Targeting the Use of Glycoprotein IIb/IIIa Antagonists—The Diabetic Patient

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Diabetes mellitus is associated with an increased prevalence of and morbidity from coronary artery disease, which is present in at least 25% of diabetic patients. Diabetes mellitus is a risk factor for recurrent cardiovascular events after myocardial infarction and after percutaneous coronary intervention procedures or coronary artery bypass surgery. Less than half of the increase in cardiovascular events with diabetes mellitus is accounted for by the presence of traditional cardiac risk factors such as hypertension, hypercholesterolemia, and hypertriglyceridemia. Vascular inflammation reflected by increased levels of high-sensitivity C-reactive protein, endothelial dysfunction associated with hyperglycemia and hyperinsulinemia, impaired fibrinolysis mediated by hyperinsulinemia, and increased platelet aggregation are now recognized as promoting the development of arteriosclerosis in diabetic patients. These factors may be present long before a diagnosis of diabetes mellitus is established. Platelets in diabetic subjects appear to be in an activated state even in the absence of vascular injury, as evidenced by greater expression of the fibrinogen-binding glycoprotein IIb/IIIa receptor, which constitutes the final common pathway of platelet activation and allows for cross-linking of individual platelets by fibrinogen molecules and formation of thrombus. Platelet inhibition with intravenous glycoprotein IIb/IIIa inhibitors has been shown to reduce morbidity and mortality in patients undergoing percutaneous coronary intervention for acute coronary syndromes, and diabetic patients appear to derive an even greater relative benefit from this treatment. The ACC/AHA 2002 guidelines for the management of acute coronary syndromes recommend the use of abciximab in diabetic patients undergoing stent implantation.

[Rev Cardiovasc Med. *2002;3(1):S20–S27*]

Key words: Diabetes mellitus • Coronary artery disease • Arteriosclerosis • Glycoprotein IIb/IIIa receptor • Thrombus • Clopidogrel • Heparin • Abciximab

Diabetes mellitus (DM) is associated with an increased prevalence of and morbidity from coronary artery disease (CAD).[1] Cardiovascular death is increased 2- to 4-fold when compared to nondiabetic patients, in diabetic patients both with and without established CAD,[2] and CAD alone is present in

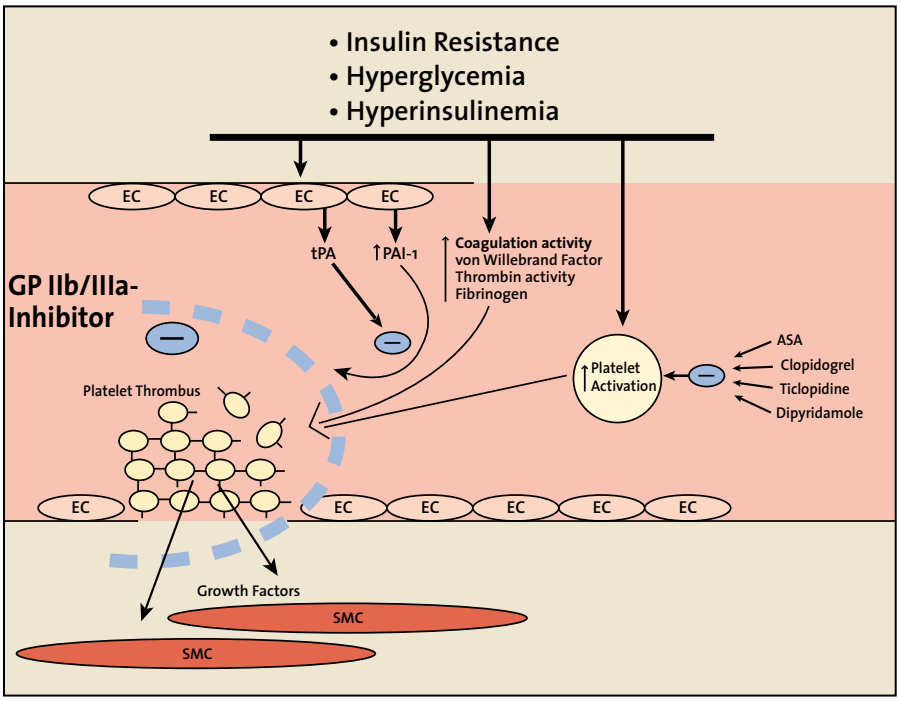

Figure 1. *Schematic illustration of vascular biology of the diabetic state. EC, endothelial cell; SMC, smooth muscle cell; tPA, tissue plasminogen activator; PAI-1, plasminogen activator inhibitor-1; GP, glycoprotein; ASA, acetyl salicylic acid.*

at least 25% of diabetic patients.[3] DM is a risk factor for recurrent cardiovascular events after myocardial infarction (MI)[1] and after percutaneous coronary intervention (PCI) procedures or coronary artery bypass (CAB) surgery.[4]

The increased risk for CAD in patients with DM is in part due to the frequent presence of traditional cardiac risk factors—for example hypertension, hypercholesterolemia, and hypertriglyceridemia—in these patients. However, less than half of the increase in cardiovascular events with DM is accounted for by the presence of these traditional cardiac risk factors.[5] Understanding of other mechanisms responsible for the propensity of diabetic subjects to develop early and diffuse arteriosclerosis has evolved dramatically in recent years. Vascular inflammation reflected by increased levels of high-sensitivity C-reactive protein, endothelial dysfunction associated with hyperglycemia and hyperinsulinemia, impaired fibrinolysis mediated by hyperinsulinemia, and increased platelet aggregation are now recognized as promoting the development of arteriosclerosis in diabetic patients (see Figure 1). There is increasing evidence that these factors are present long before a diagnosis of diabetes mellitus may be established.[6] Thrombosis is central to the development and progression of atherosclerotic plaque. Angiographic[7] and angioscopic[8] evidence has established obstructive intravascular thrombosis as the mechanism responsible for acute coronary events, and a cycle of nonocclusive vascular thrombosis with incorporation of thrombus into plaque has been proposed as the mechanism underlying the progression of "stable" coronary stenoses.[9]

Thrombosis is central to the development and progression of atherosclerotic plaque.

Platelet Activation in the Diabetic Patient

Blood platelets have an important role in thrombosis, and changes in platelet reactivity associated with DM are central to the prothrombotic state observed in these patients. Increased platelet aggregation in DM was recognized over 25 years ago,[10] and more recent studies indicate that platelet size, degranulation, and synthesis of thromboxane derivatives mediating further platelet activation[11] are increased in DM, whereas platelet-mediated vasodilation is impaired.[12] Platelets in diabetic subjects appear to be in an activated state even in the absence of vascular injury, as evidenced by greater expression of the fibrinogen-binding glycoprotein (GP) IIb/IIIa receptor assessed by flow cytometry.[13] Expression of the GP IIb/IIIa receptor constitutes the final common pathway of platelet activation and allows for cross-linking of individual platelets by fibrinogen molecules and formation of thrombus.

Growth factors and cytokines, released during platelet activation and from mural thrombus, stimulate migratory and proliferative responses of vascular smooth muscle cells.[14] Cytokines mediate expression of leukocyte adhesion molecules by endothelial cells that allow for macrophage margination and translocation, processes that are central to atherosclerotic plaque formation and destabilization.[15] The central role of platelets in promoting arte-

Table 1
Acronyms of Trial Names

ARTS	Arterial Revascularization Therapy Study
ATC	Antiplatelet Trialists Collaboration
BARI	Bypass Angioplasty Revascularization Investigation
CABRI	Coronary Angioplasty vs Bypass Revascularization Investigation
CAPRIE	Clopidogrel vs Aspirin in Patients at Risk of Ischemic Events
CURE	Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events
EAST	Emory Angioplasty vs Surgery Trial
EPIC	Evaluation of 7E3 for the Prevention of Ischemic Complications
EPILOG	Evaluation in Percutaneous Transluminal Coronary Angioplasty to Improve Long-Term Outcome with Abciximab Glycoprotein IIb/IIIa Blockade
EPISTENT	Evaluation of Platelet IIb/IIIa Inhibitor for Stenting
ESPRIT	Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrilin Therapy
FRISC II	Fragmin (dalteparin) and Fast Revascularization during Instability in Coronary Artery Disease II
GUSTO-IV-ACS	Global Utilization of Strategies to Open Occluded Coronary Arteries-IV—Acute Coronary Syndromes
PARAGON	Platelet IIB/IIIa Antagonism for the Reduction of Acute Coronary Syndrome Events in a Global Organization Network
PARAGON B	Platelet IIB/IIIa Antagonism for the Reduction of Acute Coronary Syndrome Events in a Global Organization Network B
PRISM	Platelet Receptor Inhibition in Ischemic Syndrome Management
PRISM-PLUS	Platelet Receptor Inhibition for Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms
PURSUIT	Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy
RESTORE	Randomized Efficacy Study of Tirofiban for Outcomes and Restenosis
TACTICS-TIMI 18	Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy—Thrombolysis in Myocardial Infarction 18
TARGET	Do Tirofiban and ReoPro Give Similar Efficacy? Trial
VANQWISH	Veterans Affairs Non-Q-Wave Infarction Strategies In-Hospital

riosclerosis is supported by clinical studies associating the degree of platelet reactivity to the risk of future cardiac events in nondiabetic patients.[16] The increased platelet reactivity observed in DM may explain the even higher event rate in diabetic patients. It is important to understand that the prothrombotic state in DM not only increases the propensity to develop early and widespread arteriosclerosis, but in addition amplifies the severity of acute thrombotic events and the likelihood of a detrimental outcome.

Pharmacologic Inhibition of Platelet Activation

It is no surprise that pharmacologic inhibition of platelet activation has a profound impact on the rate of future cardiac events in diabetic patients. The Antiplatelet Trialists Collaboration's (ATC) most recent meta-analysis of prophylactic therapy with aspirin[17] shows that rates of nonfatal MI, stroke, or cardiovascular death were reduced from 13.2% to 10.7% ($P < .0001$) in the overall population. This effect of aspirin alone is impressive in light of the rate of aspirin resistance of platelets in patients with CAD.[18] The CAPRIE trial tested platelet inhibition with clopidogrel (Plavix) versus a standard aspirin regimen in stable patients with CAD. Although clopidogrel reduced the rate of vascular death, MI, stroke, and rehospitalization for ischemic events only moderately in the overall study population (5.83%–5.32%; $P = .043$) at an average of 1.9 years, a larger benefit was seen in the diabetic population (17.7%–15.6%; $P = .042$) in this trial.[19] (Table 1 provides the full names of trials identified here by acronyms.)

The CURE trial[20] compared long-term treatment with a combination of aspirin and clopidogrel to standard therapy with aspirin alone in patients

with acute coronary syndromes (ACS) treated with a conservative strategy. Recurrent events (cardiovascular death, nonfatal MI, or stroke) occurred in 9.3% of subjects receiving clopidogrel plus aspirin versus 11.4% of subjects receiving aspirin alone in the overall population ($P < .001$). The benefit was independent of subgroup. Interestingly, the diabetic subgroup did not have a greater event rate reduction (14.2% vs 16.7%) than that observed in the study group as a whole.

Pharmacologic inhibition of platelet activation has a profound impact on the rate of future cardiac events in diabetic patients.

In-hospital mortality following non-Q-wave MI in diabetic patients is equal to that for acute MI in nondiabetic patients,[21] and long-term morbidity following ACS may even be increased over that after Q-wave MI in diabetic patients.[22] After the VANQWISH trial reported an equivalent outcome for an early invasive versus early conservative treatment strategy in ACS, two newer trials, employing the early use of novel adjuvant antithrombotic therapies—low-molecular-weight heparin in FRISC II, and the GP IIb/IIIa antagonist tirofiban in TACTICS-TIMI 18—showed significant superiority of the early invasive approach. Adjuvant therapy with antithrombin agents and intravenous GP IIb/IIIa antagonists now plays a central role in the preferred approach adopted by the American Heart Association/American College of Cardiology guidelines in this clinical scenario.[23]

Many trials have shown a benefit of platelet inhibition through GP IIb/IIIa antagonism in the setting of ACS in the overall population. The EPIC trial was the first to demonstrate a reduction of the composite endpoint of death, MI, urgent target vessel revascularization, or refractory ischemia with the adjuvant use of abciximab versus placebo in patients undergoing elective or urgent PCI. This combined endpoint was reduced by 35%, to 8.3% from 12.8% ($P = .008$) at 30 days. These data were confirmed in two other large trials with abciximab, EPILOG and EPISTENT. The CAPTURE trial included only patients with ACS treated with an early invasive strategy and confirmed the benefit of adjuvant abciximab treatment in this high-risk patient population (11.3% vs 15.9%; $P = .012$). Adjuvant treatment with tirofiban in the RESTORE trial did not reduce the composite endpoint of death, MI, urgent target vessel revascularization (TVR), and unplanned stenting in patients undergoing PCI in ACS at the 30-day primary endpoint, though a benefit was seen at 7 days. A positive treatment effect was seen out to 6 months in PRISM-PLUS. A modest 10% relative composite endpoint reduction with eptifibatide in ACS was observed in the PURSUIT trial. This benefit was seen in the ~20% patients undergoing early PCI, emphasizing the synergistic effect of PCI and aggressive platelet inhibition in ACS. For a detailed discussion of this topic, please see the contribution by Dr. Norman Lepor elsewhere in this supplement. (Table 2 summarizes reports of IIb/IIIa inhibitor treatment effects.)

The applicability of these results to the diabetic population can be gleaned from several secondary subgroup analyses, as well as pooled analyses of diabetic subgroups from different studies. Such an analysis from EPILOG[24] showed that diabetic patients in this study had a greater reduction of death or MI when compared to the nondiabetic subgroup (hazard ratios 0.28 vs 0.47 and 0.36 vs 0.60 for diabetic vs nondiabetic patients at 30 days and 6 months, respectively) with adjuvant therapy with abciximab. Interestingly however, the benefit seen with regard to TVR in nondiabetic patients was not apparent in the diabetic subgroup (hazard ratios 1.4 vs 0.78 for diabetic vs nondiabetic patients at 6 months). In contrast, subgroup analysis in the EPISTENT trial[25] showed that whereas the benefit of abciximab treatment with regard to death or MI was similar in diabetic and nondiabetic groups (hazard ratios 0.45 and 0.48, respectively), the diabetic subgroup had a greater reduction in need for TVR at 6 months when compared to the nondiabetic subgroup (hazard ratios 0.46 and 0.98 respectively), and results from diabetic patients in the angiographic substudy showed a trend toward decreased rates of restenosis in this group. Subgroup analysis in the PRISM-PLUS study[26] also showed that the benefit of periprocedural GP IIb/IIIa antagonism with tirofiban was greater in diabetic than nondiabetic patients at 7 and 30 days with regard to death or MI, but not with regard to

Diabetic patients in the EPILOG study had a greater reduction of death or MI when compared to the nondiabetic subgroup with adjuvant therapy with abciximab.

Table 2
Summary of Reports of Treatment Effects of IIb/IIIa Inhibitors in Diabetic Patients

					Endpoints (%)							
		No. Patients			non-DM (drug)		non-DM (placebo)		DM (drug)		DM (placebo)	
Reference	Trial	DM	non-DM	F/U (d)	D/MI	TVR	D/MI	TVR	D/MI	TVR	D/MI	TVR
Kleiman et al[24]	EPILOG*	391	1708	180	6.9	15.4	10.0	18.9	4.1	19.1	14.8	15.5
Marso et al[25]	EPISTENT†	335	1268	180	5.4	8.8	11.0	9.0	6.2	8.1	12.7	16.6
Theroux et al[26]	PRISM-PLUS‡	362	1208	180					11.2		19.2	
Bhatt et al[27]	Meta-Analysis§ EPIC EPILOG EPISTENT	1462	5072	365	2.6¶		1.9¶		2.5¶	24.2	4.5¶	25.2
Roffi et al[28]	Meta-Analysis‖ PRISM PRISM-PLUS PARAGON A PARAGON B PURSUIT GUSTO-IV	6458	23072	30	3.0¶		3.0¶		4.6¶		6.2¶	

* Standard dose (SD) heparin and placebo vs SD heparin and abciximab.
† Stent and placebo vs stent and abciximab.
‡ Placebo and heparin vs tirofiban and heparin.
§ Placebo vs abciximab.
‖ Different IIb/IIIa antagonist used in different trials; see text for details.
¶ Death only.
DM, diabetes mellitus; D/MI, death or myocardial infarction; TVR, target vessel revascularization; F/U, follow-up.

refractory ischemia. Because of the small number of patients and/or events in these subgroup analyses, none was powered to examine an effect of GP IIb/IIIa treatment with regard to mortality.

Two meta-analyses have examined this question in the high-risk group of diabetics. The first was a pooled analysis of diabetic patients from EPIC, EPILOG, and EPISTENT,[27] three trials that studied abciximab in patients undergoing urgent or elective PCI. In the pooled analysis, 1-year mortality was 4.5% in the diabetic group receiving placebo versus 2.5% in the diabetic group receiving abciximab (P = .031). The corresponding mortality rates in the nondiabetic population were 2.6% with placebo and 1.9% with abciximab (P = .099). Thus periprocedural treatment with abciximab reduced mortality in the diabetic subgroup to mortality rates seen in nondiabetic patients receiving placebo. There also was a significant reduction of non-Q-MI (9.7%–4.0%; P < .001) with abciximab in the diabetic population, whereas rates for Q-wave MI were equal in the abciximab and placebo groups. TVR at 6 months was slightly reduced in the group receiving abciximab (24.2% vs 25.2%; P = .674), but the difference was not statistically significant. In a subgroup of high-risk patients with increased body mass index, hypertension, and DM, even more dramatic reductions in mortality (5.1%–2.3%; P = .044), MI (12.0%–7.1%; P = .024) and also rates of TVR (32.7%–25.7%; P = .002) were seen.

A pooled analysis of diabetic patients from trials examining the role of GP IIb/IIIa antagonists in ACS patients treated with an early conservative strategy[28] has recently become available. Diabetic patients were included from PRISM (tirofiban alone) and PRISM-PLUS (tirofiban plus heparin), PARAGON (lamifiban alone) and PARAGON B (lamifiban plus heparin), PURSUIT (eptifibatide

with or without heparin) and GUSTO-IV-ACS (abciximab plus heparin). Comparison of pooled diabetic patients showed a significant reduction in 30-day mortality with intravenous GP IIb/IIIa antagonism in the diabetic (6.2% vs 4.6%; $P = .007$) but not the nondiabetic (3.0% vs 3.0%) patients. The most marked mortality benefit was evident within the overall 20% of diabetic patients who underwent early PCI in these trials (4.0% vs 1.2%, $P = .002$). This benefit was consistent across all six trials, suggesting that all involved GP IIb/IIIa antagonists were effective.

GP IIb/IIIa Antagonists: A Comparison

Several differences exist with regard to structure, receptor affinity, and pharmacodynamics of the three most commonly used intravenous GP IIb/IIIa antagonists.

Pharmacodynamics

Abciximab (ReoPro), a chimeric monoclonal antibody, binds irreversibly to the β subunit of the activated GP IIb/IIIa platelet receptor on platelets. Eptifibatide (Integrilin), a cyclic heptapeptide, and tirofiban (Aggrastat), a nonpeptide tyrosine derivative, designated the "small-molecule" GP IIb/IIIa antagonists, reversibly bind the GP IIb/IIIa receptor to prevent cross-linking by fibrinogen. As a result, the half-life of platelet inhibition is prolonged with abciximab when compared to the small-molecule agents. Whereas platelet inhibition is completely reversed within 24 hours of cessation of drug infusion with either eptifibatide or tirofiban, occupation of the platelet GP IIb/IIIa receptors by abciximab exceeds 30% at 8 days and is detectable for up to 2 weeks after discontinuation of drug infusion. This difference in the kinetics of platelet inhibition may translate into a sustained clinical benefit even after completion of the abciximab infusion when compared to the small-molecule agents.[29]

Receptor Affinity and Specificity

Another difference between abciximab and the small-molecule agents is with regard to receptor affinity. The β subunit of the platelet GP IIb/IIIa receptor is shared by the $\alpha_v\beta_3$ (vitronectin) receptor, and abciximab and eptifibatide specifically inhibit $\alpha_v\beta_3$.[30] Animal studies show that the vitronectin receptor is expressed on activated endothelial and smooth muscle cells and that

Main Points

- Cardiovascular death is increased 2- to 4-fold in patients with diabetes mellitus (DM) when compared to nondiabetic patients.
- Changes in platelet reactivity associated with DM are central to the prothrombotic state observed in these patients.
- Platelet size, degranulation, and synthesis of thromboxane derivatives mediating further platelet activation are increased in DM, whereas platelet-mediated vasodilation is impaired.
- Platelets in diabetic subjects appear to be in an activated state even in the absence of vascular injury, as shown by greater expression of the fibrinogen-binding glycoprotein (GP) IIb/IIIa receptor.
- The CAPRIE trial found that clopidogrel reduced the rate of vascular death, MI, stroke, and rehospitalization for ischemic events only moderately in the overall study population but at a higher rate in the diabetic population.
- Analysis from the EPILOG trial showed that diabetic patients in this study had a greater reduction of death or MI when compared to the nondiabetic subgroup with adjuvant therapy with abciximab.
- Subgroup analysis in the EPISTENT trial showed that the diabetic subgroup had a greater reduction in need for target vessel revascularization at 6 months when compared to the nondiabetic subgroup; results from diabetic patients in the angiographic substudy showed a trend toward decreased rates of restenosis.
- Subgroup analysis in the PRISM-PLUS study showed that the benefit of periprocedural GP IIb/IIIa antagonism with tirofiban was greater in diabetic than nondiabetic patients at 7 and 30 days with regard to death or MI, but not with regard to refractory ischemia.
- A pooled analysis of diabetic patients from the EPIC, EPILOG, and EPISTENT trials found that 1-year mortality was 4.5% in the diabetic group receiving placebo versus 2.5% in the diabetic group receiving abciximab.
- The ACC/AHA 2002 guidelines for the management of ACS recommend the use of abciximab in diabetic patients undergoing stent implantation.

blockade of the receptor decreases intimal hyperplasia and late vessel lumen loss after balloon injury or stenting. Abciximab also has affinity for the MAC-1 (CD11b/18) receptor, which mediates margination of leukocytes to endothelial cells and transmigration across the endothelial layer. Leukocyte-endothelial interactions are important in atherosclerotic plaque development, and leukocyte-derived cytokines may play a role in interstitial and smooth muscle cell proliferation. It is important to remember that the significance of these "pleiotropic" effects of abciximab for reduction of clinical restenosis is not known. Differences between individual GP IIB/IIIa antagonists may well be explained by the degree of inhibition of platelet GP IIb/IIIa receptors alone, decreasing the amount of mural thrombus formation and release of platelet-derived prothrombotic and growth factors.

TARGET demonstrated superiority of abciximab over tirofiban with regard to a composite endpoint of death, MI, or urgent TVR at 30 days.

GP IIb/IIIa Antagonism in a Setting of Elective PCI

Adjuvant therapy with GP IIb/IIIa antagonism has been shown to be beneficial in the setting of elective PCI in the overall population, and it is in this setting that the only head-to-head comparison of two agents has been performed. The TARGET randomized trial compared tirofiban to abciximab.[31] TARGET demonstrated superiority of abciximab over tirofiban with regard to a composite endpoint of death, MI, or urgent TVR at 30 days (6.0% vs 7.6%; $P = .038$), and trends in each of the components of the composite endpoint favored abciximab in this study. No particular information with regard to the diabetic population in this trial has been published, but procedural success rates of percutaneous coronary revascularization with or without stenting in patients with stable coronary disease are known to be similar in the diabetic compared to the nondiabetic subgroups. When compared to nondiabetic patients however, those with DM are at increased risk of in-hospital morbidity and mortality, including MI, acute and subacute stent thrombosis, and urgent target vessel revascularization.[4,32] Long-term follow-up also shows that rates of restenosis are markedly increased in the diabetic patient population, and repeat revascularizations are commonly necessary.

When comparing CAB to PCI in patients eligible for either technique, most trials to date (BARI, EAST, CABRI, ARTS) have found that the diabetic subgroup has better long-term survival and a decreased need for repeat procedures with coronary bypass surgery. In BARI this benefit was seen especially in the subset of diabetic patients receiving an arterial bypass graft.[4,33] Reasons for this finding may be the more complete revascularization by CAB when compared to PCI and the reduction in fatality rates of recurrent MI because of collateral coronary perfusion achieved with CAB.[34] Rates of stenting or adjuvant antithrombotic therapy with PCI were low in these trials when compared to rates of use in contemporary practice in the United States, and doubts remain whether the results from these trials hold true in the face of recent developments in percutaneous technology.

It is important to note that most of the benefit incurred by the combination of PCI and adjuvant GP IIb/IIIa inhibition is evident within 30 days of the procedure. The rate of events beyond this time frame continues to rise at a frightening slope in diabetic patients, and no long-term effect of periprocedural use of adjuvant agents is evident in any of the studies cited above. In contrast, medical therapy with ACE inhibition, lipid-lowering agents, and intensive glycemic control all have well-documented efficacy in reducing long-term morbidity and mortality in diabetic patients. There is also increasing information that agonists of the peroxisome-proliferator-activator receptor γ, used as insulin sensitizing treatment in DM, decrease coronary restenosis.[35] Several recent observational studies remind us that treatment rates with these modalities are well below the desired level.[36]

Conclusions

In summary, diabetic status is associated with a marked increase in prevalence of CAD, and patients with diabetes and CAD have at least twice the morbidity and mortality of patients with CAD alone. The prothrombotic state associated with metabolic changes in DM, mediated in large part by changes in platelet reactivity, has an important role in the observed morbidity and mortality in this disease state. Platelet inhibition with intravenous glycoprotein IIb/IIIa inhibitors has been shown to reduce morbidity and mortality in patients undergoing PCI for acute coronary syndromes. Diabetic patients appear to derive an even greater relative benefit from treatment. Attention to appropriate medical management of the diabetic patient with coronary

artery disease will have great impact on long-term outcome in this high-risk subgroup. ■

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