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Efficacy of beta blockade, thrombolytic therapy, and coronary angioplasty in diabetic patients with coronary artery disease

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■ Diabetes mellitus is an independent risk factor for coronary artery disease. In addition, ischemic heart disease is the major cause of mortality among diabetic patients. Early and late mortality after acute myocardial infarction is higher among diabetic patients. However, the effectiveness of newer treatments on diabetic patients with coronary artery disease has received little attention. This article reviews the effect of beta blockers and thrombolysis in diabetic patients after acute myocardial infarction and compares early and late results of percutaneous transluminal coronary angioplasty in diabetic patients with those in the nondiabetic population.

□ INDEX TERMS: CORONARY DISEASE; RISK FACTORS; DIABETES MELLITUS □ CLEVE CLIN J MED 1993;60:145–149

DIABETES MELLITUS is an independent risk factor for coronary artery disease (CAD). The Framingham study showed that the incidence of cardiovascular disease was two or three times higher among diabetic subjects than among nondiabetic subjects.[1] Other studies have shown that the mortality from CAD is also several times higher in diabetic subjects.[2] Still other studies have documented that diabetes mellitus increases mortality in acute myocardial infarction and is also a risk factor for later cardiac death in patients surviving a myocardial infarction.

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Unfortunately, the effectiveness of newer CAD treatments in diabetic patients with CAD has received little attention, despite the association of diabetes with increased mortality. Therefore, I examined the effect of three therapeutic approaches—beta blockade, thrombolysis, and percutaneous transluminal coronary angioplasty (PTCA)—in diabetic patients presenting with acute myocardial infarction and clinical CAD.

DIABETES AND ACUTE MYOCARDIAL INFARCTION

Uusitupa et al[3] followed a newly diagnosed group of diabetic patients. They found that the 5-year incidence of myocardial infarction among diabetic men was six times that of nondiabetic control subjects; among diabetic women, it was 3.7 times that of control subjects. Waller et al,[4] in a necropsy study of diabetic subjects, found that acute myocardial infarction was the most common fatal coronary event.

TABLE 1
MORTALITY AND REINFARCTION RATES
1 YEAR AFTER MYOCARDIAL INFARCTION

Study (N)	Mortality		Reinfarction	
	Diabetic patients	Nondiabetic patients	Diabetic patients	Nondiabetic patients
Ulvenstam[6] (1306)	18%	6%	18%	12%
Herlitz[7] (787)	28.2%	15.1%	21.5%	14.3%
Malmberg[10] (341)	53%	28%	41%	33%
Gundersen[11] (1884)	30.5%	15.5%	21.7%	13.5%

Kereiakes[5] reviewed the results of 10 studies from the coronary care era (1972-1984) that evaluated mortality in diabetic patients with acute myocardial infarction. Hospital mortality for diabetic patients was 31%, compared with 19.5% for nondiabetic patients ($P < .01$). Analysis of several studies suggests that this increased mortality is related to the higher incidence of congestive heart failure and cardiogenic shock unexplained by the extent of CAD[6] or infarct size as estimated by enzymatic measurement.[6–8]

Diabetic women are at particularly high risk: mortality during infarction is twice as high for diabetic women as for diabetic men. This excess mortality is attributable to an increased risk for congestive heart failure and is independent of other risk factors.[9]

Studies also show that diabetic patients surviving myocardial infarction consistently have a higher rate of early mortality than nondiabetic patients. Mortality rates in diabetic patients during the first year after myocardial infarction range from 18% to 53%, compared with 6% to 28% for nondiabetic control groups.[6,7,10] This increased mortality is primarily related to a higher incidence of recurrent infarction (*Table 1*).

Malmberg et al[10] found that the 1-year incidence of fatal reinfarction was 30% in diabetic patients but only 14% in nondiabetic patients ($P < .05$). Eventually, 72% of diabetic patients died from a reinfarction, compared with 44% of nondiabetic patients. This finding underscores the significance of reinfarction in diabetic patients.

Diabetic women have twice the incidence of recurrent infarction and up to four times the incidence of congestive heart failure compared with diabetic men; consequently, they have a worse prognosis during follow-up.[8,11]

In summary, diabetic patients show an excessive early mortality from acute myocardial infarction and a higher incidence of congestive heart failure and cardiogenic shock than nondiabetic patients. These rates are apparently independent of the extent of coronary disease and the size of myocardial infarction. Women are at particularly high risk. Among those who survive a myocardial infarction, diabetic patients—and diabetic women in particular—fare worse in follow-up, primarily because of a higher incidence of reinfarction. Regardless of sex, mortality among patients who experience recurrent myocardial infarction is nearly doubled in the presence of diabetes.

BETA BLOCKERS IN DIABETIC PATIENTS

Beta blockers have not been widely used to treat diabetic patients with acute myocardial infarction for fear of potentiating insulin-induced hypoglycemia and altering the physiologic response to hypoglycemia. However, growing evidence suggests that beta blockers not only are safe but also may significantly reduce mortality and reinfarction rates in diabetic patients with acute myocardial infarction.

The Norwegian multicenter timolol study[12] included 99 patients with diabetes mellitus. At a mean follow-up of 17 months, timolol reduced cardiac mortality by 67% in diabetic patients and by 39% in nondiabetic patients. Nonfatal reinfarction was reduced by 83% in diabetic patients and by 35% in nondiabetic patients.

In the Göteborg metoprolol trial[13] of 1395 randomly assigned patients, 120 (8.6%) were diabetic. The 3-month mortality was 7.5% in the metoprolol group and 17.9% in the placebo group ($P = 0.16$) (*Table 2*). The reduction in mortality was higher for diabetic patients (58%) than for the entire study population (36%). The reduction in late reinfarction was 76% (from 16.4% to 3.8%) in diabetic patients on metoprolol and 35% (from 7.7% to 5%) in all patients.

In another large randomized study using metoprolol, the Miami trial[13] of 5778 patients, 413 (7%) were diabetic. Fifteen-day mortality in the diabetic group was reduced from 11.3% to 5.7%. This 49% reduction in mortality was significantly higher than the 12% reduction seen in the entire patient population (*Table 2*).

These results suggest a striking reduction in mortality and reinfarction rates among diabetic patients receiving beta blockers. More importantly, diabetic patients seem to benefit more from early beta blocker administration than do nondiabetic patients. Although the data are derived from retrospective analyses of large studies not specifically designed to study diabetic patients, it seems justified to suggest early and late prophylaxis with beta blockers in diabetic patients with acute myocardial infarction.

DIABETES AND THROMBOLYSIS

Several studies have found that thrombolytic treatment reduces mortality in patients with acute myocardial infarction. Because diabetic patients with myocardial infarction have a higher mortality than nondiabetic patients, evaluating the results of thrombolysis in this subgroup of patients should be especially important.

TABLE 2
EFFECTS OF METOPROLOL ON MORTALITY AND REINFARCTION IN DIABETIC PATIENTS WITH ACUTE MYOCARDIAL INFARCTION*

Study (N)	Event	Placebo group	Metoprolol group	P	Reduction
Miami (413)	Mortality at 15 days	11.3%	5.7%	.06	49%
	Reinfarction	4.5%	3.1%	.2	31%
Göteborg (120)	Mortality at 3 months	17.9%	7.5%	.16	58%
	Reinfarction	16.4%	3.8%	.05	76%

*Adapted from Malmberg et al[13]

The concern that thrombolytic therapy could induce retinal hemorrhage and blindness in insulin-dependent diabetic patients with retinopathy has not been substantiated. Of the five large randomized prospective trials of thrombolysis in acute myocardial infarction, only the GISSI study (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico)[14] considered hemorrhagic diabetic retinopathy a contraindication to thrombolysis; in ASSET (Anglo-Scandinavian Study of Early Thrombolysis),[15] 1.5% of patients were excluded because of proliferative diabetic retinopathy. The proportion of patients with diabetes mellitus receiving thrombolysis was 7%, 7.2%, and 12.9% in ASSET, ISIS-2 (Second International Study of Infarct Survival),[16] and the ISAM trial (Intravenous Streptokinase in Acute Myocardial Infarction),[17] respectively. GISSI and AIMS (Anistreplase Intervention Mortality Study)[18] made no reference to diabetic patients in their methods or results.

Only ISIS-2 and ISAM reported on the results of thrombolysis in diabetic patients. In ISIS-2,[16] mortality in diabetic patients was reduced from 17.2% in the placebo group to 11.8% in the streptokinase group. This 31% reduction in mortality was larger than the 23% reduction in nondiabetic subjects. Similar results were seen in the group receiving a combination of streptokinase and aspirin. The group receiving aspirin alone showed no difference in mortality (*Table 3*).

In ISAM,[17] the long-term mortality at a mean follow-up of 21 months was not significantly different between the placebo group (16.1%) and the streptokinase group (14.4%). In the subgroup analysis of streptokinase therapy, diabetic patients were the only group that showed a trend towards decreased mortality (33% to 22.5%, $P = .08$). However, of four early strokes observed in the streptokinase group, three were in diabetic patients; this results in a stroke incidence of 2.7% in this group of diabetic patients on streptokinase.

TABLE 3
EFFECTS OF THROMBOLYTIC TREATMENTS ON 5-WEEK MORTALITY RATES IN DIABETIC PATIENTS WITH ACUTE MYOCARDIAL INFARCTION*

Treatment	Diabetic patients	Reduction	Nondiabetic patients	Reduction
Placebo	17.2	31%	11.5	23%
vs streptokinase	11.8		8.9	
Placebo	14.6	0%	11.5	23%
vs aspirin	14.6		8.9	
Placebo	18.5	29%	12.7	40%
vs aspirin and streptokinase	13.1		7.6	

*Data from the Second International Study of Infarct Survival[16]

TABLE 4
RESTENOSIS RATES IN DIABETIC PATIENTS UNDERGOING PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY

Study (N)	Diabetic patients	Nondiabetic patients	P
Holmes[19] (557)	47%	32%	.05
Hollman[20] (731)	46%	36%	.07
Frid[21] (739)	55%	40%	.005

In summary, thrombolytic studies have not specifically addressed results in diabetic patients. The little information that can be extracted from the studies confirms the increased mortality from acute myocardial infarction already noted in diabetic patients and suggests that this group may benefit from thrombolytic therapy more than nondiabetic patients. More information is needed regarding a possible increase in morbidity with thrombolysis among diabetic patients.

CORONARY ANGIOPLASTY IN DIABETIC PATIENTS

In the decade since its inception, PTCA has had an increasing role in the treatment of patients with CAD; however, several studies have suggested poor long-term results after PTCA in diabetic patients. Diabetes mellitus appears to be an important factor for restenosis (*Table 4*). This relationship was initially suggested by the National Heart, Lung, and Blood Institute registry and has been supported by a number of subsequent studies.[19–22]

Holmes et al[19] reported a restenosis rate of 47% in diabetic subjects compared with 32% in nondiabetic patients ($P = .05$). In our experience at The Cleveland Clinic Foundation,[20] we restudied 599 patients after single-vessel PTCA. The restenosis rate in 519 nondiabetic patients was 36%, compared with 46% in 80 diabetic patients ($P = .07$). The excess risk for recurrence was confined to 26 insulin-dependent diabetic patients with a restenosis rate of 61.5%. Among 54 non-insulin-dependent diabetic patients, the restenosis rate was 39%.

Frid et al[21] reported on 739 patients restudied at a median time of 6 months. The restenosis rate among 124 diabetic patients was 55% compared with 40% among nondiabetic patients. The incidence of restenosis was higher in diabetic patients treated with insulin (58%) and oral hypoglycemic agents (57%) than among patients treated exclusively by diet (49%).

Webb et al,[23] reporting the results of PTCA in young adults, found that hypertension and diabetes mellitus were the only significant independent predictors of late death (after hospital discharge). The cumulative 5-year survival rate was 85% in diabetic patients and 96% in nondiabetic patients ($P < .01$). Vandormael et al[24] found diabetes mellitus to be an independent predictor of cardiac mortality in patients with multivessel CAD undergoing PTCA. The estimated 3-year cardiac survival was 93% in nondiabetic patients and 82% in diabetic patients.

Despite these less favorable results, in our first 5000 PTCA procedures, 13.8% of patients were diabetic and 4.5% had insulin-dependent diabetes. To evaluate the long-term results of PTCA in diabetic patients, we compared a group of 166 insulin-dependent diabetic patients with a group of 166 nondiabetic patients matched for sex, age, and number of vessels dilated. The primary success rate was 91% in diabetic patients and 87% in nondiabetic patients. In-hospital complications did not differ between the groups. At 3 years, cardiac survival was lower in diabetic patients than in nondiabetic ones (88% vs 97%), as was survival without events such as myocardial infarction, bypass surgery, or repeat PTCA (70% vs 78%).[25]

We concluded that, whereas PTCA can be safely performed in diabetic patients, its long-term results are less favorable than in nondiabetic patients, possibly as a result of a combination of less complete revascularization, a higher restenosis rate, and progressive disease.

CONCLUSION

Diabetes mellitus is a risk factor for the development of CAD; mortality among diabetic patients with acute myocardial infarction remains unacceptably high during short-term and long-term follow-up. Recent studies suggest that interventions such as beta blockers and thrombolysis seem to benefit diabetic patients, and their use appears to be justified. In this patient group, the results of PTCA, as with coronary revascularization surgery, are less satisfactory than in nondiabetic patients.

Our knowledge regarding the efficacy of these interventions in diabetic patients with CAD derives exclusively from retrospective analyses of clinical studies. Unfortunately, none of these studies attempted to correlate results with degree of glycemic control. In the future, only randomized prospective trials involving diabetic patients will provide a definitive answer regarding the benefits of these interventions.

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