Acute Myocardial Infarction in the Diabetic Patient: Pathophysiology, Clinical Course and Prognosis

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Although there have been significant advances in the care of many of the extrapancratic manifestations of diabetes, acute myocardial infarction continues to be a major cause of morbidity and mortality in diabetic patients. Factors unique to diabetes increase atherosclerotic plaque formation and thrombosis, thereby contributing to myocardial infarction. Autonomic neuropathy may predispose to infarction and result in atypical presenting symptoms in the diabetic patient, making diagnosis difficult and delaying treatment. The clinical course of myocardial infarction is frequently complicated and carries a higher mortality rate in the diabetic than in the nondiabetic patient. Although the course and pathophysiology of myocardial infarction differ to some degree in diabetic patients from those in patients without diabetes, much more remains to be known to formulate more effective treatment strategies in this high risk subgroup.

Since the advent of insulin therapy, mortality due to diabetes mellitus has diminished considerably. As morbidity and mortality related to ketoacidosis and infections have decreased, coronary artery disease has assumed a disproportionately larger responsibility for the morbidity and mortality experienced by patients with diabetes (1). Diabetic patients suffer from an excess of coronary artery disease and the course of acute myocardial infarction is often punctuated by complications in this group. There is a significant relation between diabetes mellitus and coronary vascular disease that creates important differences between the clinical course of acute myocardial infarction in these patients and that in patients without diabetes. This review will discuss the differences in the epidemiology, pathophysiology and treatment of acute myocardial infarction in diabetic compared with nondiabetic patients.

Epidemiology

Myocardial infarction and cardiovascular mortality. Epidemiologic data derived from the Framingham Heart Study demonstrate the increased incidence of heart disease in patients with diabetes and their poor prognosis. The cardiovascular mortality rate is more than doubled in men and more than quadrupled in women who have diabetes, compared with the rate in their nondiabetic counterparts (2). The relative risk of myocardial infarction is 50% greater in diabetic men and 150% greater in diabetic women. Similarly, diabetic men succumb to sudden death 50% more often and diabetic women 300% more often than do their age-matched nondiabetic counterparts (3). Acute myocardial infarction is said to account for as many as 30% of all deaths in diabetic patients (4). Among those with insulin-dependent diabetes, the cumulative mortality rate due to coronary artery disease is 35% by age 55, far higher than the corresponding rate of 4% to 8% for patients without diabetes cited in the Framingham data (5).

Incidence and extent of coronary artery disease. Diabetes is an independent risk factor for the development of coronary artery disease (6). The overall prevalence of coronary disease, as assessed by various diagnostic methods, is as high as 55% among adult patients with diabetes compared with 2% to 4% for the general population (6). Coronary atherosclerosis is not only more prevalent, it is also clearly more extensive in diabetic than in nondiabetic patients (7). At coronary angiography or autopsy, patients with diabetes have a higher incidence of double- and triple-vessel disease and a lower incidence of single-vessel disease than those of their nondiabetic counterparts (6,8). The incidence of severe left main coronary disease is also significantly higher (13% vs. 6%) in diabetic than in nondiabetic patients (9). In one large autopsy study, 91% of patients with adult onset diabetes and no known coronary heart disease had severe narrowing of at least one major coronary artery and 83% had severe two- or three-vessel involvement (9). In a group of adults of similar age without overt diabetes or known coronary heart disease, only 33% had severe single-vessel coronary narrowing and 17% had severe two- or three-vessel disease at autopsy (10). Whether coronary atherosclerosis is actually more "diffuse" or is merely expressed as a greater number of discrete stenoses is the subject of some debate (9,11). In the autopsy study mentioned, diabetic patients who died of...
coronary artery disease had more stenoses than did nondiabetic patients but the appearance of other arterial segments was similar between the two groups. However, another autopsy study found that patients with juvenile onset diabetes had a more diffuse form of coronary artery disease with at least half of the overall length of the epicardial coronary arteries narrowed by ≥50% whereas in nondiabetic patients <1% of the length was similarly involved (12).

Factors Favoring Myocardial Infarction in Patients With Diabetes

Acute infarction most often involves interruption of myocardial blood flow due to underlying atherosclerotic plaque with further lumen compromise by thrombus (13). Progression of atherosclerosis may occur through repeated plaque rupture and thrombosis in a repetitive cycle of injury and healing that results in lumen narrowing (14). Diabetes is associated with an increased propensity for both atherosclerotic plaque formation and intraluminal thrombosis, which may increase the likelihood of infarction.

Accelerated atherosclerosis and plaque rupture. Elevated serum lipid levels induce vascular damage and promote atherosclerosis. Pathologic studies of coronary vessels in patients after infarction indicate that lipid-rich plaques may be more likely to rupture than fibrous plaques (14). Compared with persons without diabetes, patients with diabetes or hypertension, or both, appear to have a greater number of such fissured plaques (15). Despite a preponderance of lipid abnormalities in patients with diabetes, the independent contribution of total cholesterol to coronary artery disease is approximately the same as that in patients without diabetes (16). The average total cholesterol level in the Framingham study was 245 mg/dl and similar in patients with and without diabetes (17). Patients with diabetes have higher levels of very low density lipoprotein cholesterol (VLDL) and triglycerides and lower levels of high density lipoprotein (HDL) cholesterol than do patients without diabetes, whereas levels of total and low density lipoprotein (LDL) cholesterol are not substantially different between the two groups (18). The significance of the diabetic patient's altered lipid profile as it relates to risk of coronary artery disease has not yet been defined.

As mentioned, hypertension has been associated with an increased tendency toward plaque fissuring, a major precursor to myocardial infarction (15) and hypertension is more common in diabetic than in nondiabetic patients (16). It is found in >50% of diabetic patients >45 years of age (16). Its prevalence is especially high in diabetic women and is a frequent accompaniment to diabetic nephropathy. Cardiovascular mortality in diabetic nephropathy is up to 37 times that of the general population, probably at least in part because of the associated hypertension (19-21).

Hyperinsulinemia, particularly common in noninsulin-dependent diabetes mellitus with insulin resistance, appears to be a risk factor for atherogenesis. Hyperinsulinemia even in the presence of normal glucose tolerance is associated with an increase in risk factors for coronary artery disease including low HDL cholesterol levels and hypertension (22). Hyperinsulinemia may also play a role in promoting atherosclerosis by causing smooth muscle cell proliferation and cholesterol synthesis and by increasing levels of growth hormone (23). Hyperglycemia alone has been suggested as a risk factor for atherosclerosis, though the level of hyperglycemia itself is not an independent risk factor for the development of coronary artery disease.

Patients with diabetes have elevated plasma and whole blood viscosity due to high levels of plasma proteins and increased red cell aggregation and possibly decreased red cell deformability (24,25). These effects are particularly evident during periods of metabolic derangement such as diabetic ketoacidosis and appear to be improved with better glycemic control. Increased shear forces due to high viscosity could enhance a tendency toward plaque rupture. In addition, these rheologic effects could contribute to infarct extension by impeding collateral coronary blood flow, particularly in areas with low blood flow at baseline.

Hematologic abnormalities favoring coronary thrombosis. Occlusive thrombus formation is likely a dynamic process that depends on a balance between those factors that favor clotting and those that oppose it. In diabetes, abnormalities relating to platelet function, coagulation, fibrinolysis and endothelial function have been described that may favor intraluminal thrombosis at the site of plaque fissuring or rupture.

Platelet aggregation is an essential step in occlusive thrombus formation. Recently, spontaneous platelet aggregation has been shown to predict recurrent infarction after myocardial infarction (26). Spontaneous and induced platelet aggregation have been shown to be higher in patients with (27-30) than in patients without diabetes and correlate with an increase in cardiovascular events (27). Diabetic platelets seem to synthesize thromboxane A2 in abnormally high amounts (31-34), a finding that would favor platelet aggregation and vascular spasm. Elevated thromboxane levels are most often found in diabetic patients with poor glycemic control or vascular complications (29). Platelet consumption is higher in diabetic patients (29) and two platelet-specific proteins, beta-thromboglobulin and platelet factor 4, thought to reflect in vivo platelet activation, may be elevated in these patients (25,29).

The time of onset of acute myocardial infarction in diabetic and nondiabetic patients has been shown to parallel the circadian variation in platelet reactivity in these patients. Whereas the population at large exhibits a prominent morning increase in onset of Q wave infarction coincident with their period of greatest platelet aggregability (35), among diabetic patients Q wave infarction may occur more evenly throughout the day (35a). Platelet reactivity in diabetic patients has been shown to be elevated consistently throughout the day (36), an observation supporting the hypothesis...
that this heightened platelet reactivity may have a causative role in the increased incidence of myocardial infarction in patients with diabetes.

Plasma fibrinogen levels are elevated in diabetic patients (29,37) and have been shown to correlate with myocardial infarction and sudden death in diabetic men (27). Factor VIII and factor VIII ristocetin cofactor antigen are elevated in diabetic patients as well (25,27,29). Fibrinopeptide A reflects in vivo thrombin activity and may also be elevated in diabetic patients (25,29,38). Endothelial dysfunction or damage in patients with diabetes results in deficient production of prostacyclin (29,39-41) and elevated levels of the procoagulant von Willebrand factor (25,27,29). Endogenous fibrinolysis has also been found to be deficient in these patients (29,37,38).

Metabolic factors. Numerous studies have examined the relation of type of therapy for diabetes to both the extent of coronary artery disease and the outcome after acute myocardial infarction. The majority of these studies indicate that treatment with oral hypoglycemic agents or insulin is associated with a poorer prognosis (42-47) and more extensive coronary disease than those of diabetes controlled by diet alone (48,49). Elevated glycosylated hemoglobin levels, which reflect inadequate long-term glycemic control, have also been shown to be associated with a higher mortality rate after infarction (46). Despite the evidence that poor long-term glycemic control is associated with a negative outcome, no study has convincingly demonstrated that improved glycemic control leads to better clinical outcome.

Role of autonomic neuropathy. The development of symptomatic autonomic neuropathy in diabetic patients is associated with a mortality rate of up to 50% 3 years after its onset (50). Sudden, possibly cardiac, death is responsible for up to 33% of these deaths (50). Cardiac parasympathetic nerve fibers are affected before sympathetic fibers, leading initially to a relative increase in sympathetic tone that results in tachycardia at rest and attenuation of the expected increase in heart rate and blood pressure with exercise (51,52). An absence of parasympathetic tone may also be responsible for exaggerated or inappropriate coronary vasoconstriction, which may produce or worsen ischemia. Sympathetic nervous system dysfunction is usually evident within 5 years of the diagnosis of parasympathetic dysfunction. The principal clinical manifestation of sympathetic dysfunction is postural hypotension. Autonomic neuropathy thus may lead to ischemia or infarction by several routes: increasing myocardial oxygen demand by increasing heart rate at rest, reducing myocardial blood flow by increasing coronary vascular tone at the site of a coronary stenosis, reducing coronary perfusion pressure during orthostatic hypotension (53) and eliminating early warning signs of ischemia. Burgos et al. (54) found that 35% of diabetic patients compared with only 3% of nondiabetic patients required vasopressor support (p < 0.05). The increased morbidity in diabetic patients experiencing general anesthesia may be due to inability to counteract the hemodynamic effects of induction of anesthesia because of impaired cardiovascular reflexes (54). Diabetic patients who required vasopressor support had significantly greater autonomic impairment than did those patients who did not.

Autonomic neuropathy and sudden death. In addition, autonomic neuropathy may be responsible for sudden death in diabetic patients (55-59). Although some of these sudden deaths may be due to arrhythmia secondary to a silent myocardial infarction, autopsy studies have demonstrated a surprising absence of significant coronary artery disease in some diabetic patients experiencing sudden death (56,60). A relation has been noted between diabetic cardiac autonomic neuropathy and prolonged QT interval on the electrocardiogram (ECG) (57-59,61), which may predispose to life-threatening ventricular arrhythmia. Diabetic patients with autonomic neuropathy have been found to have a relative decrease in vagal tone (thus a relative increase in sympathetic tone) at the same time of day when the frequency of sudden death has been reported to be particularly high (62). It has been proposed that the combination of relatively heightened sympathetic tone or QT interval prolongation, or both, might increase the likelihood of arrhythmias leading to sudden death (61,62).

Altered perception of ischemia. Diabetic patients have a blunted appreciation for ischemic pain. As a result of this reduced sensation, myocardial ischemia or infarction may be associated with only mild symptoms and go unrecognized or may be entirely asymptomatic and thus truly silent. Although 25% of the myocardial infarctions in the Framingham study were unrecognized, symptoms referable to infarction could be elicited in nearly 50% of these cases. The remaining infarctions (or approximately 12% of the total number) were believed to be truly asymptomatic. Unrecognized infarction tends to be more common in diabetic patients (63), and comprises 39% of their infarctions compared with 22% of those in nondiabetic patients (64). Although there has been a general trend toward a higher prevalence of silent infarction in diabetic patients, conclusive proof of this phenomenon has been hindered by the limited statistical power of most studies. These data parallel the observation that myocardial scar in the absence of an antemortem history of infarction is three times more commonly found at autopsy in diabetic than in nondiabetic patients (65).

As might be inferred from the preceding data, diabetic patients may also lack angina during myocardial ischemia. The incidence of painless ST depression during exercise tolerance tests is almost double that seen in nondiabetic patients (69% vs. 35%) and is related to severe autonomic neuropathy (66). Nesto et al. (67) demonstrated that diabetic patients experience angina less commonly than do nondiabetic patients during ischemia on thallium exercise testing.
Diabetic patients who experience angina become aware of their symptoms later in the course of ischemia than do nondiabetic patients (68). The delay in time from the onset of ST segment depression to angina may be twice as long in diabetic as in nondiabetic patients and correlates with the extent of autonomic nervous dysfunction (68). Neuropathy of efferent autonomic pathways may also indicate damage to afferent autonomic fibers responsible for the transmission of sensory impulses relating to perception of myocardial ischemia. Histologic damage to cardiac afferent nerve fibers (69), as well as physiologic evidence of afferent and efferent nerve damage (55,70,71), has been shown in diabetic patients, suggesting that neuropathy involving these fibers exists and may play a role in blunting ischemic pain.

Role of atypical presenting symptoms. The diabetic patient's abnormal perception of myocardial ischemia may lead to atypical or less impressive symptoms of myocardial infarction than are seen in the nondiabetic patient. Accurate diagnosis of infarction based on historical grounds may therefore be difficult. Atypical symptoms such as confusion, dyspnea, fatigue or nausea and vomiting may be the presenting complaint in 32% to 42% of diabetic patients with myocardial infarction compared with 6% to 15% of nondiabetic patients (72). In some cases such symptoms may mimic those associated with either hypoglycemia or hyperglycemia, which can cause delay in triaging the patient. The atypical presenting symptoms seen in the diabetic patient may lower the clinician's suspicion of infarction, leading to less than optimal care. Soler et al. (43) found that 35% of diabetic patients with acute myocardial infarction were admitted initially to the general wards rather than to the coronary care unit. More than 75% of those diabetic patients assigned to ward care lacked typical chest pain, whereas nearly all of those admitted to the coronary care unit had severe chest pain. A comparison of the ECG at presentation with a prior tracing may be extremely helpful in establishing a diagnosis when a patient with suspected acute myocardial infarction has no typical symptoms.

Atypical symptoms may alter the patients' perception of the nature of their illness and interfere with their decision to seek medical care. An association has been noted between nonpainful myocardial infarction and increased cardiac morbidity and mortality (73,74). Uretsky et al. (73) examined a group of diabetic and nondiabetic patients in whom acute myocardial infarction was associated with atypical symptoms. These patients were older than patients with more classic symptoms and most had no history of prior angina. They did not seek medical care until a mean of 12 h after the onset of symptoms and ≥33% waited >24 h. Cardiogenic shock was seen in 35% of patients with atypical presenting symptoms and the hospital mortality rate was 50%. It seems likely that the delay in receiving appropriate care may contribute to the observed increase in morbidity and mortality.

Course of Acute Myocardial Infarction

In the immediate peri-infarction period, mortality is especially high in diabetic patients. In one study (75), the in-hospital mortality rate of diabetic patients experiencing a myocardial infarction was 28%. This rate was 18% in those with a first infarction but increased substantially to 41% in those with a prior infarction. Approximately 5% of patients presenting with acute myocardial infarction have previously undiagnosed diabetes mellitus. These patients share the poor prognosis of the previously diagnosed diabetic patients with acute infarction (46).

Diabetic women have a poorer prognosis than do diabetic men and nearly twice the in hospital mortality rate (75). In one study (76) the increased mortality seen in women was attributed to their high incidence of severe congestive heart failure and cardiogenic shock. The etiology of the increased frequency of congestive heart failure and shock among women is not known. Obese diabetic women may be at particular risk; this group had an in-hospital mortality rate of 43% in one study (77).

In contrast to younger patients without diabetes, who generally seem to tolerate infarction better than the elderly, younger diabetic patients constitute a particularly high risk group: Czyzak et al. (78) found that diabetic patients between the ages of 45 and 64 years have a particularly increased mortality rate compared with that of nondiabetic patients of similar age with acute myocardial infarction. Singer and colleagues (79) also found that younger diabetic patients with a low baseline risk profile had the greatest relative mortality risk from myocardial infarction.

Complications of infarction. Diabetic patients sustaining a myocardial infarction are more likely than nondiabetic patients to encounter complications. Recurrent infarction, cardiogenic shock, atrioventricular and intraventricular conduction abnormalities, chronic congestive heart failure and myocardial rupture are all more common in the diabetic than in the nondiabetic patient (44,45,78,80,81). In addition, some studies have found anterior infarction to be more common (45,79,82), and this may partially explain their overall poorer prognosis. Anterior transmural myocardial infarction in one study was associated with a 46% 30-day mortality rate in diabetic patients (79).

In older studies, clinically significant (class III or IV) congestive heart failure developed in 44% of diabetic women and 25% of diabetic men (75) and was believed to be the cause of death in 22% of diabetic women and 6% of diabetic men with acute myocardial infarction (75). The increased incidence of congestive failure in patients with diabetes, and in diabetic women in particular, is seen even though infarct size is similar in patients with and without diabetes (76). This increase in congestive heart failure occurs even though diabetic and nondiabetic patients also have similar values for left ventricular ejection fraction (45). Several factors may be responsible for these observations. Diabetic patients are likely to have antecedent hypertension, which may impair
systolic or diastolic function, or both. The presence of autonomic dysfunction may also impair reflex adaptation to hemodynamic stress imposed by infarction. The greater extent of coronary artery disease in the diabetic patient might also limit the availability of collateral blood flow to the infarct zone, thus impairing some of the functional recovery afforded by restored blood flow to the infarct zone.

**Diabetic cardiomyopathy.** Congestive heart failure out of proportion to myocardial infarct size could also be due in part to concomitant subclinical diabetic cardiomyopathy (83). In the absence of coronary disease, diabetic patients may have abnormalities of systolic and diastolic left ventricular function termed "diabetic cardiomyopathy" (45, 84-88), which differs from the "ischemic cardiomyopathy" due to multiple infarctions. Pathologic findings in diabetic cardiomyopathy include myocardial enlargement, hypertrophy and fibrosis as well as an increase in basement membrane thickening with periodic acid-Schiff-positive deposits in the interstitium and microaneurysm formation (84, 89-92). Interstitial deposits, microvascular disease and abnormal calcium uptake by sarcoplastic reticulum are potential causes of the physiologic abnormalities just noted (83, 87). The coexistence of hypertension with diabetes may result in more marked interstitial scarring, dilatation and hypertrophy than are present with either condition alone (92-94), thus augmenting the functional abnormalities seen in diabetic cardiomyopathy.

Because diabetic cardiomyopathy occurs in the absence of coronary disease, it is unlikely that it is directly involved in the pathogenesis of acute or recurrent myocardial infarction in diabetic patients. Diabetic cardiomyopathy may indirectly predispose to myocardial infarction by increasing wall tension secondary to myocardial dilatation or by further impairing myocardial perfusion at the microvascular level in a region distal to an epicardial coronary stenosis or occlusion. Acute myocardial infarction superimposed on a substrate of preexisting diabetic cardiomyopathy may then further increase wall stress and contribute to a more morbid course after infarction.

**Diabetic metabolism and outcome after infarction.** In addition, metabolic responses to ischemia peculiar to the diabetic patients could affect contractile performance. Under conditions of myocardial ischemia, glycemic control becomes particularly important. During ischemia the heart shifts from aerobic metabolism with primary use of fatty acids to anaerobic metabolism, which depends on glucose as an energy source. Glucose transport into cells is therefore crucial. Insulin favors glucose uptake, whereas ketones, high levels of free fatty acids and their oxidation products, found during insulinopenia, inhibit its transmembrane movement. Catecholamine excess, often present with infarction, may further worsen myocardial metabolism in the diabetic patient by decreasing insulin secretory reserve and favoring lipolysis and myocardial free fatty acid uptake. There is some evidence that free fatty acids may be toxic to myocardial cells (95). Studies have shown that elevated plasma glucose levels during myocardial infarction may be associated with a poor outcome after infarction (43, 44, 46). These data must be interpreted with caution because hyperglycemia or diabetic ketoacidosis may be the result of increased adrenergic tone due to more extensive infarction. Diabetic ketoacidosis occurs in approximately 4% of infarctions in diabetic patients (75) and may be the presenting symptom. When diabetic ketoacidosis complicates infarction, mortality is higher and may approach 85% (96).

**Major risk factors.** The increased in-hospital mortality rate in diabetic patients with infarction in one study was found to occur during days 2 to 7 of the hospital stay. During this period the mortality rate was more than three times that of nondiabetic patients and was seen mostly prominently in patients with insulin-dependent diabetes (78). Much of the excess mortality during this interval was due to congestive heart failure, although arrhythmias and conduction abnormalities were significant contributors as well. In this study, diabetic patients with arrhythmias, second- and third-degree atrioventricular (AV) block and left bundle branch block experienced a 47% in-hospital mortality rate—three times that of similar patients without diabetes (78). Some but not all studies (47, 97) have documented an increase in AV and intraventricular (45) conduction abnormalities in diabetic patients. Four prognostic variables in the immediate period after acute myocardial infarction in diabetic patients have been found to be independent predictors of poor prognosis. In order of descending importance they were 1) Q wave acute myocardial infarction, 2) prior acute myocardial infarction, 3) female gender, and 4) insulin treatment before hospital admission (75). Obesity and anterior location of infarction are also associated with poor prognosis in diabetic patients (45).

**Late Cardiac Complications and Mortality**

**Role of persistent ischemia.** The presence of diabetes mellitus is an independent predictor of cardiac mortality, which ranges from 26% to 62% in the 1st year after myocardial infarction and may reach 79% by 5 years (42, 45, 98). Immediate postinfarction morbidity and mortality is usually due to congestive heart failure, cardiogenic shock or conduction disturbances. Patients surviving these complications suffer from recurrent nonfatal (99) and fatal myocardial infarction to a greater degree than do nondiabetic patients. One explanation for the increased morbidity and mortality may be persistent ischemia or ongoing myocardial damage after infarction. Technetium pyrophosphate scintigraphy has been performed in diabetic and nondiabetic patients in the acute phase and 3 months after myocardial infarction (100). Sixty-two percent of diabetic patients were found to have a persistently positive technetium pyrophosphate scan at 3 months compared with only 12% of nondiabetic patients. More frequent complications after hospital discharge, including congestive heart failure, recurrent myocardial infarction and death, were seen in both diabetic and nondiabetic
patients with chronic technetium pyrophosphate uptake. Diabetic patients with chronic technetium pyrophosphate uptake exhibited marked myocardial myocyte necrosis, signifying ongoing myocardial necrosis.

**Risk factors for future cardiac events.** As in the nondiabetic patient, certain characteristics denote patients at high risk for future cardiac events. Prognostic indicators associated with a poor outcome after hospital discharge in patients who survive the coronary care unit phase of hospitalization include: 1) cardiac symptoms for at least 1 month before the infarction, 2) pulmonary edema during the initial phase of the hospital stay, 3) >10 ventricular premature beats/h before hospital discharge, and 4) at least moderately reduced left ventricular ejection fraction (<40%) by radionuclide ventriculography (42).

**Management Considerations.**

Although there are few data analyzing efficacy of therapy in diabetic patients as a subset, there are theoretic grounds for anticipating that certain therapies may be particularly useful in the patient with diabetes. Management of the diabetic patient with acute myocardial infarction is, for the most part, similar to that of the nondiabetic patient, with certain special considerations.

**Thrombolysis.** Thrombolytic therapy for myocardial infarction has proved value in patients presenting soon after the onset of infarction who demonstrate ST segment elevation on the ECG. The atypical symptoms seen in diabetic patients may not only cause delay in seeking medical care but make it difficult to determine the time of onset of infarction. These factors peculiar to the diabetic patient may interfere with the decision to initiate thrombolytic therapy. Denying treatment with a thrombolytic agent on this basis is unfortunate because the decrease in mortality with thrombolysis in these patients is at least equal to that seen in patients without diabetes (101). A recent reanalysis (102) of prior data suggests that the benefit of thrombolytic treatment may be greatest in high risk subgroups such as patients with diabetes. A high incidence of hemorrhagic complications associated with increased mortality has been reported (103) in diabetic patients >75 years of age. Thus, thrombolysis in elderly diabetic patients should probably be limited to those with life-threatening myocardial infarction until further data clarify whether the benefits in this group outweigh the risks. Although one might presume that the presence of proliferative retinopathy would represent a relative contraindication to the use of thrombolytic agents in many diabetic patients, retinal hemorrhages were not seen in the 121 diabetic patients treated with thrombolytic agents in the Thrombolysis and Angioplasty in Acute Myocardial Infarction (TAMI) trial (101).

**Invasive management.** Diabetic patients with acute myocardial infarction who manifest signs of ongoing ischemia despite medical therapy should be considered for myocardial revascularization by coronary artery bypass grafting or percutaneous transluminal coronary angioplasty. Coronary artery bypass grafting is as effective in relieving anginal symptoms in diabetic patients as in nondiabetic patients, although the long-term survival rate after bypass surgery remains consistently lower in diabetic than in nondiabetic patients (104,105). Diabetic patients may require more bypass grafts because of their more extensive atherosclerosis (104). However, late graft patency in these patients is similar to that of nondiabetic patients (105). Perioperative mortality appears to be elevated in the diabetic patient—4.5% to 5.1% compared with 2.5% in patients without diabetes (104). Poor sternal wound healing, renal failure and prolonged length of hospitalization are more common in diabetic patients (104).

Percutaneous transluminal coronary angioplasty is an effective tool to relieve ischemic symptoms in diabetic patients with suitable coronary anatomy. Although few data exist relating to coronary angioplasty on diabetes specifically in the acute infarction setting, it appears that diabetic patients may be somewhat more prone than nondiabetic patients (106) to restenosis after angioplasty. Diabetes is also an independent variable predicting restenosis after a second coronary angioplasty at a given site (107). In multivessel coronary angioplasty, diabetes is associated with a lower primary success rate and a higher rate of complications (108). Despite possible shortcomings, coronary artery angioplasty is an attractive treatment option due to its low morbidity and brief convalescence period and avoidance of the potential problems associated with bypass surgery.

**Secondary Prevention After Myocardial Infarction.**

**Beta-adrenergic receptor blockade.** The use of beta-blockers has been shown to favorably affect mortality following myocardial infarction. In the Timolol in Myocardial Infarction study (109), administration of timolol (a nonbeta-1 selective agent) was associated with a substantial reduction in overall mortality including total cardiac death, sudden death and nonfatal reinfarction. The magnitude of risk reduction for cardiac death and nonfatal reinfarction was particularly great in diabetic patients, suggesting an even greater benefit of beta-blockade in this group than in patients without diabetes. Timolol was tolerated equally well in patients with and without diabetes. Another study examining beta-blocker use in 281 diabetic patients after acute myocardial infarction found a decrease in mortality from 17% to 10% at 1 year after hospital discharge (110). In multivariate analysis in the same study, beta-blocker use was found to be an independent predictor of cardiac survival at 1 year in diabetic patients, whether or not pulmonary congestion was present on the admission chest X-ray film.

The potential benefits of beta-blockers are counterbalanced by adverse effects peculiar to the diabetic patient. These agents may attenuate reflex tachycardia, mask "warning" symptoms due to hypoglycemia and potentiate insulin-
induced hypoglycemia by inhibiting glycogenolysis. For these reasons, many clinicians have been reluctant to use beta-blockers in diabetic patients. On the contrary, beta-blockers are usually well tolerated and may be of particular benefit in the diabetic patient despite these concerns. Many of the complications seen with beta-blocker administration mentioned are encountered with doses higher than that which may be needed to provide secondary protection against cardiac death.

Aspirin. Aspirin has significant proved value after myocardial infarction in nondiabetic patients, reducing the rate of short-term mortality and reinfarction (111). Diabetic patients have a heightened platelet reactivity (27–30) that may play a role not only in the accelerated progression of atherosclerosis, but also in the development of occlusive thrombus formation at the site of coronary plaque rupture. Thus, it is likely that aspirin may be even more useful in patients with than in patients without diabetes because of this baseline increased platelet activity. Studies regarding primary and secondary prevention of myocardial infarction in diabetic patients have not been performed and would be clinically useful.

There has been some concern, however, that aspirin may potentiate the development of retinal hemorrhage in diabetic patients. The safety of long-term aspirin use in diabetic patients with early retinopathy has been demonstrated in the DAMAD study (112) in which aspirin (325 mg three times daily) was administered to 267 diabetic patients with early retinopathy with a decrease in retinal microaneurysms without a single case of worsening retinal hemorrhage (112). These data may not apply to diabetic patients with more severe degrees of retinopathy in whom the safety of aspirin has not yet been determined.

Risk factor modification. Attention must also focus on risk factor modification to reduce progressive atherosclerosis and the risk of reinfarction. Hypertension should be controlled, preferably with agents tailored to improve any systolic or diastolic left ventricular dysfunction. Hyperlipidemias and obesity should be managed aggressively. Secondary prevention efforts with risk factor modification may be most justified in diabetic women who experience a particularly high late cardiac mortality rate after surviving myocardial infarction (45,77).

Cigarette smoking is an important factor that promotes coronary atherosclerosis. Diabetic patients are as likely as the general public to be smokers (113). Cigarette smoking is an independent predictor of mortality in patients with insulin-dependent diabetes and is particularly dangerous in diabetic women with insulin-dependent diabetes, because it more than doubles their risk of cardiac mortality (113).

Conclusions

Diabetes mellitus is associated with an increased morbidity and mortality related to coronary artery disease. In addition to accelerated atherosclerosis, multiple dynamic factors related to diabetes not only predispose to acute myocardial infarction but also contribute to postinfarction complications. Further understanding of the impact of diabetes on the pathophysiology of acute myocardial infarction may lead to more specialized treatment modalities for this high risk subgroup.

References