Management of Coronary Artery Disease: Therapeutic Options in Patients With Diabetes

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OBJECTIVES
The aim of this review is to discuss the particularities of coronary artery disease (CAD), the effect of intensive medical management and the outcome of percutaneous and surgical revascularization in patients with diabetes mellitus (DM).

BACKGROUND
CAD represents the leading cause of death in patients with DM. Numerous clinical, biological and angiographic risk factors have been shown to be associated with CAD in diabetic patients.

METHODS
Metabolic abnormalities in patients with DM including insulin resistance, hyperglycemia and dyslipidemia are briefly discussed. Then the potential roles of medical management and of percutaneous and surgical coronary revascularization are more extensively reviewed.

RESULTS
More vigorous control of hyperglycemia, hyperlipidemia, hypertension and other risk factors may be of crucial importance for risk reduction. Despite remarkable progress in recent years, the choice of a coronary revascularization strategy remains a challenge in these patients. Diabetic patients with CAD are predisposed to higher cardiovascular events after balloon angioplasty. Whether stenting and new antiplatelet drugs improve the results of percutaneous revascularization in this population needs further evaluation. The superiority of the surgical approach is also not definitely established. Therefore, many aspects of coronary revascularization are still unclear in these patients.

CONCLUSIONS
The results of ongoing randomized trials comparing multiple coronary stents to bypass surgery will likely provide some answers to our questions and additional randomized trials evaluating intensive diabetic control with or without coronary revascularization are needed to determine the best therapeutic approach in these patients. (J Am Coll Cardiol 2000;36:355–65) © 2000 by the American College of Cardiology

Diabetes mellitus (DM) is associated with a markedly increased prevalence of coronary artery disease (CAD). The overall prevalence of CAD, as assessed by various diagnostic methods, is as high as 55% among adult patients with DM, compared with 2% to 4% for the general population (1). Diabetes mellitus also represents an independent risk factor for increased mortality and morbidity (1–4). The cardiovascular mortality rate is more than doubled in men and more than quadrupled in women who have DM, compared with their nondiabetic counterparts (2,4), and post-MI prognosis is also worse in these patients (5–8). Moreover, DM is a recognized risk factor for poor outcome after either percutaneous (9–17) or surgical (18–22) coronary revascularization. Yet, up to 25% of patients referred for such procedures are diabetics (9–13,15,22–27). In spite of tremendous recent progress in these procedures, the optimal therapeutic strategy in diabetics remains controversial (14,17).

This review describes specific aspects of CAD in diabetics, particularly its clinical, angiographic, metabolic and biological features. It also discusses the effects of intensive medical management as well as early and late outcome after percutaneous transluminal coronary angioplasty (PTCA) and coronary artery bypass grafting (CABG) in an attempt to determine an optimal therapeutic strategy in this patient population.

Particularities of CAD in patients with DM. Several clinical, angiographic and biological features are associated with CAD in diabetic patients; they constitute potential risk factors and confer a poor prognosis (4–47, Table 1). Endothelial dysfunction (31–37), platelet and coagulation abnormalities (38–46) and metabolic disorders (48–72) associated with DM play a major role in the accelerated atherosclerotic process and in the formation of coronary thrombosis, and they contribute substantially to the complex healing process after arterial wall injury. Angiographic features related particularly to diffuse and distal coronary disease may lead to incomplete revascularization or increase the risk of surgical or percutaneous intervention in these patients (9–22). The risk of morbidity and mortality is also increased by several unfavorable clinical characteristics that are more common in diabetic patients (6,9,11,13,26–28).

Metabolic abnormalities associated with DM. INSULIN RESISTANCE. This metabolic syndrome, first described by Reaven, has been proposed as a unifying concept in an attempt to explain the different abnormalities frequently observed in patients with non-insulin-requiring DM (NIDDM) (48,49). It regroups hyperinsulinemia and several cardiovascular risk factors for CAD, including abnormal lipid profile, impaired glucose tolerance, hypertension and...
upper-body obesity (48,49). Increased plasminogen activator inhibitor-1 (PAI-1), reduced vasodilatory response to acetylcholine and the presence of microalbuminuria have also been described as part of this syndrome (50). The effect of hyperinsulinemia on the occurrence of CAD has been studied in various large prospective studies, but as yet, no unequivocal relationship has been established (51–54). A meta-analysis done by Ruige et al. (53), regrouping data from 12 prospective studies evaluating this association, found that hyperinsulinemia was a weak risk indicator for CAD and that the relationship was influenced by patients’ ethnic background and the type of insulin assay involved in these studies. Many cross-sectional studies have indicated that insulin resistance is associated with ultrasonographically or angiographically assessed atherosclerosis even in the absence of other risk factors (55–58). However, there is still controversy about the mechanisms by which the insulin resistance syndrome appears to induce, or at least enhance, atherosclerosis. This syndrome may be related to common cardiovascular risk factors or may be directly accelerated by hyperinsulinemia (44,50,52,59). Reaven hypothesized that insulin resistance and compensatory hyperinsulinemia might be the primary events causing hypertension, leading subsequently to an increased risk of CAD (59). However, the exact role of insulin remains controversial because epidemiological and experimental data suggest that insulin does not accelerate atherosclerosis (58,60). Moreover, recent data suggest that impaired microvascular function may be a central mechanism linking insulin sensitivity to increased blood pressure, and therefore to macrovascular disease in insulin resistance states (61).

HYPERGLYCEMIA. Traditional risk factors account only for 25%–50% of the increase in risk of CAD in diabetics (62). Thus, there can be little doubt that hyperglycemia and lipid abnormalities associated with DM play an important role in the pathogenesis of CAD in these patients. Several prospective studies have reported that poor glycemic control predicts CAD risk in diabetic patients (63–65). The important Finnish study of Lehto et al. (63) in more than 1,000 diabetic patients showed that the simultaneous presence of high fasting blood glucose levels and abnormal lipid profile is associated with a threefold increase in the risk of CAD mortality and morbidity at seven years. Hyperglycemia appears to be involved in each step of the atherosclerotic process. Acutely it attenuates endothelium-dependent vasodilation in humans in vivo (66) and leads to adverse modifications in lipid (32,62,67,68) and coagulation factors (43,62). Chronic hyperglycemia can glycosylate proteins and damage the kidneys, leading to vascular damage and secondary hypertension (32,44,62). It may also exert direct toxic effects on the vasculature, potentiating the development of atherosclerosis (36,44). Finally, there is unequivocal evidence that hyperglycemia interacts with other CAD risk factors to exacerbate the risk of CAD mortality (2).

DYSLIPIDEMIA. Hypertriglyceridemia associated with atherogenic, small and dense low-density lipoprotein (LDL) cholesterol and decreased levels of high-density lipoprotein (HDL) cholesterol are the most common abnormalities in type II DM (44,67). Triglycerides’ baseline levels change with the development of diabetes, and they are correlated with levels of fasting hyperglycemia; control of hyperglycemia improves but does not normalize these abnormalities (68). Although there is still no consensus on the best marker of CAD in diabetics (44,67,69), strategies based essentially on LDL-cholesterol reduction in these patients have recently provided unequivocal arguments for the role of these abnormalities in diabetic vasculopathy (44,67,69–72).

In summary, metabolic abnormalities associated with DM play an important role in the formation and accelera-

### Table 1. Potential Risk Factors Associated with Diabetes Mellitus

<table>
<thead>
<tr>
<th>Clinical</th>
<th>Biological</th>
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<tr>
<td>Older patients (6,9,26,28)</td>
<td>Endothelial dysfunction (31,32) with reduced coronary flow reserve (33–35)</td>
</tr>
<tr>
<td>Female gender (6,9,11,27,28)</td>
<td>Endothelial cell multiplication and migration abnormalities (36,37)</td>
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<tr>
<td>Obese (6,9,11,26)</td>
<td>Increased platelet activity (38–40)</td>
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<tr>
<td>High prevalence of high blood pressure (9,11,13,26,28)</td>
<td>Increased thromboxane A2 secretion (42)</td>
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<td>More severe angina (9,13)</td>
<td>Increased platelet activated fraction (41)</td>
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<tr>
<td>Congestive heart failure antecedents (9,11,13,27)</td>
<td>Higher fibrinogen and factor VII levels (43)</td>
</tr>
<tr>
<td>Previous MI (6,13,27,28)</td>
<td>Lower antithrombin III and plasma fibrinolytic activity (43)</td>
</tr>
<tr>
<td>Previous CABG (6,26,28)</td>
<td>Role of insulin and insulin-like growth factor (32,44)</td>
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<tr>
<td>Worse post-MI prognosis (4–8)</td>
<td>High plasminogen activator inhibitor 1 (45,46)</td>
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<tr>
<th>Angiographic</th>
<th>CAD = coronary artery disease; CABG = coronary artery bypass graft; MI = myocardial infarction.</th>
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<td>Diffuse and distal CAD (6,13)</td>
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tion of atherosclerosis. Their control can possibly exert a notable benefit in CAD prevention in these patients.

Management of CAD in patients with DM. It has been shown that, even without prior myocardial infarction (MI), diabetic patients have the same level of cardiovascular risk as nondiabetics having sustained an MI (73), suggesting perhaps that all type II diabetic patients should undergo secondary prevention. However, there is also substantial evidence that most patients with DM do not receive optimal recommended treatment (74,75), especially regarding the use of lipid-lowering drugs and angiotensin-converting enzyme inhibitors.

BEHAVIORAL RECOMMENDATIONS. Cigarette smoking is an independent predictor of mortality in patients with DM (2,3,76). It is particularly hazardous in diabetic women with insulin-requiring DM (IRDM) because it more than doubles their risk of cardiac mortality (76). Cigarette smoking cessation is strongly recommended for all diabetic patients (2,4,75,76). Weight loss and increased physical activity are also strongly indicated because of their beneficial effects in improving lipid profile, insulin resistance, glycemic control, hypertension, obesity, and platelet coagulation abnormalities (75,77).

CONTROL OF HYPERGLYCEMIA. Recent studies show that intensive glycemic control is highly effective in preventing and retarding microvascular and, to a lesser degree, macrovascular complications in both type I and type II DM (78–81). The Diabetes Control and Complications Trial (DCCT) provided definite evidence of major reduction in chronic microvascular complications among a group of type I diabetic patients with tight glycemic control (78) and suggested a potential beneficial effect of this strategy on macrovascular disease. Tight glycemic control reduced major macrovascular events by one-half in diabetics compared with conventionally treated patients (79). However, this reduction did not reach statistical significance. The randomized United Kingdom Prospective Diabetes Study (UKPDS) (80) has reported that, over 10 years of follow-up, intensive glycemic control by either insulin or sulphonylureas significantly reduced (by 25%) the risk of microvascular complications in NIRDM patients. Diabetes-related mortality and MI incidence were also reduced by 10% and 16% respectively, but these reductions did not reach statistical significance (80). A similar reduction was observed in diet-treated obese NIRDM patients taking metformin (81). In addition, a recent retrospective study has reported that optimal glycemic control in diabetic patients can favorably influence major cardiac events following PTCA (82).

LIPID-LOWERING THERAPY. Although no published studies have specifically investigated the effects of lipid-lowering therapy on the development of CAD in diabetic patients, some solid arguments support the efficacy of this therapy in primary and secondary prevention trials (69–72). A subgroup analysis of the Scandinavian Simvastatin Survival Study (4S) (70) indicated that, in diabetic patients with hypercholesterolemia, normal triglycerides and established CAD, lowering LDL-cholesterol levels with the HMG CoA reductase inhibitor simvastatin was associated with a marked reduction of major CAD and related atherosclerotic events. Five-year mortality was decreased by 43% in diabetic versus 29% in nondiabetic patients. Similar outcomes were reported by the Cholesterol And Recurrent Events (CARE) trial (71), evaluating the benefits of pravastatin in patients with average cholesterol levels after MI. There was a greater benefit of pravastatin in diabetics than in nondiabetics, with greater relative risk reduction for CAD major events and for revascularization procedures during a five-year follow-up. Finally, in the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) trial (72), pravastatin therapy also showed a 19%, albeit not statistically significant, reduction of the composite end point of CAD-related death and MI during a 6.1-year follow-up in a subgroup of diabetics with a history of MI or unstable angina and with a broad range of initial cholesterol levels.

CONTROL OF HYPERTENSION. Recent studies have shown that adequate blood pressure control markedly reduced major cardiovascular events related to macrovascular complications (83–86). An important beneficial effect on microvascular disease was also demonstrated in the UKPDS study, where blood pressure was controlled by beta-blockers or angiotensin-converting enzyme inhibitors (84). However, there is still some uncertainty concerning blood pressure levels needed for maximal benefit, as well as the optimal drug classes to be used in these patients (44,83,87). The recently revised guidelines for the treatment of hypertension by the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure recommended a level around 130/85 mm Hg for diabetic patients, which is compatible with the smallest decline in renal function in these patients (83,87). First-line therapy should be based on cardioselective beta-blockers and diuretics that have been convincingly shown to reduce mortality and morbidity in patients with diabetic nephropathy and in NIRDM patients (83). Angiotensin-converting enzyme inhibitors and calcium channel blocking agents can be added as second-line therapy (83,87).

Other therapeutic considerations. THROMBOLYTIC AGENTS. Recent studies have confirmed that DM is a major independent predictor of acute and long-term post-MI mortality and morbidity, particularly in women and in IRDM patients (5–8). Numerous factors, including more severe CAD, associated comorbidity, metabolic derangements, silent ischemia and late or atypical presentation may contribute to a lesser use of fibrinolytic agents (88) and to a worse post-MI prognosis in these patients (5,6). An overview by the Fibrinolytic Therapy Trialists’ Collaborative Group (89), including 43,073 patients among whom 4,529 were diabetics, confirmed the benefit of thrombolysis in diabetic patients. The absolute reduction in mortality was
greater in diabetics than in nondiabetics (3.7% vs. 2.1%) despite a greater 35-day mortality rate in diabetics (13.6% vs. 8.7%). Diabetics also had a slightly greater absolute increase, albeit not statistically significant, in the risk of haemorrhagic stroke (0.6% vs. 0.4%), but vitreous hemorrhage was rare. Data from a recent British study suggest that retinopathy is not a contraindication to thrombolysis except in the presence of a recent vitreous hemorrhage (90).

INSULIN-GLUCOSE INFUSION. Long-term mortality in diabetic patients hospitalized for acute MI may be reduced by an insulin-glucose infusion followed by multidose insulin treatment, as demonstrated recently by a Swedish prospective study (91,92). Insulin therapy appears to beneficially influence all cardiovascular causes of mortality, with a particular impact on fatal reinfarction and left ventricular failure (91). Another recent study reported a favorable mortality trend following glucose-insulin-potassium infusion in acute MI patients given reperfusion therapy (93).

ANTIPLATELET AGENTS AND ANTICOAGULANTS. Platelet and coagulation abnormalities contribute to CAD in diabetics (5,38,62). Although more clinical trials are needed, current evidence supports antiplatelet therapy for diabetics. The meta-analysis of the Antiplatelet Trialists’ Collaboration Group included 47,000 patients (10% diabetes) and reported an important benefit of aspirin therapy in diabetics with or at an increased risk for vascular disease (94). The combined end point of vascular death, MI or stroke was 22.3% in the control group and 18.5% in those receiving aspirin. The magnitude of this benefit in diabetics was similar to that observed in nondiabetics, without an excess in bleeding complications. Recent trials have shown that low-molecular-weight heparins are more effective than placebo and as beneficial as or more beneficial than unfractionated heparin in the acute treatment of patients with unstable angina or non-Q-wave MI (95–97). In general, these studies show a consistent treatment effect among patient subgroups, and the ESSENCE trial in particular has shown comparable benefits in patients with or without DM (98). In the TIMI 11B trial, the superiority of enoxaparin over unfractionated heparin in preventing death and cardiac ischemic events was greatest in high-risk patients (99). In the GUSTO IIIB trial, hirudin, a direct thrombin inhibitor, was modestly more effective than unfractionated heparin in the treatment of diabetic patients with acute coronary syndromes and was not associated with an increased risk (100).

Recent clinical trial evidence suggests that glycoprotein IIb/IIIa inhibitors reduce the early and mid-term incidence of death, MI and recurrent angina in patients with unstable angina or non-Q-wave MI (101–105). In PRISM-PLUS, the reduction in clinical events in the group receiving tirofiban plus heparin compared with that receiving heparin-only was important for both DM and non-DM subgroups (102). However, as compared with heparin therapy only, combination therapy reduced the secondary end point of death and MI to a much greater extent (88% versus 43%, p = 0.005) in diabetics than in the overall study population (103). In the PURSUIT study, death and nonfatal MI were also significantly reduced by eptifibatide therapy as compared with placebo in both DM and non-DM subgroups (104). However, compared with nondiabetics, 30-day mortality was significantly more reduced in IRDM patients (105). Finally, a meta-analysis pooling all diabetic patients in 10 recent clinical trials of the effects of glycoprotein IIb/IIIa antagonists showed that diabetics had twice the absolute reduction in event rates seen in nondiabetics (106). There was a trend favoring a DM interaction that, however, did not reach statistical significance. The efficacy and benefits of glycoprotein IIb/IIIa inhibitors in diabetic patients undergoing percutaneous coronary interventions are discussed in the next section.

BETA-BLOCKERS. Pooled trial results of beta-blockers given soon after MI have shown a 37% mortality reduction in diabetics compared with 13% in all treated patients, and a similar beneficial decrease in the incidence of reinfarction (107). These drugs are also effective in reducing mortality when given long-term after MI (107,108).

ANGIOTENSIN-CONVERTING ENZYME INHIBITORS. Sub-group analysis of several studies has suggested that angiotensin-converting enzyme inhibition in diabetics with acute MI is associated with larger reductions in short-term mortality and occurrence of congestive heart failure than in nondiabetic patients (109,110). Similar data support an important long-term benefit of these drugs in diabetics suffering from acute MI with left ventricular dysfunction (111,112). Recent results from the Danish TRACE study showed that angiotensin-converting enzyme inhibition after MI complicated by left ventricular dysfunction in diabetics saved lives and substantially reduced the risk of progression to severe heart failure (112). Furthermore, diabetic patients represent fairly large subgroups of congestive heart failure patients in whom angiotensin-converting enzyme inhibitors were extensively evaluated. In these studies, angiotensin-converting enzyme inhibitors often reduced mortality and morbidity even more in diabetic than in nondiabetic patients (113).

The final results of the Heart Outcome Prevention Evaluation (HOPE) study were reported recently (114,115). In this trial, a predefined subgroup of 3,657 middle-aged diabetic patients at risk for renal and cardiovascular disease was randomized to receive the angiotensin-converting enzyme inhibitor ramipril or a placebo for four years. The primary end point of cardiovascular mortality, MI and stroke was reduced by 24% and mortality alone was reduced by 38% in the angiotensin-converting enzyme inhibitor group. Diabetic complications and microvascular disease were reduced by 17%. An important finding of this trial is that the reduction of outcome events was similar in patients with or without left ventricular dysfunction (115).

In summary, data from recent prospective studies have
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provided solid arguments for intensive glycemic, lipid and blood pressure control in diabetics. In addition, several evidence-based pharmacological treatment strategies have been convincingly shown to confer major benefit on morbidity and mortality in diabetic patients with CAD. Additional randomized studies should evaluate the role of tight metabolic control on reduction of major cardiovascular events with or without coronary revascularization.

**Percutaneous coronary revascularization in patients with symptomatic CAD and DM. ROLE OF BALLOON ANGIOPLASTY.** *In-hospital outcomes.* Angiographic success rates of balloon PTCA in diabetics (85%–96%) are usually similar to those observed in nondiabetics (9,13). The composite end point of mortality, nonfatal MI and urgent revascularization was respectively 11.0% in diabetics versus 6.7% in nondiabetics in the National Heart, Lung, and Blood Institute Registry (p < 0.01), with higher mortality rates in diabetics (3.2% vs. 0.5%) (13). However, lower mortality rates (<0.5%), comparable with those of nondiabetics, were reported by other groups (9,11,15). There were also evident trends toward higher rates of urgent revascularization (9–11,13) and acute coronary occlusion in diabetics (13).

**SHORT- AND LONG-TERM FOLLOW-UP.** It is well recognized that restenosis rates may be very high (up to 63% in some series) after PTCA in diabetics (14,116). Late clinical outcome after PTCA in these patients is also often unfavorable. Stein et al. (9) reported that five-year MI-free survival was lower and that additional revascularization was more frequently needed in 1,133 diabetics versus 9,300 nondiabetics undergoing PTCA. Similarly, Kip et al. (13) found that nine-year mortality was twice as high in diabetic patients treated by PTCA (35.9% vs. 17.9% in nondiabetics), with significantly higher incidences of MI and repeat revascularization. In the Bypass Angioplasty Revascularization Investigation (BARI), post-PTCA five-year survival was 73.3% in diabetics versus 91.3% in nondiabetics (p < 0.0001). The benefit of CABG was most evident in IRDM patients (10,11,16). Similar results were observed in the Coronary Angioplasty versus Bypass Revascularization Investigation (CABRI) (12), and a trend toward superiority of CABG was observed in the BARI registry, even though CAD was less extensive in PTCA than in surgical patients (16,17). On the other hand, better CABG results were not observed in the small subgroups of diabetics enrolled in the first Randomized Intervention Treatment of Angina One (RITA-1) study (23) and in the Emory Angioplasty versus Surgery Trial (EAST) (24). Five-and 10-year survival rates were similar in diabetic patients undergoing PTCA versus CABG in the large nonrandomized series (n = 2,639) reported by Weintraub (15), and comparable six-year results were also reported by Gum et al. in 525 diabetics (117). Inability to fully revascularize all ischemic territories, high restenosis rates and progression of atherosclerosis leading to repeat revascularization procedures are the most frequently suggested reasons for the long-term unfavorable results (9,13–15,17,117,118).

In summary, in the majority of published series, PTCA in diabetic patients is feasible with high angiographic success rate. However, DM appears to be predictive of higher risk of in-hospital complications, substantially increased restenosis rates and relatively poor long-term outcome.

**ROLE OF CORONARY STENTING.** Most studies evaluating stenting in diabetics are retrospective, and except for the series of Elezi et al. (n = 715 diabetics) (28), have enrolled relatively small numbers of patients (116–121).

**IN-HOSPITAL OUTCOMES.** Angiographic success rates of stenting in diabetics (92%–100%) are often similar to those observed in nondiabetic patients (119–122). The composite end point of mortality, nonfatal MI and urgent CABG, ranging from 0.7% to 6.75%, is similar in diabetic versus nondiabetic patients in most series (28,119). These inhospital complications after stent implantation compare favorably to the 3% to 11% rates reported after balloon PTCA in diabetics (9,13,15). However, Elezi et al. (28) have found a clear trend toward higher rates of subacute stent thrombosis in diabetics (3.2% vs. 2.0% in nondiabetics, p = 0.06). A similar trend was reported by Abizaid et al. (119) in the IRDM patients.

**SHORT- AND LONG-TERM FOLLOW-UP.** Ranging from 24% to 40%, angiographic restenosis rates after stenting in diabetics were higher than the 20% to 27% rates observed in nondiabetic patients (28,120). However, some reports have found more favorable results in diabetics (116,122). In the series reported by Van Belle et al. (116), restenosis rates were similar (25% vs. 27%) after stenting, but different (63% vs. 32%) after PTCA in diabetic versus nondiabetic patients.

In addition, major cardiac event-free survival is often lower in diabetics (28,29,119,120); Elezi et al. (28) reported a one-year event-free survival in diabetics of 73.1% versus 78.8% for nondiabetics (p < 0.001). However, long-term outcome after stenting is not influenced by diabetic status, according to other groups (116,122). Additional revascularization was increased in target or new lesions in stented diabetics (28,121), especially in the IRDM patients (119).

On the other hand, although some reports suggest that multivessel coronary stenting is feasible in carefully selected patients (with or without DM) with a high success rate, low in-hospital major complications and favorable long-term results (123,124), data concerning the role of this therapeutic strategy in a specific diabetic population are not available. In summary, stenting is feasible in diabetics with favorable procedural and in-hospital success rates. However, angiographic restenosis rates and long-term outcome after stenting may be worse in this population, particularly in IRDM patients.

**MECHANISMS OF RESTENOSIS AND ROLE OF INSULIN.** The basic mechanisms responsible for restenosis after PTCA or stenting in diabetics are unclear. The metabolic, hemato-
logic and biological abnormalities observed in these patients all participate in the complex restenotic reaction following vessel injury (32). These patients’ coronary lesions are more often associated with thrombus formation at angioscopy (47), a predictor of late coronary occlusion after PTCA (125). A recent study has shown that vessel occlusion is a frequent mode of restenosis in diabetics undergoing conventional balloon angioplasty (126). Moreover, intravascular ultrasound data suggest that intimal hyperplasia is the main reason for increased restenosis in both stented and nonstented lesions in diabetics (127), and several studies have found angiographic or ultrasound evidence consistent with this mechanism (28,119,121). However, the results of some groups reporting favorable restenosis rates after stenting in diabetics do not appear to support the excessive intimal hyperplasia hypothesis (116,122,126).

On the other hand, the multiple effects of insulin can contribute to the pathogenesis of restenosis by inducing smooth muscle cell migration and proliferation and extracellular matrix production (32,44). Hyperinsulinemia can lead to coronary vasoconstriction (128,129) and to thrombus formation through stimulation of plasminogen-activator inhibitor-1 and attenuation of fibrinolytic activity (45,46). The poor short- and long-term results of coronary revascularization in some IRDM patients also emphasize the major role of this hormone (9,11,15,16,119). In addition, hyperinsulinemia in patients with impaired glucose tolerance and mild DM induces greater intimal hyperplasia after stent implantation (130), and treatment by triglitazone, an insulin sensitizer, reduces this intimal proliferation (131).

In summary, intimal hyperplasia and late vessel occlusion are two potential mechanisms implicated in the complex phenomenon of restenosis following angioplasty in diabetics. However, further investigations should determine the mechanisms of this reaction and evaluate the pejorative role of insulin in restenosis.

**ROLE OF GLYCOPROTEIN IIb/IIIa PLATELET RECEPTOR ANTAGONISTS.** Data related to the usefulness of glycoprotein IIb/IIIa receptor antagonists in diabetic patients are limited to subgroup analyses from recent prospective randomized trials. At least six trials of the effects of glycoprotein IIb/IIIa inhibitors in patients undergoing coronary interventions have been reported, four with abciximab, one with eptifibatide and one with tirofiban (25–27, 132–134). In the EPIC trial, abciximab therapy showed a 35% reduction in the primary end point of death, MI and urgent revascularization at one month, with a similar risk reduction in DM and non-DM patients (25). At three years, however, the clinical benefits were sustained in the total population (135), whereas diabetics experienced a progressive deterioration with more clinical events than nondiabetics (136). In the EPILOG trial, abciximab therapy in diabetic patients undergoing elective PTCA led to a significant reduction of death and MI at 30 days and at six months (26). However, target vessel revascularization (TVR) at six months was reduced only in the nondiabetic subgroup, and diabetics treated with abciximab and standard-dose heparin had a marginally greater benefit than those assigned to abciximab and low-dose heparin. Pooled data from the EPIC, EPILOG and EPISTENT trials showed that abciximab decreases the one-year mortality of diabetic patients to that of placebo-treated nondiabetic patients (157). In the IMPACT-II trial, treatment with eptifibatide during coronary intervention reduced rates of early abrupt closure and ischemic events at 30 days; the benefit of therapy was similar in patients with and without DM (133). In the RESTORE trial, tirofiban reduced early cardiac events in patients undergoing PTCA for acute coronary syndromes, but this effect was no longer statistically significant at 30 days (134). Twenty percent of all patients in this trial were diabetics; however, no subgroup analysis was reported.

The EPISTENT trial was the largest study evaluating the benefit of abciximab therapy in patients undergoing coronary stenting (27,138). It demonstrated a significant reduction of major cardiac events at 30 days and at six months in the abciximab groups compared with the stent-plus-placebo group. In addition, the combination of stenting and abciximab therapy among diabetic patients resulted in a significant reduction in six-month rates of death, MI and TVR compared with stent plus placebo or balloon angioplasty plus abciximab therapy (138). The substantial TVR reduction associated with a significant increase in angiographic net gain and a trend toward a decrease in late loss index in stented diabetics treated by abciximab versus those treated with placebo suggests for the first time a potential additional benefit of abciximab in reducing restenosis in stented diabetics (138, 139). In this context, the ERASER trial has provided intravascular ultrasound data suggesting that, compared with placebo, abciximab decreases neointimal proliferation in stented diabetics but not in the overall study population (140).

In summary, the EPISTENT trial demonstrates a significant reduction of major ischemic cardiac events and TVR in stented diabetic patients and confirms the net benefit of glycoprotein IIb/IIIa antagonists in this population. However, further investigations are needed to explain the interaction of abciximab with DM status and whether a similar reduction in coronary restenosis will be observed with other glycoprotein IIb/IIIa antagonists.

**CABG in patients with symptomatic CAD and DM.** Diabetes mellitus is a recognized risk factor for poor early and late outcome after CABG (18–22), and is also identified as an important predictor of progression and occlusion of bypassed and nonbypassed coronary segments (20,24).

As discussed above, the BARI randomized trial (10,11), and to a lesser extent the BARI registry (16), have shown that patients with DM and multivessel disease assigned to an initial strategy of CABG have a striking reduction in cardiac mortality compared with PTCA. Post-hoc analyses were also performed in subsets of diabetic patients in three smaller randomized trials comparing PTCA and CABG.
Results similar to those of BARI were obtained in one trial (12), but CABG outcome was not superior to that of PTCA in the two other trials (23,24). Large retrospective databases of diabetic patients who have undergone coronary intervention procedures may not be suitable to compare CABG and percutaneous intervention because patients in the two treatment groups are almost certainly not comparable in terms of prognosis. Be that as it may, two large databases of patients with multivessel CAD from Emory (15) and Duke (22) university studies assessing the results of revascularization procedures in diabetic patients have been reported. In the Emory study, only the IRDM subgroup treated by PTCA had lower five- and 10-year survival rates than the CABG group (15). In the Duke study, DM was associated with worse five-year survival, but the effect of DM on prognosis was similar in both treatment strategies (22).

In patients undergoing CABG, the superiority in terms of long-term survival of internal mammary artery (IMA) conduits to the left anterior descending coronary artery over autologous saphenous vein grafts is well established (141). Therefore, it is not surprising that the benefit of CABG in the diabetic subgroup in BARI was confined to those receiving at least one IMA graft (10,11). Whether bilateral IMA grafting confers yet an additional benefit in these patients is not known, particularly because this technique carries a greater risk of sternal wound complications in diabetics than in nondiabetics (142–144). However, DM should not be an absolute contraindication to bilateral IMA use, which should be adjusted to the coronary bed needing revascularization and to the patient’s age (144).

In summary, the superiority of CABG over PTCA in diabetics is not well established. Conclusions drawn from the diabetic subgroup of the BARI trial must be confirmed in larger randomized trials.

Summary and future directions. The optimal strategy of coronary revascularization in diabetics remains to be determined. Many biological, hematological and metabolic abnormalities predispose diabetic patients undergoing percutaneous revascularization to a high incidence of in-hospital and long-term cardiovascular events, presumably because of incomplete revascularization, high restenosis rates and CAD progression. Whether stents will improve outcome in this population is still controversial, and prospective investigation of this issue is required. Moreover, the superiority of a surgical strategy over percutaneous revascularization in this population remains unproven. These conclusions were drawn from trials done at the end of the 1980s and beginning of the 1990s, when stents were emerging and the important class of GP IIb/IIIa inhibitors had not yet been developed. These two important catheter-based advances should have a positive influence on clinical outcome in future investigations, as suggested by the results of the diabetic subgroup in the EPISTENT study. Locally delivered ionizing radiation and gene therapy may also have a potential role in this high-risk population. Furthermore, treatment advances are not confined to interventional cardiology, as less invasive surgical techniques may offer advantages over conventional CABG. Final results from the two European randomized trials of stenting versus CABG (Arterial Revascularization Therapy Study [ARTS] and Stent or Surgery [SOS]) will probably shed some new light on coronary revascularization in diabetic patients. Moreover, the demonstrated benefit of strict glycemic, lipid and blood pressure control indicate that this management strategy should be routinely enforced in these patients and that their effect after coronary revascularization should be prospectively evaluated. Data from the planned BARI-II trial, which will randomize diabetic patients and will include coronary stenting as well as intensive glycemic and lipid control, should answer the major questions concerning therapeutic strategies in this population.

In conclusion, many aspects related to coronary revascularization in diabetics remain unclear, and further randomized investigations evaluating the latest new progress in percutaneous as well as surgical revascularization will help physicians make better therapeutic decisions. Until the results of ongoing and future trials are available, management of CAD in patients with DM will continue to pose a challenge to the medical profession.

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