually spent in the activity.

Disclaimer

Participants have an implied responsibility to use the newly acquired information to enhance patient outcomes and their own professional development. The information presented in this activity is not meant to serve as a guideline for patient management. Any procedures, medications, or other courses of diagnosis or treatment discussed or suggested in this activity should not be used by clinicians without evaluation of their patients' conditions and possible contraindications or dangers in use, review of any applicable manufacturer's product information, and comparison with recommendations of other authorities.

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Financial Disclosure Information

Report Card on the Pharmacologic Management of Coronary Artery Disease in the Catheterization Laboratory

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Method of Participation

There are no fees for participating and receiving CME credit for this activity. During the period September 2004 through September 2005, participants must 1) read the learning objectives and faculty disclosures; 2) study the educational activity; 3) complete the post-test by recording the best answer to each question in the answer key on the evaluation form; 4) complete the evaluation form; and 5) mail or fax the evaluation form with answer key to the Postgraduate Institute for Medicine.

Report Card on the Pharmacologic Management of Coronary Artery Disease in the Catheterization Laboratory

Introduction

For at least a decade, the mainstay of thrombotic risk reduction strategies following percutaneous coronary interventions (PCIs) has depended on the use of glycoprotein (GP) IIb/IIIa inhibitors. Among the agents successfully used for this purpose, abciximab has consistently emerged as safe and effective and the only member of the GP IIb/IIIa family shown in randomized clinical trials to exert a clinical benefit across the spectrum of patient presentations, including elective PCI and, as an adjunct to PCI, in the settings of non-ST-segment elevation (NSTEMI) and ST-segment elevation myocardial infarction (STEMI). As the development of PCI technology accelerates to overcome current limitations, so too does the search for risk-reduction strategies to reduce adverse event rates. To clarify the continuing role of GP IIb/IIIa inhibition, identification of such higher-risk patient groups who could benefit the most from a risk-reduction strategy should include those presenting with STEMI, chronic kidney disease (CKD), diabetes, and the elderly—a process that should lead to improved outcomes. The mechanism of heightened risk associated with these groups may in some ways be unique, but for the most part such risk would seem to be mediated by abnormalities of coagulation, platelet activity, inflammation, and vascular function. That clearance of abciximab is independent of renal function makes it uniquely useful in patients with CKD.

The introduction of drug-eluting stents largely overcame the problem of restenosis, and resulted in treatment of more complex obstructive coronary artery disease occurring in longer lesions, smaller vessels, and at bifurcations. While rates of restenosis are reduced with drug-eluting stents in these higher-risk lesions, the rates of early major adverse thrombotic events are not reduced, and may actually be increased. GP IIb/IIIa inhibitors, noted for their ability to prevent platelet aggregation, provide an effect which is complemented—and not replaced—by the ability of aspirin and adenosine diphosphate (ADP)-receptor inhibitors to prevent platelet activation. This may have important implications in patients who are resistant to the effects of aspirin and the thienopyridines such as clopidogrel, where thrombotic complication rates are higher following PCI.

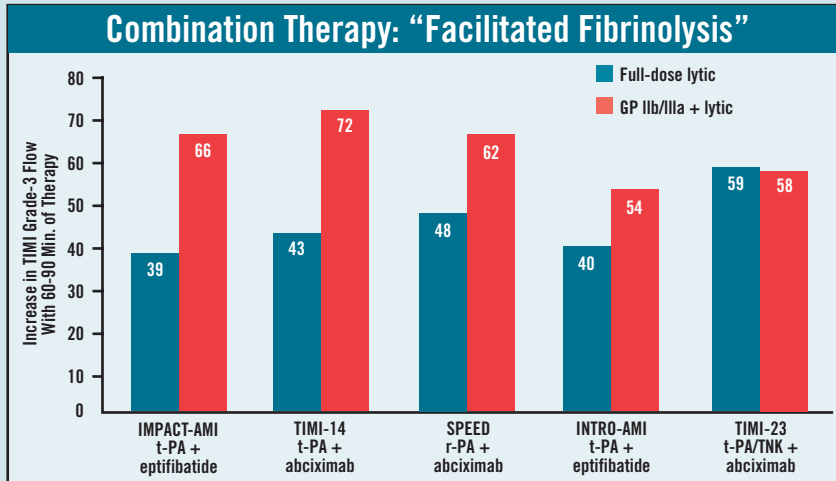
As newer compounds (including low-molecular-weight heparins [LMWH], direct thrombin inhibitors, and second-generation thienopyridines) are developed and find their place in the catheterization laboratory, we are challenged to determine an optimal pharmacologic approach. The GP IIb/IIIa inhibitors, by virtue of their safety and efficacy records, will almost certainly maintain their role as adjuvant therapy in the treatment of patients undergoing PCI.

Current Perspectives on Pharmacoinvasive Therapy for Acute ST-Elevation MI: Integrating Pharmacologic and Mechanical Reperfusion Strategies

Despite recent advances in the care of high-risk patients with acute STEMI, the limitations of current standard therapies underscore the need for further improvement. Fibrinolytic therapy, for example, is limited by the risk of impaired microvascular flow, reocclusion, and intermittent (or incomplete) patency, creating an “illusion of reperfusion” characterized by incomplete epicardial patency, impaired microvascular perfusion, or both.¹ Contemporary trials with novel fibrinolytic agents combined with LMWH or direct thrombin inhibitors have not led to improvements in mortality over fibrinolytic therapy alone, indicating a “ceiling of reperfusion” for epicardial patency has been reached.²⁻⁷

Recent clinical trials have been performed comparing reduced doses of fibrinolytic agents combined with full-dose GP IIb/IIIa antagonists with full-dose lytic therapy. (Figure 1)

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FIGURE

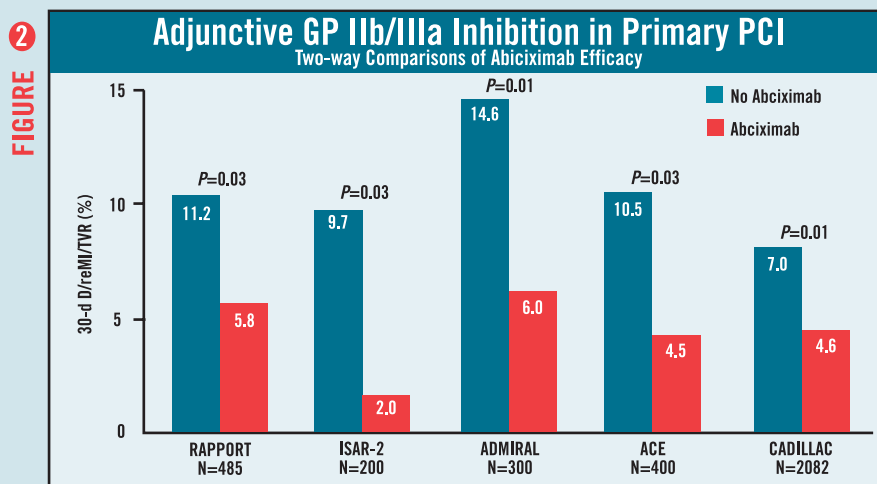


GP IIb/IIIa inhibitors evaluated in randomized trials in patients with an AMI seen within 6-12 h of symptom onset. pEP: TIMI-3 flow. **IMPACT-AMI**: Dose-ranging comparison, eptifibatide vs placebo. pEP at 90 min met by 66% in high-dose group vs 39% placebo group ($P=0.006$). **TIMI-14**: Open-label comparison, comb of abciximab, thrombolytics, IV heparin. pEP met more often w/tPA/abciximab than w/tPA alone at 60 min ($P=0.0009$) and 90 min ($P=0.02$). **SPEED**: 2-phase, dose-finding comparison abciximab + reteplase. Phase A: abciximab + 1 of 6 reteplase dosing strategies; Phase B: best of phase A vs reteplase alone. pEP met at 60-90 min, Phase A, by 62% comb ther and 27% monother ($P=0.001$); and in Phase B, 54% comb ther, 47% monother ($P=0.32$). **INTRO-AMI**: Phase 2, open label, dose escalating, eptifibatide in pts on low-dose (50 mg) alteplase. 60- and 90-min patency rates highest w/alteplase + eptifibatide. pEP met, 65% at 60 min and 78% at 90 min (comp w/typical alteplase rates, ~42%, high 50s respectively). **TIMI-23**: Comb study, enoxaparin or UFH, TNK, and abciximab. pEP met: 48% UFH, 47% enoxaparin/TNK, 48% TNK/abciximab/UFH (or enoxaparin). Secondary EP (death/recurrent MI to day 30) met: 15.9% full-dose TNK group vs 5.5% enoxaparin. TIMI: thrombolysis in MI; t-PA; tissue plasminogen activator; r-PA: recombinant plasminogen activator (reteplase); UFH: unfractionated heparin; TNK: tenecteplase; AMI: acute myocardial infarction.

The theoretical advantages of this “facilitated fibrinolysis” include prevention of the platelet-activating effects which result from the thrombolytics, which may lead to improved vessel patency, myocardial perfusion, and reduced reocclusion and recurrent ischemia. At present, pivotal randomized trials have not yet confirmed a mortality advantage for fibrinolytic therapy combined with GP IIb/IIIa inhibitors or LMWH compared with fibrinolytic therapy alone, and the potential for an increased incidence of hemorrhagic stroke in elderly patients and an overall increased risk of major bleeding remain important safety concerns.^{8,9} In the GUSTO-V (Global Use of Strategies To Open occluded coronary arteries V) trial ($N = 16,588$), 30-day survival did not significantly differ between those treated with reteplase-abciximab combination therapy compared with reteplase alone (5.9% vs 5.6% for reteplase vs combination therapy, respectively; $P = 0.43$).⁹ However, combination therapy in GUSTO-V was associated with significantly fewer nonfatal ischemic complications, including recurrent ischemia, the need for urgent target vessel revascularization, and life-threatening ventricular arrhythmias.^{8,9} Because these benefits must be balanced against the absence of a survival benefit and an increased incidence of bleeding complications, combination therapy cannot be presently adopted as the standard of care for pharmacologic reperfusion.

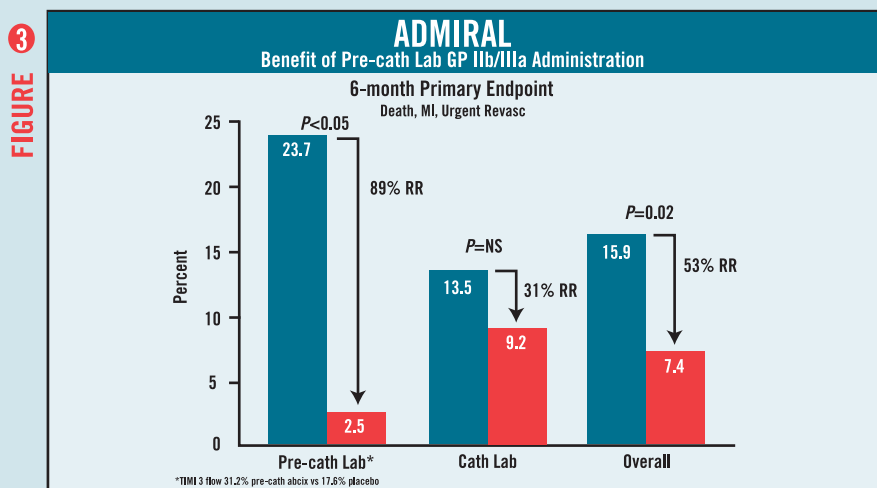
In contrast to pharmacologic strategies, successful infarct artery reperfusion is achieved with primary PCI in more than 90% of cases, and is associated with improved early and late clinical outcomes compared with fibrinolysis.^{10,11} Unfortunately, a primary angioplasty strategy is limited in many instances by the availability of a 24-hour cardiac catheterization laboratory, experienced operators and staff, and the ability to provide catheter-based reperfusion therapy in a timely fashion.¹² The results of clinical trials evaluating the effectiveness of GP IIb/IIIa inhibitors as an adjunct to primary PCI demonstrate the complementarity of pharmacologic and catheter-based reperfusion strategies, including increased early survival, a reduced incidence of recurrent ischemic events, improved ventricular function, and an increased rate of vessel patency.¹³⁻¹⁸ (Figure 2) Considering its potential for intrinsic anticoagulant and clot-dissolving activity,¹⁹⁻²¹ early treatment with abciximab prior to arrival in the catheterization

laboratory may provide mechanistic support for the higher rates of infarct artery patency and improved clinical outcomes among patients receiving early therapy in the ADMIRAL (Abciximab before Direct angioplasty and stenting in Myocardial Infarction Regarding Acute and Long-term follow-up) trial. Aside from achieving earlier infarct artery patency, upfront treatment with abciximab may also improve myocardial perfusion and microvascular integrity.



Abciximab has been consistently shown to reduce event rates in AMI in patients undergoing primary PCI. Source: Kandzari et al.¹⁶

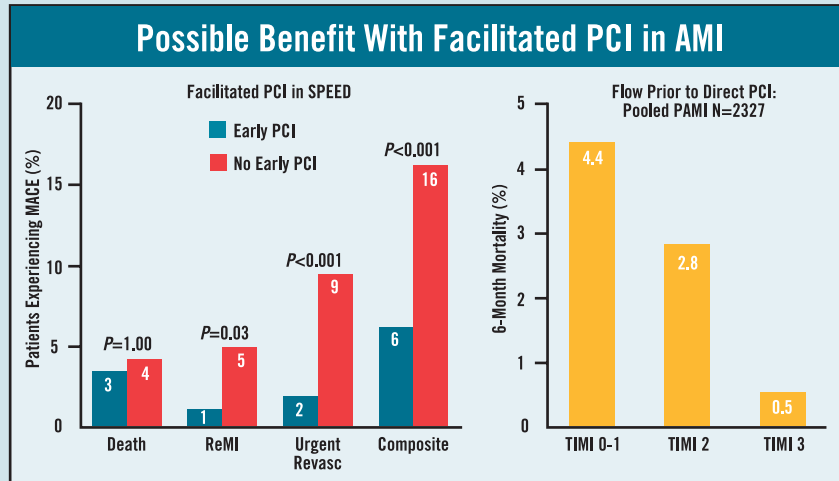
This may be due to earlier achieved reperfusion and reduced microvascular dysfunction due to a reduction of pre-procedural distal embolization. (Figure 3)



The ADMIRAL trial evaluated the effectiveness of adjuvant abciximab in patients undergoing PCI for AMI. Early (pre-cath) administration of abciximab was associated with an 89% reduction of the 6-month primary endpoint of death, MI, and urgent revascularization. Early administration may lead to early reperfusion by detrombosis or by preventing early distal embolization. Overall, there was a 53% reduction of the 6-month endpoint. Source: Montalescot G et al.¹⁵

Facilitated PCI (PCI following pharmacologic reperfusion therapy) may combine the best aspects of pharmacology and primary PCI to ensure optimal management of STEMI. For patients presenting with an acute myocardial infarction (AMI) when it is anticipated that there will be delays in gaining access to primary treatment with a catheter-based revascularization, it may be appropriate to initiate pharmacologic reperfusion therapy in the emergency department (ED). Whether initial pharmacologic reperfusion therapy with a reduced-dose fibrinolytic and/or abciximab followed by PCI may facilitate the process of reperfusion and provide additional clinical benefits during mechanical revascularization,^{22, 23} will require confirmation in larger, pivotal trials. (Figure 4)

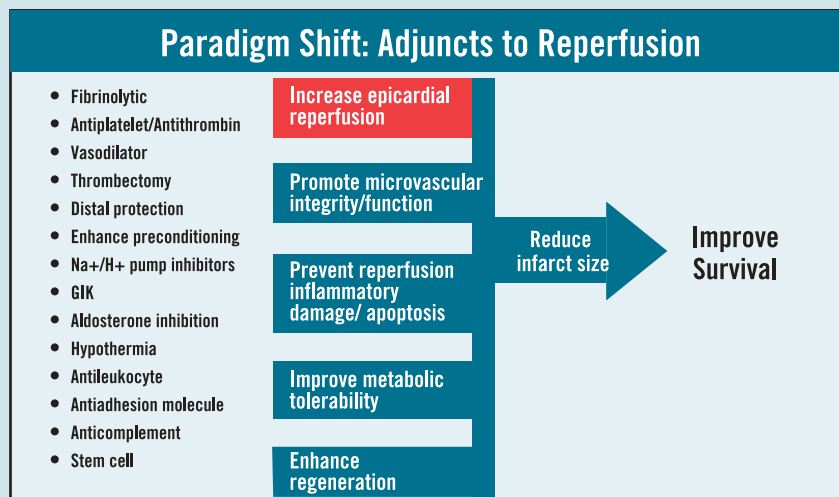
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FIGURE



The improved outcomes of early PCI facilitated by abciximab in AMI was identified in the SPEED (Strategies for Patency Enhancement in the Emergency Department) trial, in which the composite endpoint of death, recurrent MI, and need for urgent revascularization was seen in only 6% of patients who underwent a PCI early in the course of the disease, compared with 16% in those for whom the PCI was delayed ($P < 0.001$). By facilitating early reperfusion prior to undergoing PCI, improvements in mortality should be observed. PCI, percutaneous coronary intervention; AMI, acute myocardial infarction; PAMI, Primary Angioplasty in Acute Myocardial Infarction; MACE, major adverse cardiac event; TIMI, Thrombolysis In Myocardial Infarction.

Novel angiographic techniques (eg, the Thrombolysis in Myocardial Infarction [TIMI] myocardial blush score) and noninvasive diagnostic tests (eg, continuous ST-segment monitoring, nuclear cardiology imaging, and contrast echocardiography) have been used to evaluate for restoration of coronary perfusion.²⁴ Impaired microvascular function and inadequate myocardial perfusion often occur despite epicardial vessel patency, and both are associated with an increased risk of early and late mortality.²⁵⁻²⁸ An appreciation of the need for normalization of reperfusion to maximize benefits of a reperfusion strategy has inspired investigators to develop clinical trials of catheter-based and pharmacologic strategies for improving epicardial perfusion and microvascular integrity, as well as to prevent reperfusion injury and enhance cardiomyocyte regeneration. (Figure 5)

5
FIGURE



A variety of trials have been performed to improve survival with most proving disappointing.

At present, however, the effects of novel catheter-based therapies used as adjuncts to primary PCI (including mild systemic hypothermia, aqueous oxygen, and distal embolic protection) have been disappointing.²⁹⁻³¹ However, in the randomized, phase II Complement and Reduction of Infarct Size After Angioplasty or Lytics (CARDINAL) trial, treatment with pexelizumab (a specific

complement inhibitor) as adjunctive therapy to primary PCI has demonstrated improved survival despite the absence of a significant difference in infarct size between the two groups.³² Early experiences with the use of bone marrow transfer and the transplantation of progenitor cells have also suggested improved ventricular function and reduced infarct size.³³

The need for identification of the ideal pharmacologic regimen for patients presenting with AMI remains necessary. Important issues concerning pharmacologic reperfusion that warrant further study include: the increased risk for bleeding seen with combination therapy (particularly in elderly and high-risk patients); the complexity of dosing regimens; and the need for accelerated treatment protocols to assure prompt administration. Clinical results of forthcoming trials should further clarify the safety and efficacy of reperfusion therapies. (Figure 6) Unfortunately, many patients with AMI do not receive any reperfusion therapy or even routine evidence-based therapy (eg, aspirin, beta-blockers, or angiotensin-converting enzyme inhibitors), which mandates a continued need to promote awareness of simple measures of proven clinical benefit to treating physicians.

6
FIGURE

Upcoming Trials			
Clarifying the Role of Antithrombins, GP IIb/IIIa Inhibitors, Fibrinolysis, and Early PCI			
Trial	N	Primary PCI	Comparison
ASSENT-4 PCI	4000	yes	PCI vs TNK/enox + PCI
CARESS	2500	yes	PCI vs t-PA1/2 /abcix/PCI
FINESSE	4000	yes	PCI vs PCI/abcix vs r-PA1/2 /abcix
CLARITY	2200	no	Clopidogrel vs placebo
EXTRACT	21,000	no	Enoxaparin vs UFH
OASIS-6	10,000	+/-	Penta vs control (UFH/placebo)
Total	43,700		

ASSENT, Assessment of the Safety and Efficacy of New Thrombolytic Regimens; CARESS, Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic Carotid Stenosis; FINESSE, Facilitated Intervention with Enhanced Reperfusion Speed to Stop Events; CLARITY, Clopidogrel as Adjunctive Reperfusion Therapy; EXTRACT, Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment; and OASIS-6, PCI, percutaneous coronary intervention; TNK, tenecteplase; enox, enoxaparin; t-PA, tissue plasminogen activator; abcix, abciximab; r-PA, recombinant plasminogen activator (reteplase); UFH, unfractionated heparin; penta, pentasaccharide (fondaparinux).

Use of GP IIB/IIIA Inhibitors in Special High-Risk Populations Undergoing PCI (Elderly, Chronic Kidney Disease, and Diabetes)

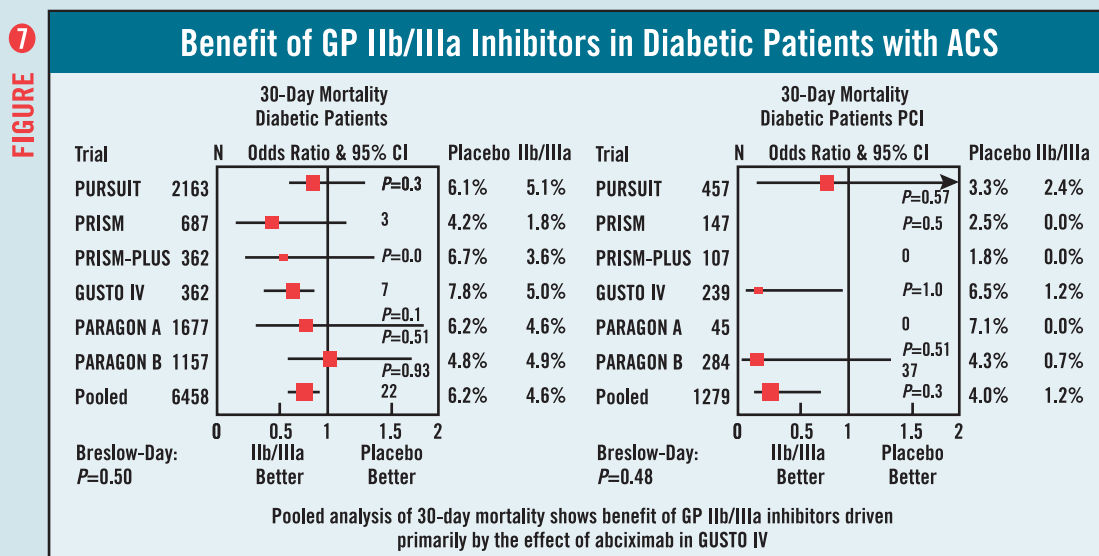
Optimizing the treatment of important high-risk patients, particularly the elderly and those who have diabetes or CKD has not been extensively evaluated in clinical trials. As these patients make up a significant portion of those presenting with symptomatic obstructive coronary disease, they are worthy of discussion.

Diabetes Mellitus

There are approximately 17 million patients with diabetes in the United States and an estimated 125 million worldwide. By the year 2025, the prevalence of diabetes may reach 22 million in the United States and exceed 300 million worldwide.³⁴ It is estimated that 77% of hospitalizations for chronic complications of diabetes can be attributed to cardiovascular disease (CVD).³⁵ Patients with diabetes accompanied by coronary artery disease (CAD) have a worse prognosis than patients without diabetes, as indicated, for example, by the higher incidence of adverse clinical events and restenosis after PCI with diabetes.³⁶ In a recent report of results of the PRESTO (Prevention of Restenosis with Tranilast and Its Outcomes) trial, diabetes was associated with an 87% increase in 9-month mortality ($P < 0.01$), a 27% increase in risk for target vessel revascularization (TVR) ($P < 0.01$), and a 26% increase in

risk for the composite endpoint of death, MI, and TVR at 9 months ($P < 0.01$), even after adjustments were made for age, smoking, sex, congestive heart failure, abciximab use, prior MI, coronary artery bypass graft (CABG) surgery, number of diseased vessels, lesion type, and stent type.³⁷ Interestingly, the incidence of in-hospital complications in patients undergoing stent implantation was similar for patients with and without diabetes.³⁸

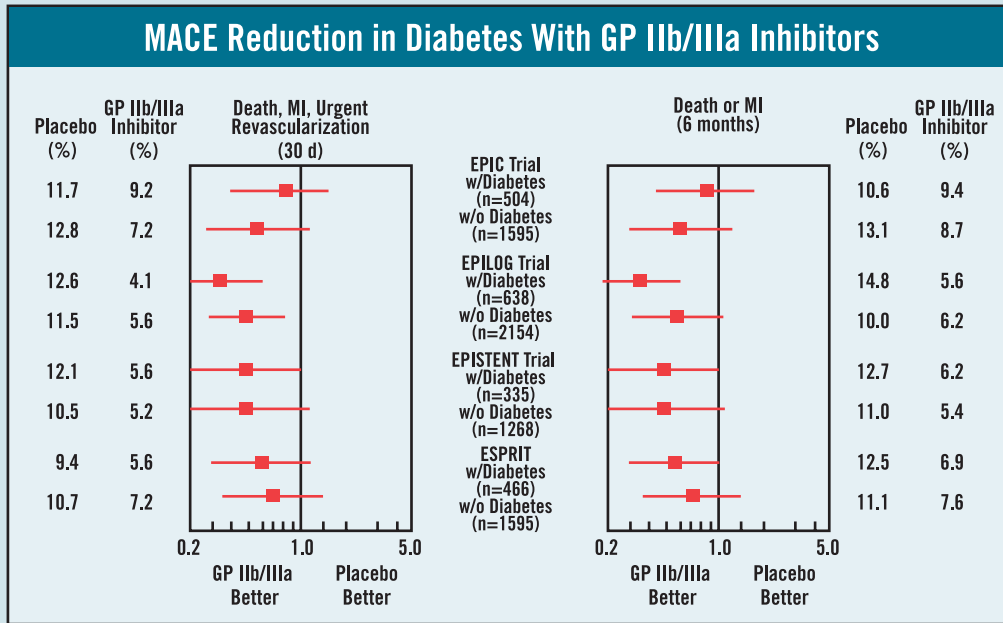
In a recent meta-analysis of six large trials of GP IIb/IIIa inhibitors involving 6458 patients with diabetes who presented with NSTEMI, GP IIb/IIIa inhibition was associated with a 26% reduction in 30-day mortality ($P = 0.007$).³⁹ In patients with diabetes and acute coronary syndrome (ACS) who underwent a PCI, the reduction in 30-day mortality was even more striking at 70% ($P = 0.002$). Of the four GP IIb/IIIa inhibitors used in this meta-analysis—abciximab, tirofiban, eptifibatide, and lamifiban—only abciximab was associated with a significant reduction in mortality (6.5% to 1.2%; $P = 0.037$). (Figure 7)



An analysis of 689 patients who underwent multivessel stenting indicated patients with diabetes have a significantly greater risk for mortality at 1 year following the procedure, and an increased rate of MI, DM. MI, myocardial infarction; DM, diabetes mellitus; ACS, acute coronary syndrome; PCI, percutaneous coronary intervention. Adapted from Roffi M et al.³⁹

Four trials of GP IIb/IIIa inhibitor efficacy during PCI included outcomes for patients with diabetes—EPIC (The Evaluation of c7E3 for Prevention of Ischemic Complications), EPILOG (Evaluation in PTCA to Improve Long-term Outcome with abciximab GP IIb/IIIa blockade), EPISTENT (Evaluation of Platelet Inhibition in Stenting), the ESPRIT (Enhanced Suppression of the Platelet GP IIb/IIIa Receptor with Integrilin Therapy) study. (Figure 8) The short-term risk (death, MI, and need for urgent revascularization at 30 d) and long-term risk (death or MI at 6 mo) were reduced to a similar extent in patients with or without diabetes.⁴⁰ In EPISTENT, a strong trend toward a reduced mortality at one year was seen in patients with diabetes undergoing stent implantation with abciximab (71%) and with eptifibatide (63%) in ESPRIT. In the Do Tirofiban and ReoPro Give Similar Efficacy Outcome Trial (TARGET)—the only head-to-head randomized trial of a “small” molecule versus a “large” molecule—the relative reduction in 30-day endpoint with abciximab versus tirofiban was 14% in patients with diabetes versus 22% in those without diabetes.⁴¹ Of note was the significant reduction in the primary endpoint of death, MI, and urgent TVR at 30 days in patients with diabetes who required insulin, as observed with abciximab (3.1% vs 8.1% for tirofiban) compared with a nonsignificant difference between abciximab and tirofiban in patients with diabetes who do not require insulin. When abciximab and placebo were compared in patients who presented with an AMI and who were treated with primary PCI in ADMIRAL, a much greater reduction in mortality was observed in those with diabetes compared to those without diabetes.¹⁵

FIGURE 8



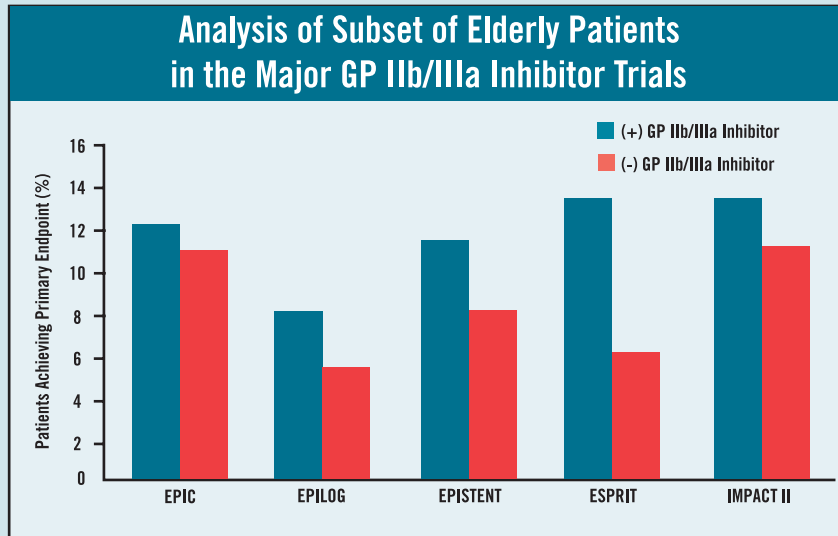
The results of 4 major trials—EPIC (N=2099), EPILOG (N=2792), EPISTENT (N=1603), ESPRIT (N=2061)—suggest that GP IIb/IIIa inhibitors are just as effective in reducing the short-term risk for the composite endpoint of death, MI, and need for urgent revascularization within 30 days after therapy and the long-term risk for death and MI within 6 months after therapy in patients who have diabetes as they are in those who do not have diabetes. MACE, major adverse cardiac event; MI, myocardial infarction.

Elderly

Although the elderly comprise the fastest growing segment of our population, no interventional trials to evaluate therapeutic efficacy and safety have been carried out. As the highest incidence of cardiac events is seen in the elderly, they would be expected to benefit most from any intervention. This population has a high frequency of comorbidities that increase cardiovascular risk and thus the risk for major adverse coronary events (MACE) following PCI, including diabetes (23%), renal failure (11%), and a personal history of CABG (24%) or stroke (18%).⁴² Analyses of a registry of 449 consecutive older patients presenting with an ACS, of whom 251 were elderly (70–79 y) and 198 were very elderly (≥80 y), revealed the older cohort was more likely to have an MI (35% vs 9.7%; $P < 0.0001$), heart failure (33% vs 19%; $P < 0.001$), renal dysfunction (22% vs 12%; $P = 0.01$), and a poorer 2-year survival (67% vs 83%; $P < 0.001$).⁴³ There seems to be some resistance to performing elective revascularization in elderly patients even though as a group they benefit more from revascularization than medical therapy for symptomatic obstructive coronary disease. When they do present to the catheterization laboratory it is more likely to be with an acute coronary syndrome and its attendant risk.

In a retrospective analysis of GP IIb/IIIa inhibitor safety in octogenarians (N = 1392) undergoing PCI,⁴⁴ those who received a GP IIb/IIIa inhibitor (33%) had a higher acuity than those who did not, because they were more likely to present with an ACS or infarct (17% vs 8%), a recent MI (25% vs 16%), or the need for an intraaortic balloon pump counterpulsation (5.5% vs 1.7%). The use of GP IIb/IIIa inhibitors in these patients seems to have compensated for their increased acuity, as there was no difference in mortality or the incidence of STEMI. A small increase in procedure-related bleeding was observed, perhaps related to the high mean intraprocedural activated clotting times (ACT) of 336 seconds achieved. Therefore, the use of such agents in the very elderly seems to compensate for higher cardiac risk. In an analysis of the EPIC, EPILOG, EPISTENT, ESPRIT, and IMPACT II (Integrilin to Minimize Platelet Aggregation and Coronary Thrombosis in Stenting) trials, a consistent reduction of adverse events was observed in elderly patients treated with GP IIb/IIIa inhibitors compared to control groups.⁴⁵ (Figure 9)

FIGURE 9



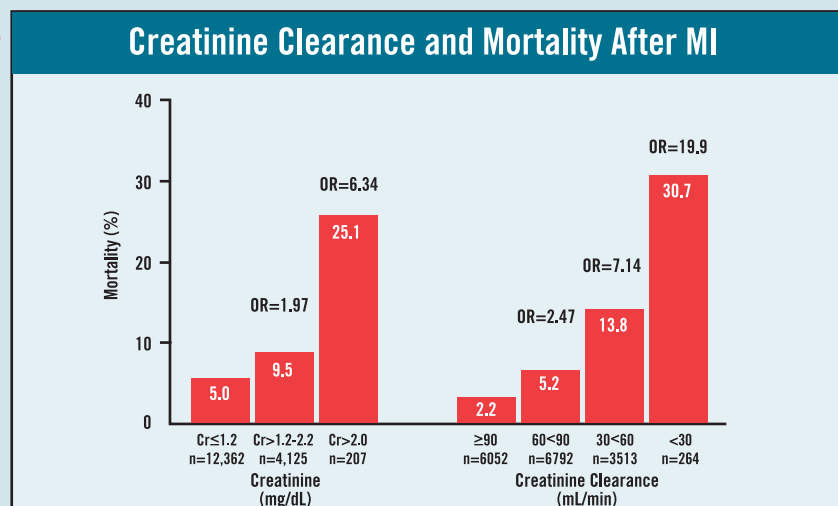
GP IIb/IIIa inhibition was associated with a reduced risk for major adverse cardiac events in patients older than 65 years who participated in the EPIC, EPILOG, EPISTENT, ESPRIT, and IMPACT II trials.

Chronic Kidney Disease

CKD is defined by an estimated glomerular filtration rate (GFR) of less than 60 mL/min/1.73 m² and is associated with a constellation of metabolic abnormalities including insulin insensitivity, decreased levels of apolipoprotein A1 and elevated levels of homocysteine, lipoprotein(a), fibrinogen, and C-reactive protein (CRP).⁴⁶ In the ARIC (Atherosclerosis Risk in Communities) study, GFR was an independent risk factor for mortality when it fell in the range of 15 to 59 mL/min (hazard ratio of 1.38) and for atherosclerotic coronary vascular disease events when it fell in the range of 60 to 89 mL/min (hazard ratio of 1.30) compared with GFR values of at least 90 mL/min/1.73 m².⁴⁷

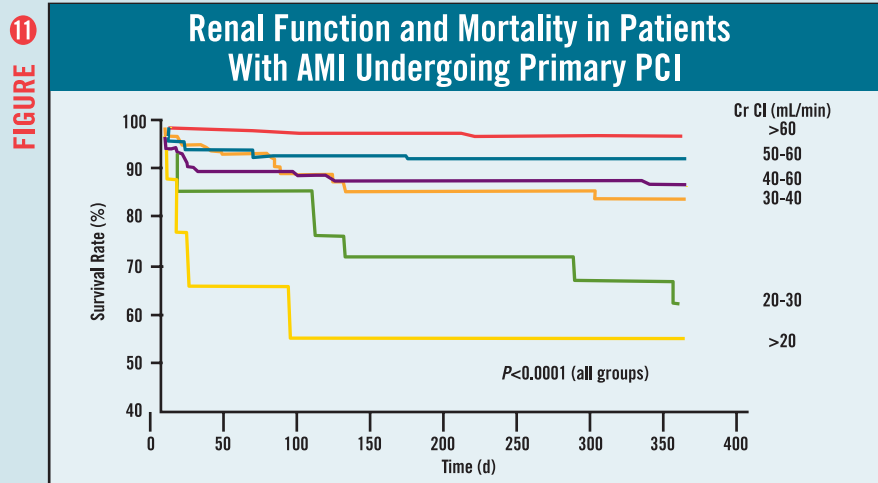
In an analysis of patients presenting with an AMI and treated with fibrinolysis in the TIMI 10A, 10B, and 14 trials, and in the InTIME-II (Intravenous nPA for the Treatment of Infarcting Myocardium Early) trial, increased serum creatinine (SCr) levels and a reduced creatinine clearance (CrCl) were associated with higher mortality rates, even after correcting for TIMI risk score and congestive heart failure.⁴⁸ (Figure 10) The 30-day adjusted mortality increased by 52% in patients with mild renal impairment (SCr: 1.2-2.0 mg/dL) and 273% in patients with more severe renal impairment (SCr: >2.0 mg/dL) compared with those with normal renal function (SCr: <1.2 mg/dL).

FIGURE 10



An increase in serum creatinine and decrease in creatinine clearance were associated with an increased mortality risk. MI, myocardial infarction; Cr, creatinine; OR, odds ratio. Source: Gibson CM et al.⁴⁸

The elevation of mortality risk with loss of renal function is also observed in patients presenting with AMI undergoing PCI.



Elevated CrCl has an inverse relationship with mortality in AMI patients treated with primary PCI. AMI, acute myocardial infarction; PCI, percutaneous coronary intervention; CrCl, creatinine clearance. Source: Sadeghi HM et al.⁴⁹

In one study of 312 patients who presented with ACS and renal insufficiency (CrCl: <60 mL/min, based on the Cockcroft-Gault formula), in-hospital mortality was higher in patients with renal insufficiency compared with those without renal insufficiency (8.1% vs 2.6%; $P < 0.001$). In this analysis GP IIb/IIIa use dropped from 39% when the CrCl exceeded 90 mL/min to only 12% when CrCl was less than 30 mL/min. Regardless, GP IIb/IIIa inhibitors were associated with a 66% reduction in mortality with a 2-fold increase in the rate of intracranial hemorrhage. This study was limited by the lack of documentation of the specific type of GP IIb/IIIa inhibitor used, and the intraprocedural ACT achieved in patients undergoing a PCI. Factors which could have a profound impact in events of the CKD populations.

It is clear CKD represents a significant risk for atherosclerotic coronary vascular events and poorer outcomes following an AMI or ACS, or with PCI, and that use of GP IIb/IIIa inhibitors may reduce mortality. Among the three GP IIb/IIIa inhibitors commercially available, abciximab is the only one that does not depend on renal function for its clearance. The major trials with eptifibatide—PURSUIT (Platelet Glycoprotein IIb/IIIa Unstable Angina: Receptor Suppression Using Integrilin Therapy Trial) and ESPRIT—excluded patients with an SCr greater than 2.0 mg/dL and 350 μ mol/L, respectively, and required a dose reduction in drug-naïve dialysis patients with SCr exceeding 2.0 mg/dL. In major clinical trials of tirofiban—PRISM-PLUS (Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms) and RESTORE (Randomized Efficacy Study of Tirofiban for Outcomes and Restenosis)—patients were excluded if SCr levels exceeded 2.5 mg/dL and 2.0 mg/dL, respectively.⁵⁰ No limitation in SCr was made in two major trials of abciximab (EPILOG and EPISTENT).

12 **FIGURE** **Using Clinical Trial Data To Guide GPI Use with CKD**

GPI Trial	GPI Studied	Serum Creatinine Exclusion
EPILOG	Abciximab	NONE
EPISTENT	Abciximab	NONE
PRISM-PLUS	Tirofiban	>2.5 mg/dL
RESTORE	Tirofiban	>2.0 mg/dL
PURSUIT	Eptifibatide	>2.0 mg/dL
ESPRIT	Eptifibatide	>350 μ mol/L

Source: Physician's Desk Reference. 2004.⁵⁰

Based on available clinical trial data, it would seem prudent to consider the use of GP IIb/IIIa inhibitors in patients with CKD undergoing a PCI. Furthermore, without clinical trial data evaluating the safety of the small molecules or direct thrombin inhibitors in patients with moderate to severe CKD or on dialysis, abciximab would be the agent of choice in this high-risk patient population.

Is the Use of GP IIB/IIIA Inhibitors More or Less Relevant in Drug-Eluting Stent Applications?

The evolution of PCIs has been dramatic. From the beginning, coronary intervention outcomes have been compared with those of CABG. In the balloon-only era, angioplasty appeared to have an equivalent survival outcome (except in patients with diabetes) but a higher rate of events caused by restenosis. Compared to balloon angioplasty, stent implantation reduced the requirement for late revascularization by approximately 50%; drug-eluting stents have further reduced the risk for late restenosis substantially, so the incidence of late outcomes is comparable to that of CABG. Acute adverse events related to PCI can be related to either primary mechanical complications such as intimal dissection and plaque shifting or thrombotic complications. While restenosis is an important symptomatic and clinical problem, it has not been associated with an increase in mortality observed with the acute mechanical and thrombotic complications. Thus, while restenosis following intervention has declined markedly with the advent of drug-eluting stents, the risk for major nonrestenotic adverse events has not been eliminated, and may actually be more of a concern as we apply this technology to higher-risk anatomy, including longer lesions and bifurcation disease.

The overall incidence of early events trended higher in the drug-eluting stent group compared to the bare metal stents in both the TAXUS™ IV paclitaxel-eluting coronary stent system and the Sirolimus-eluting Balloon Expandable Stent in the Treatment of Patients With De Novo Native Coronary Artery Lesions (SIRIUS) trials. (Table 1)^{51,52} While post-procedural thrombosis is an unusual occurrence it has not been eliminated by drug-eluting stents. Recent findings identifying platelet resistance to the effects of aspirin and clopidogrel and association with a greater tendency for early thrombotic complications cause concern, particularly since the drug-eluting stents delay new intimal coverage. The persistence of thrombotic complications in patients undergoing drug-eluting stent placement coupled with the higher-risk lesions being treated with this new technology should result in consideration of the use of adjuvant GP IIb/IIIa inhibition.

1
TABLE

Relative Risk of Early CV Events With and Without DES: SIRIUS and TAXUS IV

All-Event Occurrence	SIRIUS (%)		TAXUS IV (%)	
	DES	Bare Stents	DES	Bare Stents
≤ 1 mo	2.4	1.5	2.9	2.5
9 mo	7.1	18.9	8.5	15.0

In both the SIRIUS and TAXUS-IV trials, the rate of short-term adverse events trended higher with the DES group than the bare stent group. Late events consisting mostly of target vessel revascularization were less in both DES groups. DES, drug-eluting stent. Sources: Stone GW et al.⁵¹ Moses JW et al.⁵²

Recent clinical trial data raises the question of whether high loading doses of clopidogrel (600 mg) obviate the need for GP IIb/IIIa inhibition. The ISAR-REACT (Intracoronary Stenting and Antithrombotic Regimen—Rapid Early Action for Coronary Treatment) trial demonstrated that in the patient with low or intermediate risk, preloading with clopidogrel 600 mg reduced the risk for thrombosis to the same extent as abciximab. However, the extent to which this holds true for the higher-risk patient (diabetes, CKD, elderly, ACS) and for more complex coronary lesions is less clear. The PEACE (Platelet activity Extinction in non-Q-Wave myocardial infarction

with Aspirin, Clopidogrel, and Eptifibatide) trial demonstrated that further suppression of platelet activity is achieved by adding a GP IIb/IIIa inhibitor to preexisting aspirin, enoxaparin, and clopidogrel therapy.⁵³ (Table 2) Based on these data, it would appear that clopidogrel is probably not sufficient to optimally inhibit platelet activity in high-risk patients. This was also demonstrated in the TARGET trial, in which the addition of abciximab to patients pretreated with clopidogrel was associated with additional benefit. Thus, the use of GP IIb/IIIa inhibitors remain extremely relevant in the drug-eluting-stent era and may result in optimal patient and lesion outcomes, particularly in certain patient subgroups.⁵⁴

2

TABLE

PEACE Trial

- A mechanism study
- Sequential sampling of 32 NSTEMI patients
 - Sample 1: ASA, enoxaparin
 - Sample 2: Clopidogrel (3 h after treatment)
 - Sample 3: Eptifibatide 180 µg/kg IV, then 2µg/kg•min⁻¹ (12 h after treatment)
- PAC-1 MAb and fibrinogen levels suppressed further by the GP IIb/IIIa inhibitor
- Conclusion: In high-risk patients, clopidogrel may not be sufficient to control platelet activation

The PEACE trial examined the effects of successive doses of clopidogrel and eptifibatide, in combination with aspirin and enoxaparin, in NSTEMI patients before PCI. The goal was to test the hypothesis that eptifibatide offered further antiplatelet efficacy above clopidogrel in NSTEMI patients before an expeditive coronary intervention. The study concluded that high-risk patients benefit from the combination of clopidogrel and eptifibatide and that clopidogrel monotherapy may not be sufficient for optimal antiplatelet activity in this patient population. Source: Dalby M et al.⁵³

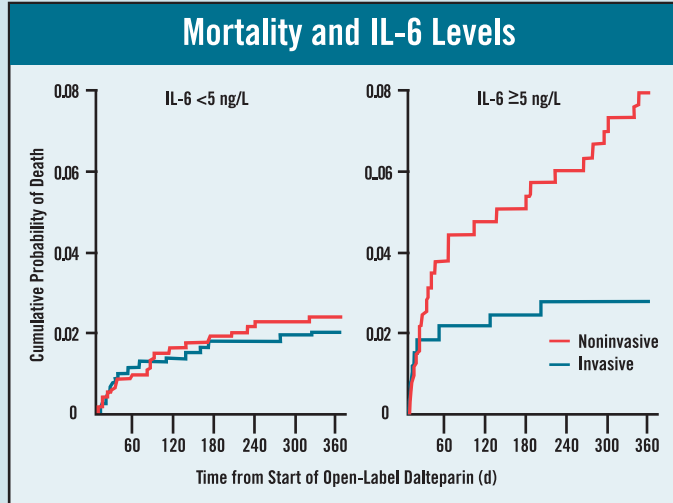
Reviewing the Effects of GP IIB/IIIA Inhibitors on Platelet Function, Inflammation, and Microcirculation

Factors Contributing to Thrombogenesis

The bone marrow of younger individuals contains *hemangioblasts*, which serve as precursors to endothelial progenitor cells and probably as progenitors of other components of the arterial wall. The production, function, and release of endothelial progenitor cells seem to become impaired with age. Progenitor-induced repair of the arterial wall occurs following arterial injury whether as a result of the effects of atherosclerosis or PCI. When damage to the arterial wall mediated by inflammatory cells such as activated macrophages overwhelms vascular repair capabilities because of an adequate supply of these progenitor cells, plaque rupture and thrombosis are more likely to occur, leading to ACS and STEMI.

With inflammation playing such a pivotal role in the pathogenesis of arterial injury and thrombosis, it is not surprising that biological markers of inflammation (eg, CRP, interleukin-6 [IL-6]) have been used successfully to identify patients at particular risk for coronary events, and who may benefit the most from an invasive strategy.⁵⁵ (Figure 13)

13
FIGURE



As a key biological marker of inflammation, the inflammatory cytokine IL-6 has been used successfully to identify patients who are at high risk for coronary events. In an open-label study of the parenteral antithrombotic anticoagulant dalteparin, IL-6 blood levels of 5 ng/L or greater correlated strongly with the risk for death during dalteparin therapy in patients undergoing noninvasive vs invasive procedures. IL-6, interleukin-6. Source: Lindmark E et al.⁵⁵

A key physiological function of some of these inflammatory markers is to help recruit participants in the cellular repair process, particularly the vascular progenitor cells. Effective recruitment requires the availability of a competent bone marrow. Once the vascular repair has been completed, blood levels of these inflammatory markers return to baseline. Without a large enough contingent of competent progenitor cells available to complete the repair process, the production of inflammatory markers continues causing further recruitment of inflammatory cells to the site of injury, leading to further vascular damage predisposing the subject to thrombosis which, if significant, can lead to a clinically significant ischemic event.⁵⁶ (Figure 14) Persistently elevated inflammatory markers including CRP, IL-6, and CD40 ligand (CD40L) indicate a lack of repair of the vascular wall. Among the elderly, the aged bone marrow is deficient in vascular progenitor cells, perhaps explaining the progression of coronary atherosclerosis, incidence of thrombotic complications, and poorer response to PCI.

14
FIGURE

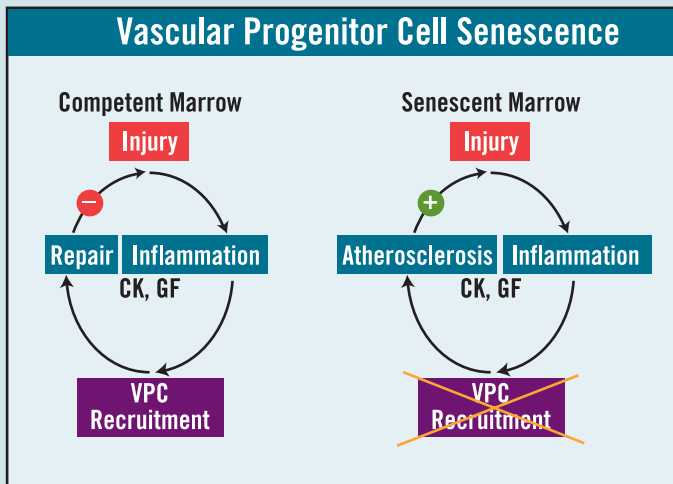


Figure 14. Inflammatory markers (eg, cytokines and growth factors) can recruit VPCs and other participants in cellular repair—provided a competent bone marrow is available. The inflammatory reaction is limited because once the repairs are made, inflammatory marker levels return to baseline. Recent studies indicate that VPCs undergo senescence and thus become less competent with age. In the absence of competent VPCs, inflammatory markers remain active and can prolong the inflammatory response, thus introducing the risk for vascular injury. CK, cytokine; GF, growth factor; VPC, vascular progenitor cells. Source: Rauscher FM et al.⁵⁶

It is instructive to note that the administration of competent bone marrow progenitors in mouse models of atherosclerosis that have exhausted their repair capacity not only prevents atherosclerosis, but also decreases the levels of inflammatory markers in the blood.⁵⁵

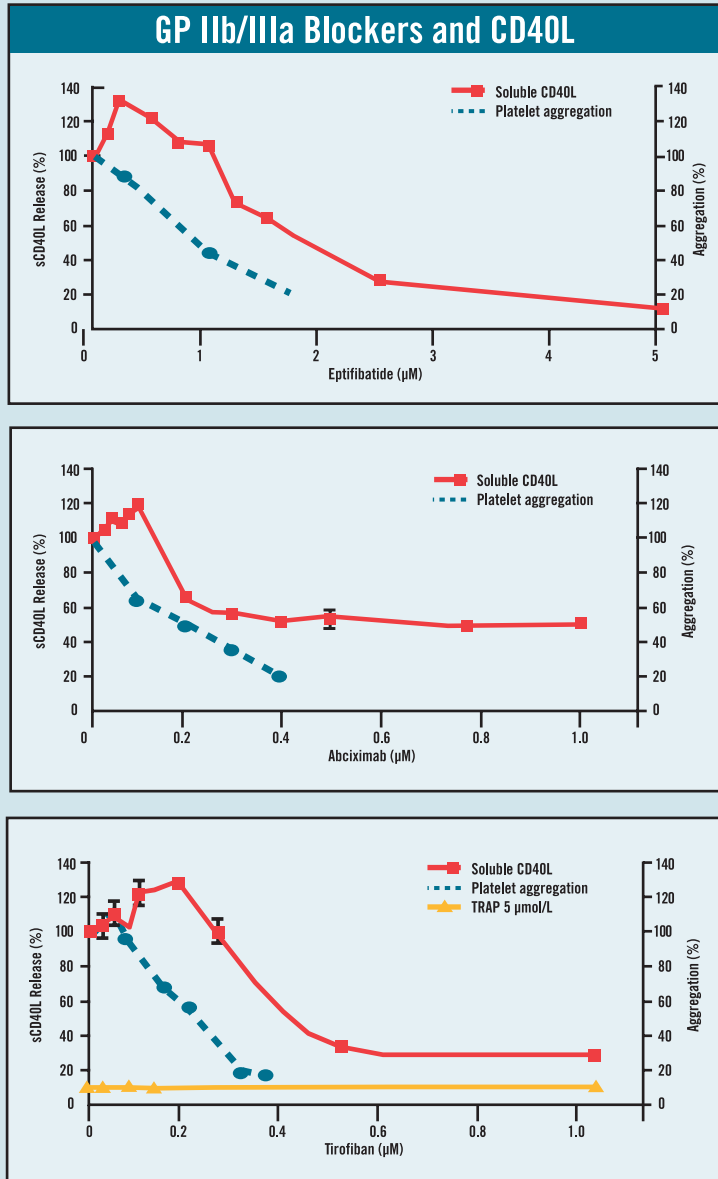
Even if the absolute number of progenitors that circulate in the blood of patients with ACS might be elevated, the relative level of competent progenitors might be too low to lead to successful repair. It is highly likely that ACS can result from an acute shortage of competent circulating progenitor cells to repair the arterial wall. This relative progenitor cell shortfall can predispose to a generalized vasculopathy and explain why multiple lesions can be activated concurrently in coronary and cerebral circulations. The inflammatory response to the vascular injury associated with PCI can affect distant bone marrow tissues and induce the recruitment of progenitor cells. Progenitor cell recruitment in this case is associated with substantial stimulation of platelet aggregation within PCI-treated coronary vessels. This pro-aggregatory activity has been efficiently kept in check with the use of parenteral GP IIb/IIIa receptor blockers.⁵⁷

The results of clinical trials evaluating the effectiveness of long-term administration of oral GP IIb/IIIa blockers have been disappointing. This may be in part related to the reduction of platelet-mediated progenitor cell recruitment to maintain intact arterial structure and cardiac function as observed with the chronic use of potent platelet inhibitors. Hence, long-term, but partial platelet blockade (eg, with aspirin or clopidogrel) seems more appropriate for maintaining the right balance between platelet-mediated repair processes and platelet-mediated arterial thrombosis than does long-term use of oral GP IIb/IIIa inhibitors.⁵⁸

In the absence of sustained arterial homeostasis, activated macrophages attracted and activated by inflammatory cytokines along the arterial wall promote the destruction of arterial structures. Preexisting plaques are weakened and made more likely to rupture, resulting in thromboembolic complications.⁵⁹ We have shown that activated macrophages can kill the structurally important vascular smooth muscle cells by a two-step process: (1) anchoring to the smooth muscle cell through a bond between the Mac-1 receptor (CD11b-CD18) on the macrophage and the intercellular adhesion molecule (ICAM-1) on the smooth muscle cell; and (2) binding of the Fas-ligand to the Fas receptor on smooth muscle cells to engage the Fas receptor, thereby triggering the cell-death machinery and consequent apoptosis of the smooth muscle cell. The GP IIb/IIIa receptor blocker abciximab can bind to an epitope on the Mac-1 receptor, thereby preventing interaction between the macrophage and the smooth muscle cell.⁶⁰

This anti-inflammatory effect may, at least in part, account for the reported ability of abciximab to reduce blood levels of inflammatory markers such as CRP and IL-6 in patients undergoing a PCI.⁵⁷ A comparison of intravenous GP IIb/IIIa inhibitors suggests that their ability to reverse the elevation in inflammatory marker levels that accompanies PCI is variable. An example of the effect is seen in the presence of CD40L, which is derived from the surface of activated platelets and contributes to several steps in the development of atherosclerosis and thrombosis.⁶¹ While all intravenous GP IIb/IIIa inhibitors seem to prevent the release of CD40L, this effect seems to be highly dose dependent. (Figure 15) Of particular concern is the fact that subtherapeutic doses of GP IIb/IIIa inhibitors appear to allow soluble CD40L levels to rise slightly and may be pro-inflammatory.⁶²

15
FIGURE



CD40L is an important marker of inflammation and contributes to thrombogenesis. All IV GP IIb/IIIa blockers prevent the release of soluble CD40L (which is derived from the surface of activated platelets) even in the presence of platelet agonists, eg, TRAP. This effect appears to be dose dependent. sCD40L, soluble CD40 ligand; TRAP, thrombin receptor activating peptide; IV, intravenous. Source: Nannizzi-Alaimo L et al.⁶²

Demystifying the Clinical Data with Regard to the Efficacy and Safety of Eptifibatide vs Abciximab vs Bivalirudin

Despite a decade or more of investigations into the efficacy of monotherapy with the GP IIb/IIIa inhibitor abciximab⁶³ (Figure 16) and the direct thrombin inhibitor bivalirudin, comparative studies of these agents are still lacking.

FIGURE 16

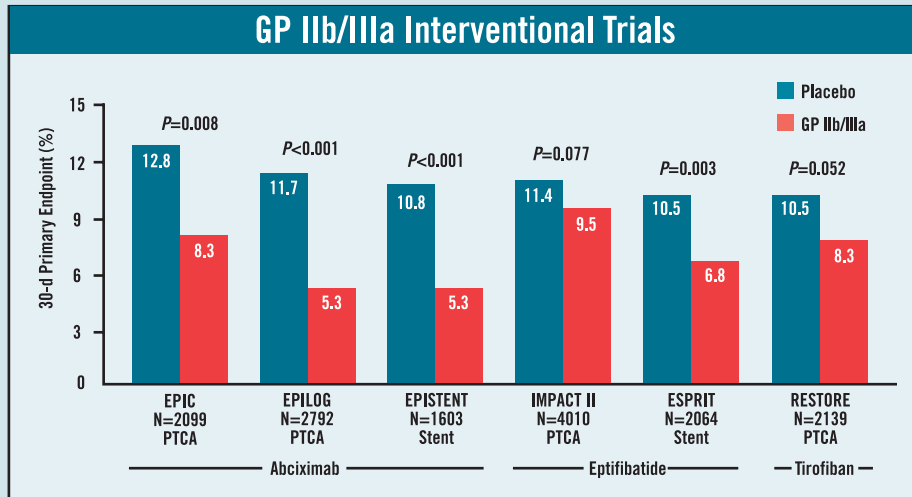


Figure 16. 3 IV GP IIb/IIIa inhibitors commercially available: abciximab, eptifibatide, tirofiban. All reduce risk of thrombogenesis by preventing fibrinogen binding with its platelet receptor. 6 major studies (approx. 15,000 pts) evaluated by PTCA or stenting revealed all 3 agents significantly reduce risk of death, MI, and urgent need for revascularization up to 30 days following procedure. pEP: 30-d death, MI, urgent revascularization. IV: intravenous; PTCA, percutaneous transluminal coronary angioplasty. Source: Roffi et al.⁶³

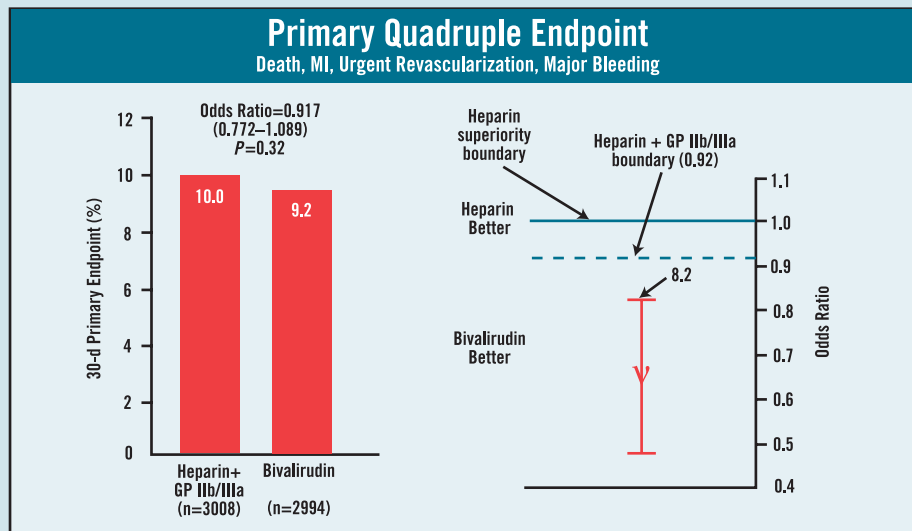
The available data suggest that efficacy is greatest for abciximab. The mortality benefit demonstrated for abciximab adds to the pool of evidence supporting the superior efficacy of GP IIb/IIIa inhibitors compared with direct thrombin inhibitors.⁶⁴ This benefit is clearly increased in high-risk patients, but patients who are classified as being at low to moderate risk for postprocedural thrombosis may also derive a substantial benefit from these agents.

A review of data from two key comparative studies—REPLACE-2 (Randomized Evaluation of PCI Linking Angiomax to Reduced Clinical Events) trial and the ISAR-REACT study—have provided much of the evidence to support this hypothesis.^{65,66}

Comparative Studies: REPLACE-2 and ISAR-REACT

Data from REPLACE-2 indicate that low- to moderate-risk patients may benefit from the use of the direct thrombin inhibitor bivalirudin, whose efficacy is shown to be superior to unfractionated heparin (UFH) and not inferior to heparin plus routine GP IIb/IIIa inhibitors.⁶⁵ (Figure 17)

FIGURE 17

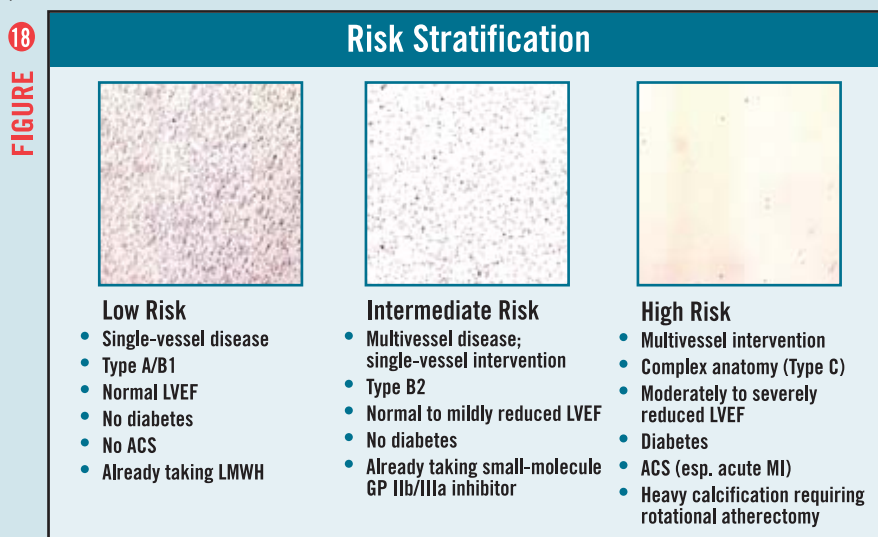


In the REPLACE-2 trial, bivalirudin was shown to be noninferior to heparin plus GP IIb/IIIa inhibition. MI, myocardial infarction; PCI, percutaneous coronary intervention. Source: Lincoff AM et al.⁶⁵

Bivalirudin appeared to be associated with a lower incidence of bleeding compared with heparin plus routine GP IIb/IIIa inhibition, at a cost, however, of an increased incidence of myocardial infarction.⁶⁵

The excess bleeding seen with GP IIb/IIIa inhibition + heparin combination may have been the result of ACTs achieved. In patients receiving abciximab, an ideal ACT would be 200 seconds, and higher levels were measured in REPLACE II. Additional studies may be warranted to determine whether GP IIb/IIIa inhibition with abciximab can be optimized using a bolus-only strategy, perhaps in combination with bivalirudin. This would allow for superior clinical benefits associated with the platelet-paralysis and anti-inflammatory effects of abciximab, and the safety benefits of bivalirudin over heparin.

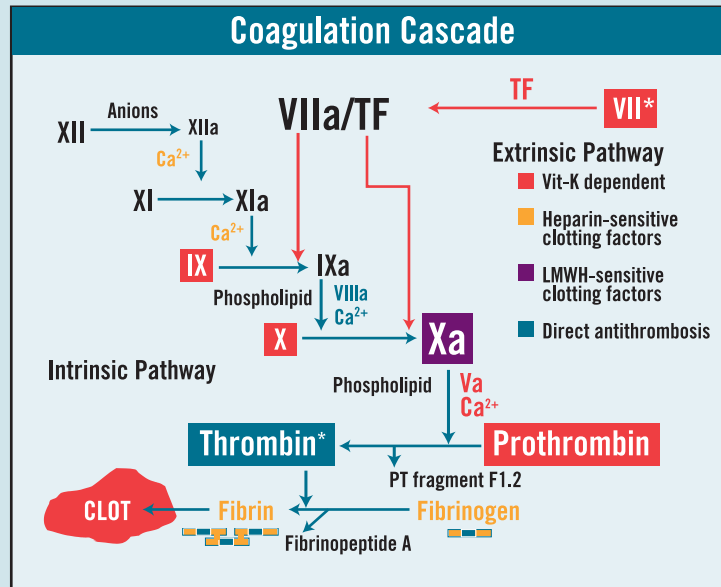
ISAR-REACT provides more recent data in a low-risk PCI population, evaluating the effectiveness of pretreatment with a 600-mg bolus of clopidogrel.⁶⁶ Pretreatment hours before a PCI seemed to provide adequate protection in this low-risk patient cohort. From a practical perspective, it may be difficult at times to delay an ad-hoc PCI following a just-completed diagnostic coronary angiogram for the four hours necessary to realize the clinical benefit of the clopidogrel bolus. Without the concomitant use of GP IIb/IIIa inhibition, patients who are resistant to the effects of clopidogrel may be at an increased risk of thrombotic complications. Thus, in the low-risk patient, favorable results may be obtained with heparin (either UFH or LMWH) monotherapy and adequate pretreatment with clopidogrel. In the moderate-risk patient, the use of bivalirudin, a small-molecule GPIIb/IIIa inhibitor, or both, is probably a reasonable choice. In the higher-risk patient, who may represent the largest fraction of patients undergoing PCI (which includes patients presenting with ST-segment elevation MI, diabetes, CKD, and the elderly) abciximab would be the agent of choice. (Figure 18)



Most appropriate antithrombotic strategy for PCI may vary with risk of thrombogenesis. *Low-risk patients*: either UFH or LMWH alone may produce favorable results (outcome may improve with pretreatment with clopidogrel). *Intermediate-risk patients*: efficacy of bivalirudin may prove superior to UFH and equivalent to heparin + GP IIb/IIIa inhibition. *Higher-risk patients* (including patients with diabetes): abciximab may be agent of choice. LVEF, left ventricular ejection fraction; ACS, acute coronary syndromes; LMWH, low-molecular-weight heparin; MI, myocardial infarction.

Recent and Future Developments in Antithrombin and Antiplatelet Therapies for PCI

PCI is inherently thrombogenic, in that the response to mechanical arterial injury results in the release of proteins that participate in critical steps of the coagulation cascade (eg, tissue factor, which drives the extrinsic coagulation pathway), facilitates exposure to arterial matrix proteins (eg, collagen and von Willebrand factor), and enhances platelet adhesion through the upregulation of adhesion molecules (ICAM and vascular cell adhesion molecule [VCAM]). (Figure 19)



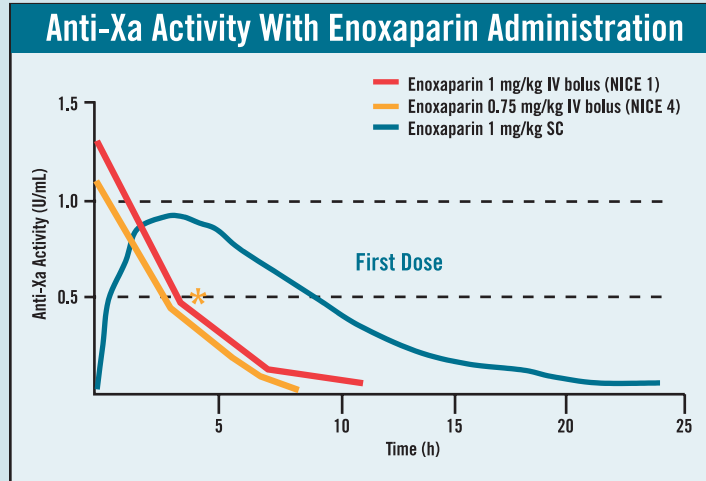
The platelet prothrombinase complex is comprised of factor Xa, factor Va, calcium ions, and the platelet phospholipid membrane. This complex converts prothrombin to thrombin. *Thrombin participates in feedback amplification of its own activity by activating factor XIIa, factor Va, and platelets. TF, tissue factor; Vit-K, vitamin K; LMWH, low-molecular-weight heparin.

By activating platelets, consuming antithrombin III (AT III), and converting fibrinogen to form fibrin, thrombin assures efficient clot formation along the injured endothelium. Thrombin also augments its presence by means of a feedback loop in which it activates factor XII (intrinsic coagulation pathway) as well as factor V and platelets to amplify its production.

Traditional antithrombin therapy involves the use of indirect thrombin inhibitors (eg, UFH and LMWH) that exert their effect by binding to AT III, which augments the affinity of AT III (1000X) to dislodge thrombin from its bond with fibrin rather than exerting an effect directly on the thrombin molecule. Thrombin binds to fibrin at exosite 1 (the substrate recognition site). Heparin also binds to thrombin at exosite 2 (binding site for highly-sulfated polysaccharides). The result is the ternary thrombin-fibrin-heparin complex where thrombin is “sandwiched” between fibrin and heparin molecules.⁶⁷ There are many limitations to UFH therapy which include: the inability to bind clot-bound thrombin or Factor Xa with the platelet-prothrombinase complex, the “rebound” effect following the cessation of heparin therapy which leads to a hypercoagulable state; direct platelet activation and aggregation; susceptibility to inactivation by platelet factor 4 (PF-4) as well as nonspecific protein and cellular binding that results in biphasic/saturation kinetics and an unpredictable dose response.^{67,68} Despite these limitations, a significant reduction in periprocedural ischemic events has been observed with UFH administration during PCI with ACTs of at least 300 seconds.⁶⁹

Low-Molecular-Weight Heparin (LMWH)

The potential advantages of LMWH over UFH include its greater affinity for Factor Xa, a reduced likelihood of protein and cellular binding (ie, a more predictable dose response), relative absence of thrombin rebound, lack of sensitivity to PF4, and a lower incidence of thrombocytopenia.⁶⁸ In largely nonrandomized comparisons of patients administered the LMWH enoxaparin IV for PCI, the antithrombotic effect of enoxaparin appeared to be at least as safe as weight-adjusted doses of UFH. Indeed, the incidence of major non-CABG bleeding events within 30 days after a PCI was extremely low with either enoxaparin monotherapy (1.0 mg/kg) or with reduced-dose enoxaparin (0.75 mg/kg) administered in combination with abciximab.^{70,71} (Figure 20)



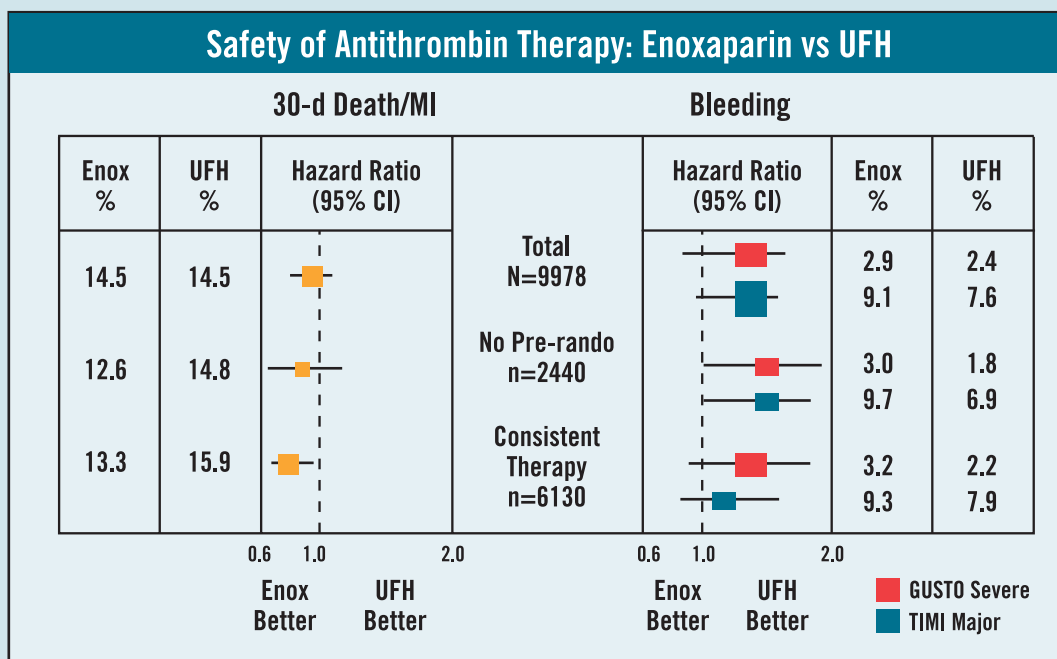
In the NICE 1 and 4 trials, vascular access sheaths were removed approximately 4 hours (*) after IV enoxaparin administration. Following repetitive dosing with SC enoxaparin, steady-state pharmacokinetics resulted in peaks >1.0 mg/kg and a more protracted therapeutic effect. IV, intravenous; SC, subcutaneous. Source: Kereiakes DJ et al.⁷¹

In the NICE (National Investigators Collaborating on Enoxaparin) 1 and NICE 4 registry experiences, vascular access sheaths were systematically removed 4 hours after an IV enoxaparin bolus. The antifactor Xa activity of enoxaparin falls below the threshold for therapeutic efficacy (0.6 U/mL) within this time frame following IV administration. By contrast, subcutaneous (SC) enoxaparin has a more extended duration of action. Because enoxaparin can achieve steady-state pharmacokinetics after 2 consecutive SC doses,⁷² the risk for drug accumulation in patients with renal insufficiency is evident.

The SYNERGY Trial

In the SYNERGY (Superior Yield of the New Strategy of Enoxaparin, Revascularization, and Glycoprotein IIb/IIIa inhibitors) trial, patients with acute coronary syndromes having at least 2 of 3 clinical risk factors (age ≥ 60 y; ST-segment deviation; or positive biomarkers) were randomized to weight-adjusted UFH IV or enoxaparin SC 1.0 mg/kg every 12 hours.⁷³ Remarkably, 76% of these patients had received antithrombin therapy (UFH, enoxaparin, or both) prior to enrollment. Following enrollment patients were randomly assigned to receive either enoxaparin or UFH, and subsequently, almost 800 patients were arbitrarily “crossed over” to a nonrandomly assigned therapy at the discretion of the investigator. Coronary angiography and PCI were performed in 92% and 47% of patients respectively, at an average time interval from enrollment of 22 and 23 hours, respectively.⁷⁴ Thus, the majority of patients enrolled in the SYNERGY trial had achieved steady-state enoxaparin pharmacokinetics by the time of catheterization (12–24 h after enrollment). An additional 0.3 mg/kg “booster” dose of enoxaparin IV was administered if patients arrived in the catheterization laboratory 8 to 12 hours after a prior enoxaparin SC dose.⁷⁵ An analysis of trial data for the primary endpoint (composite of death and MI at 30 d) demonstrated that enoxaparin was not inferior to UFH (hazard ratio [95% CI] = 0.96 [0.86–10.6]). No significant differences in the occurrence of GUSTO study group-defined severe bleeding events, intracranial hemorrhage, or need for red blood cell transfusion were observed between the UFH and enoxaparin treatment groups. However, the rate of major non-CABG bleeding (by TIMI study group definition) increased significantly with enoxaparin compared with UFH (2.4% vs 1.7%; $P = 0.025$). When safety and efficacy endpoints were analyzed for antithrombin-naïve patients (patients not treated with an antithrombin prior to randomization) and those receiving “consistent therapy” (patients treated with the same antithrombin therapy prior to and following randomization) the benefit of enoxaparin (vs UFH) in reducing the incidence of the primary endpoint events is evident.⁷⁶ However, the trend for a relative increase in bleeding events with enoxaparin (Figure 21) persists.

FIGURE 21



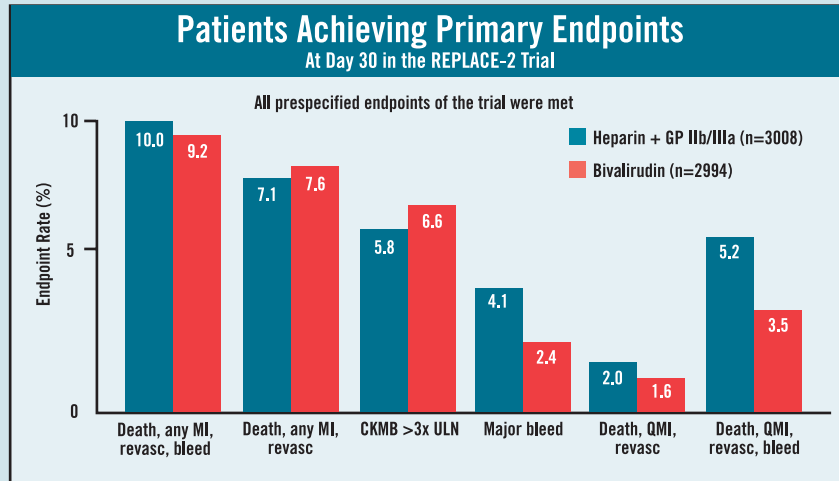
Analysis of SYNERGY trial data for primary endpoint (composite of death and MI to 30 d) and bleeding events in patients who never received antithrombin before enrollment and those who received the same agent before and after randomization (consistent therapy). The clinical benefit (reduction in death and MI) of enoxaparin vs UFH is evident. A tendency for increased bleeding is observed with enoxaparin. MI, myocardial infarction; Enox, enoxaparin; UFH, unfractionated heparin. Source: SYNERGY Executive Committee.⁷⁶

Because LMWH is dependent on renal function for clearance it cannot be given to patients with renal insufficiency. This is particularly important in the elderly population and in elderly women where renal insufficiency is more prevalent. From the TIMI study group database in 16,000 patients with ST-elevation MI, 1 in 4 patients have a calculated creatinine clearance of less than 60 mL/min.⁷⁷ As the average age of SYNERGY patients (68 y) far exceeds that of patients enrolled in the TIMI studies, the prevalence of mild-moderate renal insufficiency is likely higher in SYNERGY. Thus, in SYNERGY, many patients with moderate renal insufficiency (creatinine clearance < 60 mL/min) who had steady state enoxaparin pharmacokinetic (> 2 SC doses) and who received an additional “booster” dose of IV enoxaparin (0.3 mg/kg) whether needed or not, had catheterization and PCI. These same patients often had extended post-procedural vascular access sheath dwell times, in the absence of monitoring which might have facilitated earlier sheath removal. These factors (enoxaparin accumulation, prolonged sheath dwell times) likely contributed to the excess bleeding event rates observed in enoxaparin-treated patients. A mechanism to effectively monitor enoxaparin therapy might have reduced the frequency of “booster” dose administration and may have facilitated earlier vascular sheath removal and access site homeostasis.

Direct Thrombin Inhibition

The efficacy of bivalirudin compared with UFH in PCI was evaluated in REPLACE-2⁶⁵ as well as in CACHET (Comparison of Abcixamab Complications with Hirulog® Ischemic Events Trial)⁷⁸ and in the REPLACE-1 trial⁷⁹ which compared the effect of bivalirudin + GP IIb/IIIa to UFH + GP IIb/IIIa. In REPLACE-2, patients undergoing PCI were randomized to receive either bivalirudin with provisional GP IIb/IIIa inhibitor therapy or UFH (a 65-U/kg bolus) plus GP IIb/IIIa inhibitor therapy (abciximab or eptifibatide, at the investigator’s discretion). By day 30, bivalirudin was not inferior to UFH with respect to either the primary endpoint (composite of death, MI, revascularization, and bleeding) or secondary endpoint (composite occurrence of death, MI, or revascularization).⁶⁵ (Figure 22)

FIGURE 22



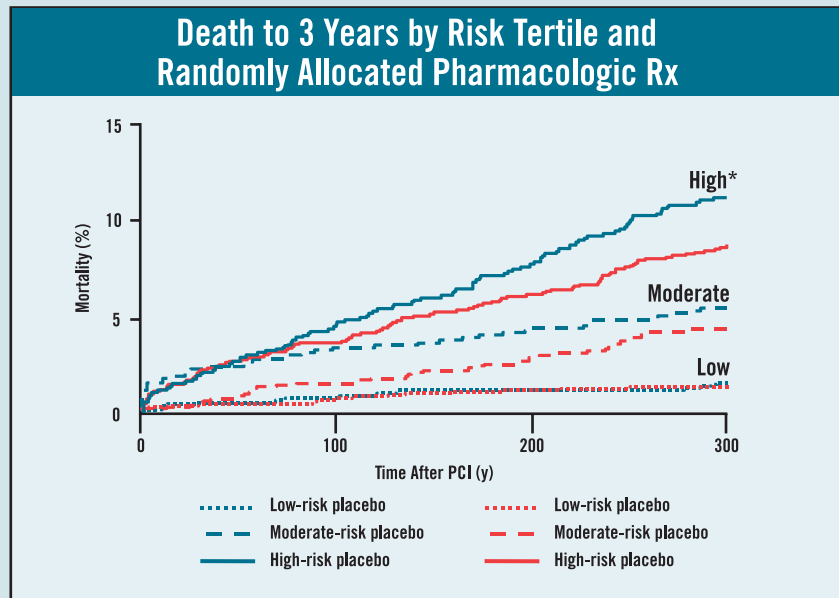
All pre-specified endpoints at day 30 in the REPLACE-2 trial were met. MI, myocardial infarction; revasc, revascularization; CKMB, creatine kinase-myocardial band; ULN, upper limit of normal; QMI, Q-wave myocardial infarction. Source: Lincoff AM et al.⁶⁵

Periprocedural MI (defined by a creatinine kinase-myocardial bond elevation to 3X ULN) was observed more frequently in patients treated with bivalirudin than with heparin + GP IIb/IIIa (6.6% vs 5.8%, respectively) and major bleeding events were observed less frequently (2.4% vs 4.1%, respectively).

Platelet GP IIb/IIIa Receptor Blockade

In two large meta-analyses of randomized, placebo-controlled trials, investigators reported a significant reduction in mortality at both 30 days and 6 months after PCI with adjunctive platelet GP IIb/IIIa inhibition in patients treated with UFH.^{69,80} The GP IIb/IIIa survival benefit was mainly ascribed to trials which utilized abciximab. In a pooled analysis of 6000 patients who received abciximab in the EPIC, EPILOG, and EPISTENT trials, a 22% relative (1.3% absolute) reduction in mortality was observed compared with placebo over 3 years follow-up ($P = 0.03$).⁶⁴ This survival advantage was particularly evident in patients with the highest clinical risk,⁸¹ who demonstrated an approximately 3% absolute mortality reduction. (Figure 23)

FIGURE 23



Analysis of mortality with abciximab in PCI during a 3-year follow-up in the EPIC, EPILOG, and EPISTENT trials, by clinical risk tertile (low, moderate, and high). The clinical risk profile was defined by 9 simple bedside clinical variables. *Three lives saved per 100 patients treated. Source: Kereiakes DJ et al.⁸¹

An analysis of a subset of patients enrolled in these trials also demonstrated a significant survival advantage with abciximab in diabetes following PCI (particularly with multivessel interventions).⁸²

Thienopyridine Update

As discussed previously, pretreatment with clopidogrel improves the clinical outcomes of GP IIb/IIIa inhibitor therapy.⁸³ The optimal duration of pretreatment with clopidogrel before PCI has been debated. Data from the Clopidogrel for Reduction of Events During Observation (CREDO) trial suggest that pretreatment with a 300-mg oral loading dose administered 6 to 15 hours before PCI and followed by 75 mg daily is required to achieve a significant reduction in ischemic outcomes to 30 days post-PCI.⁸⁴ A larger loading dose (600 mg) shortens the time required to achieve maximal platelet inhibition (2–4 h), but the clinical benefit of this strategy is unknown.^{85,86} Importantly, one in four patients has a decreased platelet inhibitory response to oral clopidogrel (“nonresponders”),⁸⁶ which appears to be directly related to the activity of CYP3A4, a hepatic enzyme necessary for the conversion of clopidogrel from prodrug to active metabolite.⁸⁷ Clopidogrel “resistance” was recently found to correlate with the occurrence of adverse ischemic events for up to 6 months after primary PCI for MI. Furthermore, a reduction in the degree of platelet inhibition has been demonstrated in response to an oral clopidogrel loading dose in both diabetes and in patients with ACS.⁸⁸ Newer clopidogrel-like agents (eg, CS-747) that do not require CYP3A4 enzyme activity for bioconversion are currently in clinical trials and may make these concerns irrelevant.

Conclusion

The search for the optimal adjunctive antithrombotic therapy for PCI has prompted investigators to take a closer look at a variety of pharmacologic agents. The challenge is to find the agent(s) capable of addressing the heightened level of platelet activation and thrombin generation while maintaining optimal safety profiles. The optimal strategy will likely involve varying degrees of both thrombin and platelet inhibition which may be tailored to the patient’s specific risk profile. Platelet GP IIb/IIIa inhibitors have consistently demonstrated enhanced efficacy and safety in specific patient groups, particularly those at high-risk such as STEMI, and those patients with diabetes or chronic renal insufficiency. Furthermore, a late survival advantage has been demonstrated following abciximab therapy, particularly in clinically high-risk subsets of patients. Platelet GP IIb/IIIa blockade provides additive antiplatelet inhibition effects to those of clopidogrel and is particularly attractive in acute coronary syndromes, complex coronary stenting procedures or for patients who may be hyporesponsive (~25%) to clopidogrel therapy. Clinical outcomes may be optimized by targeting patients with the greatest risk for thrombotic complications and by finding appropriate alternatives for patients with a lower risk. For example, lower-risk patients may benefit from either bivalirudin or heparin monotherapy preceded by adequate clopidogrel pretreatment. Higher-risk patients are more likely to benefit from platelet GP IIb/IIIa inhibition in combination with either UFH or bivalirudin. The optimal dosing regimen for combining bivalirudin and a GP IIb/IIIa inhibitor remains to be determined. Considerable interest and enthusiasm exists for the combination of abciximab bolus-only and bivalirudin. For patients at highest risk for adverse outcomes (patients with an AMI, diminished left ventricular function, diabetes, or renal insufficiency) abciximab remains the GP IIb/IIIa agent of choice.

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Highlights from the Panel Discussion

Pascal J. Goldschmidt, MD: Let me bring up an issue that you and I discussed at the meeting—the substantial overlap between renal failure and diabetes. In your presentation, you focused on renal failure. Which do you think is the real culprit, diabetes or renal failure?

Norman E. Lepor, MD: It seems that chronic kidney disease, in and of itself, leads to a significant incremental rise in cardiovascular risk in both univariate and multivariate analyses. I think that when you put diabetes and chronic kidney disease together, the increase in risk is more than just additive.

George W. Vetovec, MD: I certainly would agree with that. A significant proportion of those patients has diabetes; a significant number do not. These patients are at risk for cardiovascular events. Diabetes is one the best predictors of an adverse long-term outcome involving coronary disease. So, I think it's not just diabetes-related kidney failure that causes the risk. I think kidney failure has a separate role.

Dr. Lepor: Pascal, you mentioned between sessions that as we get older, we lose reparative mechanisms, and that may have a role in the change in renal function with aging. Would you care to expound on that?

Dr. Goldschmidt: Certainly. I think that it is becoming increasingly obvious that both chronic renal failure and diabetes have a tremendous negative impact on arterial repair, and that they synergistically damage normal repair mechanisms.

Dean J. Kereiakes, MD: Pascal, it's been said that some cases of chronic renal insufficiency represent an inflammatory state in which there are elevated c-reactive protein and interleukin-6 levels. Is that a function of the renal insufficiency?

Dr. Goldschmidt: As you know, the kidneys carry out an endocrine function that results in the generation of a number of cells responsible for a normal immune response. When that function is lost, an inflammatory condition can arise. The inability of the host to get rid of toxins may compromise normal kidney function and trigger an inflammatory response. Therefore, the primary goal is to enhance the repair process.

Dr. Lepor: There have been some recent studies looking at the relationship between anemia and poorer outcomes following a PCI, as well as with patients suffering from congestive heart failure. Do you think that the anemia associated with chronic kidney disease may be a surrogate indicator of renal function and thereby the inability—seen with chronic kidney disease—to mount the reparative processes?

Dr. Goldschmidt: In that specific situation, I would say yes. As we all know, a slight decrease in hematocrit would theoretically be favorable for patients undergoing a PCI because of the risk for thrombosis. In cases of chronic renal failure, however, anemia might actually indicate the inability of the kidneys to mount the repair response, and that might be the reason why anemia is associated with a poor outcome.

Dr. Lepor: How would you treat the hypothetical patient presenting to the cath lab with an acute coronary syndrome and a serum creatinine level of 3.0?

Dr. Kereiakes: For the patient you described, there's really only one GP IIb/IIIa blocker to use. And I can tell you that it's abciximab, because it's not cleared by the kidney. We'd use a reduced dose of unfractionated heparin because it does not have the same level of renal clearance as, say, enoxaparin or bivalirudin. Although bivalirudin has a relative benefit over unfractionated heparin, the patients who would benefit from this drug are not the ones for whom GP IIb/IIIa blockers are prescribed and they're not like the patients you're describing, who have creatinine levels well above 2 to 2.5. Those patients have been systematically excluded from all the clinical trials.

Dr. Vetovec: I would agree with that. I think, in terms of safety, that's certainly the best way to do it.

Jonathan D. Marmor, MD: I agree with Dr. Kereiakes' point that the GP IIb/IIIa of choice is abciximab. Because thrombotic problems comprise a smaller portion of the problems we face, bleeding has become much more the focus for interventionalists. I think one of the contributions of the REPLACE-2 trial has been to steer the conversation a little more towards bleeding, which is appropriate given the better outcomes seen with stents. I think that one way to counter this concern about bleeding in patients with chronic kidney disease and other populations at a higher risk of bleeding complications, and not deny them the benefit of abciximab, is the use of an abciximab bolus-only strategy. We may also have to be very careful about the dosing of heparin in these patients. In our experience, one way of dealing with that issue in patients is to give modest doses of heparin and carefully follow the activated coagulation time, or ACT, with a goal ACT of 200 seconds. Thus, my management plan for the patient with renal failure focuses very much on a bolus-only strategy using abciximab, with an infusion given if there are complications.

Dr. Lepor: You raised a good point about the bolus-only use of abciximab. In the pre-stent era, before the widespread use of thienopyridines, the bolus-only strategy as observed in the EPIC trial did not provide the same benefit as the bolus-plus-infusion strategy. Have changes that have occurred since the EPIC trial—including the use of stents, ADP blocking agents, and lower doses of intraprocedural heparin—made an abciximab bolus-only approach appropriate in some patients? In terms of cost, the bolus-only approach could provide savings as well. What experience is out there that would cause us to consider using a bolus-only strategy with abciximab?

Dr. Kereiakes: There's a significant reduction in mortality at 7 years with both the bolus-only strategy as well as with the bolus followed by a 12-hour infusion. That is possibly due to non-target lesion stabilization caused by mechanisms that Pascal described. It would make a lot of sense to use the bolus-only strategy on a risk-stratified basis, as we described in our analysis of the EPIC, EPILOG, and EPISTENT trials.

Dr. Vetrovec: I've always been under the impression that the posttreatment strategy is more important than pretreatment. The CAPTURE trial is an example of pretreatment with abciximab in patients with high-risk acute coronary syndromes with only 1 hour of abciximab posttreatment, which may have limited its ability to reduce longer-term complications. I have always thought one of the reasons that it might be important to maintain the postprocedure infusion is the ability to have a greater impact on reducing inflammation—and that might make a big difference.

Dr. Goldschmidt: The long-term survival benefit—now out to 7 years—is really quite extraordinary with abciximab, and not yet observed with any other GP IIb/IIIa inhibitor or any other pharmacologic agent given in the catheterization laboratory. It's certainly rare to see a survival benefit with other therapeutics.

Dr. Marmur: Let me just point out a couple of things that support the notion of a bolus-only strategy. The REPLACE-2 study had a bivalirudin arm that used a bolus-only strategy. Bivalirudin does not have the platelet-activating effects of unfractionated heparin, although this may be offset during the hours following the bolus-only taper. I think that GP IIb/IIIa agents need to become more user-friendly to reduce the risk for bleeding. In the EPIC trial, the lowest mortality in the 7-year group was seen with the bolus-only strategy. I think the ideal therapy for our patients, particularly those with renal failure, is abciximab. My concern is that people are not using it because they are concerned about the risk for bleeding, the cost, and the inconvenience. The EPIC trials showed that the retroperitoneal bleed rate with the bolus-only strategy was identical to that for placebo, but rose with the bolus-plus-infusion strategy. It would be very interesting to look at the time course of these MIs. When exactly were they happening during the REPLACE-2 study? Was it truly periprocedural, that is, occurring after the stent went in? Or was there a 12-hour delay? It may be worthwhile to look at the data hour by hour to see when these events happen.

Dr. Kereiakes: If you look at the 30-day endpoint of myocardial infarction, you'll see a 1.5% absolute reduction with abciximab plus unfractionated heparin in REPLACE-2—6.2% versus 7.7% with bivalirudin. I think that the real trial hasn't been done. That is testing the potential for abciximab to benefit patients given bivalirudin, which was not tested in REPLACE-2.

Speaker: We also have to be concerned about the influence of drug-eluting stents. With drug-eluting stents, patients are going to think, "I'm fixed—now and forever." Which is, of course, unrealistic. I think doctors will be much more sensitive to the fact that things happen in the future, and I think we'll start noticing that a growing proportion of the events aren't necessarily related to the stent. If you want the analogy, when we started doing angioplasty, people who developed terrible groin hematomas didn't pay attention to them because they were happy to be alive.

Now that these procedures go well and patients get out of the lab quickly, when they develop a groin problem it's a big deal. So, I think the idea of getting the perfect long-term result will become a little more important than it was in the past.

Dr. Kereiakes: I think stent thrombosis has reared its ugly head again, although no objective data are available yet. Two parameters that significantly influenced the risk for procedural stent thrombosis in small vessels were long stents and the absence of GP IIb/IIIa blocker therapy.

I'm not sure that bivalirudin is adequate, because it doesn't adequately block platelet activation periprocedurally and there's still an ill-defined relationship between bivalirudin and abciximab that needs to be clarified.

Speaker: Let me change the topic discussion for a minute to focus on a population of patients that probably represents the majority of those that we see in the cath labs. These are the patients who have abnormal glucose metabolism.

There are data indicating that diabetic and prediabetic conditions represent an inflammatory, hypercoagulable state. Taking into account available chronicled data, what's our perception of the patient with diabetes? Let's assume that this patient has mild renal impairment or microscopic albuminuria. What would the treatment algorithm look like for this patient?

Dr. Marmur: In the patient with diabetes and diffuse multivessel disease, the default mode should be coronary artery bypass surgery. The utility of drug-eluting stents in the left main coronary artery is questionable, given that restenosis can be fatal in these patients. There's an idea that the drug-eluting stent may be more effective than the bare metal stent and therefore as good or better than surgery, but that remains to be seen. I think the approach should be surgical.

Dr. Vetrovec: It's easy to say that patients with diabetes are optimally treated with surgery. However, a lot of those patients have other problems that make them less than ideal for surgery—including small-vessel disease and renal failure. The surgeon doesn't want to take these cases and we end up with them. While I agree very strongly about how these patients should be treated, in reality these cases are very complicated, and I think we're handling more of them than we want to.

Dr. Kereiakes: We have to consider the odds ratio for mortality for these patients. In the patient with diabetes, whether it is insulin-dependent or not, a significant increase in risk of mortality is seen following multivessel revascularization, whether by percutaneous coronary intervention or bypass surgery. Patients treated with a PCI fared less well than those treated with bypass surgery.

Speaker: Do patients with diabetes really get a tremendous mortality benefit from GP IIb/IIIa inhibitors? And I'd like to get your opinion on the distinction between abciximab and the small-molecule agents, with respect to PCIs in diabetes.

Dr. Marmur: I think that evidence in the literature strongly supports the use of PCIs in diabetes with a GP IIb/IIIa inhibitor. The distinction between abciximab and small-molecule agents is really striking. Because of cost issues, however, interventionalists really have to define the clinical scenarios in which a commitment to this strategy can be sustained. Certainly serious consideration for the use of abciximab in patients with diabetes and an acute coronary syndrome has to be included, along with patients with acute MI, in my opinion. Patients with renal failure may have to be included as well.

Dr. Vetrovec: Looking at patients who were going to the cath labs, I found that patients with diabetes were number one on my list; then patients with an acute coronary syndrome, because of all of the associated issues; and of course, patients with an acute MI—certainly anybody with a visible clot. Then there are the patients who are considered high risk, based on both their history and their anatomic profile. These may include patients with left ventricular dysfunction, diabetes, and the like. Many physicians really aren't of the belief that GP IIb/IIIa agents are necessary for these patients despite the wealth of clinical trial data supporting their use.

Dr. Marmur: Some information has come out in the last couple of months concerning the patient with diabetes and an acute coronary syndrome. The McGuire paper, which was published in the *American Heart Journal*, reports the findings of a study of more than 15,000 patients from the SYMPHONY trial. It turns out that those patients who received the insulin-sensitizing drugs, as opposed to insulin secretagogues, had improved outcomes. As interventionalists, we must be aware of the fact that novel glucose control agents may have a substantial impact on patient outcomes and play a role in prescribing these therapies when appropriate.

Dr. Goldschmidt: I agree that the very specific type of medical therapy that you use for patients with either diabetes or renal failure is very important, but I think it's also important to remember that the data suggest that any intervention is better than no intervention, and that medical therapy alone is probably not an appropriate solution for most patients with diabetes or renal failure. In previous years, and probably for a very large part of the world's population, medicine was still considered the best approach, owing to the belief that these patients are too high risk or would have too many side effects if treated with a PCI or bypass. But today, this is probably not considered the right thing to do.

Dr. Lepor: Let's change the subject to the use of GP IIb/IIIa inhibitors in patients presenting with AMI and focus this discussion on abciximab, which is the only agent in that class with clinical trial data supporting its use. When would you give that GP IIb/IIIa inhibitor? Would you give it precath lab, for instance, while the patient is still in the emergency department?

Dr. Vetrovec: I would start it in the emergency room on the way to the cath lab. However, if I don't have control over the choice of agent that's going to be given in the emergency department, then I'd just as soon wait until they get to the cath lab so I can give them abciximab, because, I think, in that kind of high-risk, highly thrombotic patient, that's the drug I want.

Dr. Marmur: I certainly do think that GP IIb/IIIa inhibitors should be used, and liberally in patients presenting with AMI. The ADMIRAL data certainly support the idea that they should be given as soon as possible. The risk-benefit ratio favors the use of abciximab and from a safety point of view there is no increase in intracranial risk with abciximab or, for that matter, any GP IIb/IIIa agent, in patients with an acute MI. And I should mention that the CADILLAC trial showed a subacute stent thrombosis rate of zero in the abciximab group. Getting back to Dean's point about longer drug-eluting stents and the risk for increased rates of stent thrombosis, I think these are additional reasons for considering abciximab. I'm not 100% gung-ho about the bolus-only strategy yet because of the risk for subacute stent thrombosis. That is where an infusion may play a key role.

Dr. Kereiakes: Your point's well taken. When you look at the Kandzari pooled analysis in the *American Heart Journal*, or if you look at the Topol editorial that appeared in the *Journal of the American College of Cardiology* late last year, the data with abciximab are compelling.

Post-Test

Report Card on the Pharmacologic Management of Coronary Artery Disease in the Catheterization Laboratory

- Age as a risk factor for the development of atherosclerosis results:
 - From vascular progenitor cell senescence
 - In reduced vascular cell repair in response to injury
 - In a greater risk of complications from vascular injury
 - All of the above
- The effects of unfractionated heparin are limited by:
 - Inability to bind to clot-bound fibrin
 - Susceptibility to deactivation by platelet factor 4 (PF4)
 - The glycoprotein IIb/IIIa receptor inhibitors
 - a and b
- Clopidogrel:
 - Loading dose results in less platelet inhibition in diabetics than in nondiabetics
 - Effect on platelet function is modified by CYP 3A4 activity
 - Effect on platelets is reduced in patients who are unstable versus those who are stable
 - Is a prodrug and requires bioactivation by CYP 3A4
 - All of the above
- Renal insufficiency:
 - Leads to greater risk of mortality following AMI and PCI
 - At levels considered mild has no effect on complication rates following PCI
 - Does not interfere with the metabolism of abciximab
 - Limits the utilization of eptifibatid and tirofiban
 - a, b, and d
- Diabetics:
 - With overt coronary artery disease have higher levels of inflammatory markers than nondiabetics with coronary artery disease
 - Have higher levels of late major adverse cardiac events than nondiabetics
 - Presenting with acute coronary syndromes benefited from GP IIb/IIIa use, particularly those undergoing PCI
 - All of the above
- Diabetic patients undergoing drug-eluting stent implantation were much more likely to develop restenosis than nondiabetics.
 - True
 - False
- Which of the following does not apply to unfractionated heparin?
 - Inability to bind clot-bound thrombin or factor Xa within the platelet prothrombinase complex
 - Heparin "thrombin" rebound
 - Direct platelet activation and aggregation
 - Nonspecific cellular and protein binding
 - Direct binding and inhibition of circulating factor Xa
- Regarding the SYNERGY trial, which of the following statements is true?
 - 76% of patients received antithrombin therapy prior to enrollment
 - The average age of enrollees was 68 years
 - For those patients with "consistent" antithrombin therapy (no crossover), a significant reduction in primary endpoint events was observed in favor of enoxaparin
 - TIMI major bleeding events were increased with enoxaparin
 - All of the above
- Which factor(s) may account for the marked impact of aging on cardiovascular events?
 - Change in smoking habits
 - Worsening blood pressure
 - Worsening lipid levels
 - Lack of exercise
 - All of the above
- Which of the following regarding combination of reduced-dose fibrinolytics with full-dose glycoprotein IIb/IIIa inhibitors is not true?
 - Achieves higher rates of TIMI-3 flow in the infarct-related artery
 - Results in improved survival compared with fibrinolytic therapy alone
 - Is associated with significant reductions in recurrent infarction
 - Is associated with higher rates of major bleeding
- Which of the following catheter-based therapies has been shown to improve survival in primary PCI?
 - Distal embolic protection
 - Drug-eluting stents
 - Endovascular hypothermia
 - None of the above
- In the REPLACE-2 trial, the duration of the infusion of bivalirudin (Angiomax) post-PCI was similar to the duration of the infusion of GP IIb/IIIa inhibitors post-PCI.
 - True
 - False
- In long-term (over 7 years) follow-up of the abciximab PCI trials, the greatest mortality benefit was seen with the bolus-only arm of the EPIC trial.
 - True
 - False
- The ISAR-REACT population was a moderate-risk population, and therefore it is likely that only a minority of patients undergoing PCI would benefit from GP IIb/IIIa inhibitor therapy.
 - True
 - False
- Current evidence suggests that coronary intervention is associated with:
 - A decrease in inflammatory markers following stent placement
 - An increase in inflammatory markers following stent placement
 - No change in inflammatory markers unless MACE occurs
 - A lower risk of restenosis associated with increased inflammatory markers

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Report Card on the Pharmacologic Management of Coronary Artery Disease in the Catheterization Laboratory—Monograph

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Extent to Which Program Activities Met the Identified Objectives

- State the effect of glycoprotein IIb/IIIa inhibitors on coronary artery inflammation, microcirculation, and platelet function
 - Discuss the role of abciximab in a catheterization laboratory approach to acute myocardial infarction
 - Identify patients undergoing drug-eluting stent placement who could benefit from the concomitant use of glycoprotein IIb/IIIa-receptor inhibitors
 - Review the nuances involved in the care of high-risk patients (diabetics, patients with chronic kidney disease)
 - Discuss the future of new antiplatelet and antithrombotic therapies and their potential clinical implications
- Overall Effectiveness of the Activity**
- Was timely and will influence how I practice
 - Will assist me in improving patient care
 - Fulfilled my educational needs
 - Avoided commercial bias or influence

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