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Influence of Diabetes on Mortality in Acute Myocardial Infarction: Data From the GISSI-2 Study

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Objectives. This study was conducted to determine the role of insulin-dependent and noninsulin-dependent diabetes in the prognosis of patients after myocardial infarction and treatment with fibrinolytic agents.

Background. Several studies have shown that diabetic patients have a high mortality rate after acute myocardial infarction. However, the impact of diabetes on survival in patients treated with fibrinolytic agents is still undefined. It is also not known whether the type of diabetes or gender affects prognosis.

Methods. We analyzed prevalence and prognostic significance of a history of diabetes in patients enrolled in the GISSI-2 study, all of whom received fibrinolytic agents. The incidence of deaths in the hospital and at 6 months after study entry was computed for patients without diabetes and for insulin-dependent and noninsulin-dependent diabetic patients; relative risks were evaluated by univariate and multivariate analysis.

Results. Information on diabetic status was available for 11,667 patients, 94.2% of those randomized in the GISSI-2 study. The prevalence of diabetes was higher in women than in men (8.75% vs. 1.85%, $p < 0.01$ for insulin-dependent and 23.7% vs. 13.8%, $p < 0.01$ for noninsulin-dependent diabetic patients). The type of fibrinolytic agent did not affect mortality rates; the increase in in-hospital mortality of diabetic patients was moderate and similar for men with insulin- and noninsulin-dependent diabetes (8.7% and 10.1%, respectively, vs. 5.8% in nondiabetic patients); in women, mortality was markedly higher for insulin-dependent and only slightly higher for noninsulin-dependent diabetic patients (24.0% and 15.8%, respectively, vs. 13.9% for nondiabetic patients). The adjusted relative risks were 1.9 (95% confidence interval 1.2 to 2.9) for insulin-dependent diabetic women and 1.4 (95% confidence interval 1.1 to 1.8) for noninsulin-dependent diabetic men. The mortality rate after discharge showed a similar gender difference, and in insulin-dependent diabetic women, prognosis was ominous even in the absence of left ventricular damage before discharge.

Conclusions. A history of diabetes is associated with a worse prognosis after myocardial infarction, even in patients treated with fibrinolytic agents. Gender and type of diabetes appear to be critical in affecting survival. In men, both insulin-dependent and noninsulin-dependent diabetes are associated with a moderately higher mortality rate; in women, insulin-dependent diabetes is, in itself, a strong risk factor for death after myocardial infarction.

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Several studies (1–4) performed before the introduction of fibrinolysis as a routine treatment of patients with myocardial infarction have shown that diabetes mellitus has a negative influence on survival after myocardial infarction. As recently reviewed by Jacoby and Nesto (5), the reasons for this are still debated. Some of the studies suggested that a higher prevalence of other risk factors (hypertension, hyperlipidemia, extensive coronary artery disease and advanced age) or a higher degree of left ventricular damage after infarction may explain the higher mortality rate in diabetic patients. Conversely, other studies (2) indicate that the detrimental effect of diabetes on survival is most evident in patients whose baseline characteristics would indicate a relatively low risk of death after infarction, thus suggesting that pathophysiologic derangements accompanying diabetes that apparently do not affect the clinical status of the patients may play a subtle but critical role as they reduce survival after myocardial infarction. In addition, because the prevalence of type 1 or type 2 diabetes in patients with myocardial infarction differs in men and women, it is not known whether the presence of diabetes may largely account for the higher postmyocardial infarction mortality rate in women, as suggested by recent studies (6). Thus, at a time when the advent of fibrinolysis has dramatically changed the prognosis of patients with acute myocardial infarction, several questions on the effect of diabetes on survival remain unanswered. Is a history of diabetes still a strong independent risk factor for death after acute myocardial infarction in

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patients treated with fibrinolytic agents? Is there any gender influence on the impact of diabetes on survival? Is the prognosis of insulin- and noninsulin-dependent diabetes different? Is the effect of diabetes independent of other risk factors in both men and in women? These questions are addressed in the present study.

Methods

Study patients. Data obtained from the patients enrolled in the GISSI-2 study were analyzed. The details of the design and the results of GISSI-2 have been provided in the original reports (7,8). Briefly, patients entered the study if 1) they had chest pain with ST segment elevation of ≥1 mm in any limb lead of the electrocardiogram (ECG) or ≥2 mm elevation in any precordial lead, 2) they were admitted to the coronary care unit within 6 h of the onset of symptoms, and 3) they had no clear contraindications to fibrinolytic treatment or heparin administration. No age restriction was imposed and exclusion criteria were limited to the presence of contraindications to thrombolytic treatment. A total of 12,381 patients were randomized within 6 h of the onset of acute myocardial infarction symptoms: 6,199 to receive streptokinase (1.5 million U over 30 to 60 min), 6,182 to receive recombinant tissue-type plasminogen activator (rt-PA [Actylise], 100 mg over 3 h). According to the factorial design, 6,175 patients were also randomly allocated to receive subcutaneous heparin (12,500 U twice daily) and 6,206 patients were allocated to the no-heparin group.

In-hospital data collection. A variety of information on clinical history of the patients, including data on a history of type 1 insulin-dependent diabetes, type 2 noninsulin-dependent diabetes and related treatment; hypertension, hypercholesterolemia and its treatment; stable (>1 month) angina pectoris, and the presence of previous myocardial infarction, was collected by the attending physician during the hospital stay.

Quality control of the collection of epidemiologic and clinical data by the several physicians involved in the study was ensured by local monitors responsible for coronary care units of specific geographic areas. The extent of the infarction at admission was evaluated by computing the number of leads in which ST segment elevation occurred, and a noninvasive index of reperfusion was obtained (9,10) by computing the sum of ST elevation in all leads in the ECG and by defining successful reperfusion whenever the ST segment elevation in the ECG taken 4 h after fibrinolysis had decreased by ≥50% compared with that in the ECG at randomization.

Data on clinically relevant in-hospital events (death, reinfarction and cerebrovascular accidents) and interventions, such as percutaneous transluminal coronary angioplasty and coronary artery bypass surgery were carefully collected in the study forms.

Risk stratification at discharge. Laboratory examinations (24-h ECG [Holter] monitoring, two-dimensional echocardiography and ECG stress testing) were required by the study protocol to obtain the main prognostic variables needed for a risk stratification of patients at discharge (11). The type and frequency of ventricular arrhythmias were obtained from Holter recordings; an exercise stress test was performed to evaluate the presence of postmyocardial infarction ischemia. Left ventricular dysfunction was defined as the presence of late (beyond day 4) clinical congestive heart failure (the presence of a third heart sound, rales, dyspnea or evidence of pulmonary congestion on chest X-ray study) or extensive, not clinically evident left ventricular damage, defined as either an echocardiographic left ventricular ejection fraction ≤35% or ≥45% injured myocardial segments (calculated from the left ventricle as evaluated by two-dimensional echocardiography and divided into 11 segments).

Postdischarge follow-up. Information on clinically relevant events and interventions such as coronary angioplasty and coronary bypass surgery occurring in patients in the hospital or within 6 months from admission to the trial was obtained from the participating coronary care units. Sudden cardiac death was defined as unexpected death occurring within 1 h of the onset of symptoms. Information on survival for patients not traced by local monitors (11% of the total study group) was obtained through the census offices of the towns of residence of the patients.

Statistical methods. For the purpose of this analysis, patients were classified by gender and, for each gender, in three groups according to their history of diabetes: negative (no diabetes) or positive for insulin-dependent or noninsulin-dependent diabetes.

The chi-square statistic was used to test the statistical significance of differences for each gender in the prevalence of concomitant diseases in the different groups of patients, according to their diabetic status. Nondiabetic patients served as reference group. Significance of the difference observed was defined as a two-tailed p value <0.05. In-hospital mortality and total and sudden mortality rates after 6 months of follow-up were compared in diabetic and nondiabetic patients by chi-square statistics. Results are expressed in terms of Mantel-Haenszel odds ratio, with their 95% confidence intervals defined for mortality.

Multiple logistic regression analysis was used to assess the independent prognostic value of diabetes for in-hospital mortality. The following variables were considered in the model because they represented all the risk factors possibly linked but not consequent to the acute myocardial infarction: age (<70 or ≥70 years), previous myocardial infarction, history of angina, history of treated hypertension, history of hypercholesterolemia, Killip functional class at admission (≤2 or >2) and infarct size at admission (one or two, three or four or more than four ECG leads showing an elevated ST segment). The results of the multivariate analysis are presented in terms of relative risks with their 95% confidence intervals.

Table 1. Epidemiologic Characteristics (n = 11,667)

	No Diabetes	Diabetes Mellitus: Insulin-Dependent	Diabetes Mellitus: Noninsulin-Dependent	Total
Men				
No.	8,069	150	1,116	9,335
% with				
Age >70 yr	16.5	18.0	21.2*	17.1
Hypertension	24.3	32.0	30.6*	25.2
History of angina	20.5	30.0*	24.8*	22.2
Previous MI	16.0	35.3*	21.9*	17.0
Hypercholesterolemia	21.9	27.3	26.8*	22.6
Smoking	57.4	38.7*	44.8*	55.6
Anterior MI	31.4	36.0	38.4*	32.3
Non-Q wave MI	13.6	14.0	11.1†	13.3
Women				
No.	1,760	154	418	2,332
% with				
Age >70 yr	43.0	39.0	46.9	43.4
Hypertension	43.1	53.2†	52.9*	45.5
History of angina	23.2	31.2†	31.6*	25.6
Previous MI	9.1	26.6*	14.8*	11.3
Hypercholesterolemia	24.7	24.0	34*	26.3
Smoking	28.6	6.5*	12.9*	24.4
Anterior MI	34.4	35.1	38.3	35.2
Non-Q wave MI	15.6	10.4	12.2	14.6

*p < 0.01, †p < 0.05 versus nondiabetic patients. MI = myocardial infarction.

Table 2. In-Hospital Events

	No Diabetes	Diabetes Mellitus: Insulin-Dependent	Diabetes Mellitus: Noninsulin-Dependent	Total
Men				
No.	8,069	150	1,116	9,335
% with				
Killip class <2	2.6	5.3	5.0*	3
Acute LV dysfunction	13.5	26.0*	21.1*	14.6
Shock	3.4	3.3	4.1	3.5
Post-MI angina	8.9	10.0	9.0	8.9
Reinfarction	2.1	3.3	1.1	2
II–III AV block	8.5	9.3	6.2†	8.2
Women				
No.	1,760	154	418	2,332
% with				
Killip class >2	4.7	9.7†	7.2	5.4
Acute LV dysfunction	18.9	35.1†	24.6†	21.0
Shock	7.3	12.3†	7.9	7.7
Post-MI angina	12.7	12.3	13.4	12.8
Reinfarction	2.9	2.6	2.6	2.8
II–III AV block	9.3	13.6	11.0	9.9

*p < 0.01, †p < 0.05 versus nondiabetic patients. LV = left ventricular; MI = myocardial infarction; II–III AV block = second or third degree atrioventricular block.

Results

Patient characteristics. Information on diabetic status was available for 11,667 (9,335 men and 2,332 women) subjects, representing 94.2% of the 12,381 patients randomized in GISSI-2. Table 1 shows the main characteristics of these patients according to gender. The overall prevalence of diabetes was significantly higher in women than in men for both type 1 insulin-dependent diabetes (8.75% vs. 1.85%, $p < 0.01$) and type 2 noninsulin-dependent diabetes (23.7% vs. 13.8% $p < 0.01$) and increased progressively with age for noninsulin-dependent diabetes. Among both men and women, diabetic patients more frequently had a history of ischemic heart disease (angina or previous myocardial infarction); patients with noninsulin-dependent diabetes were older than patients without diabetes. Note that for the two genders, differences of similar magnitude may or may not reach statistical significance, depending on the number of patients.

In-hospital morbidity and mortality. As expected from the results of the main study (7,8), the type of fibrinolytic treatment during the acute phase, rt-PA or streptokinase with or without heparin did not affect in-hospital mortality. Mortality rates in patients treated with rt-PA were 7.4% in patients without diabetes, 15.4% in patients with insulin-dependent diabetes and 12.4% in those with noninsulin-dependent diabetes; in patients treated with streptokinase, the respective mortality rates were 7.2%, 17.4% and 10.9%, with no significant differences between treatments. For each age group, mortality rates were higher for women than for men; this trend was similar for nondiabetic and diabetic patients. As shown in Table 2, diabetic patients were in general more prone to develop acute left ventricular dysfunction. The noninvasive index indicated that reperfusion was achieved less frequently in diabetic patients than in nondiabetic patients, and the difference was most evident for insulin-dependent diabetic women (Fig. 1).

In-hospital mortality rates (Table 3) were higher for both men and women with diabetes. In men, both the insulin-dependent and noninsulin-dependent types of diabetes were linked to a higher mortality rate that was most significant for noninsulin-dependent diabetic patients (10.1% vs. 5.8%, odds ratio 2.1, 95% confidence interval [CI] 1.6 to 2.7), whereas in women, only the mortality rate of insulin-dependent diabetic patients was strikingly higher (24.0% vs. 13.9%, odds ratio 2.2, 95% CI 1.4 to 3.6). These differences remained significant even after adjusting for age, previous myocardial infarction, concomitant history of angina, hypertension, hypercholesterolemia, Killip functional class and infarct size at admission. Adjusted relative risks were 1.9 (95% CI 1.2 to 2.9) for insulin-dependent diabetic women and 1.4 (95% CI 1.1 to 1.8) for noninsulin-dependent diabetic men compared with nondiabetic patients. Causes of in-hospital deaths were not significantly different in the three groups: acute cardiac insufficiency (cardiogenic shock or acute pulmonary edema) accounted for 50% to 65% of total in-hospital deaths in all groups of patients.

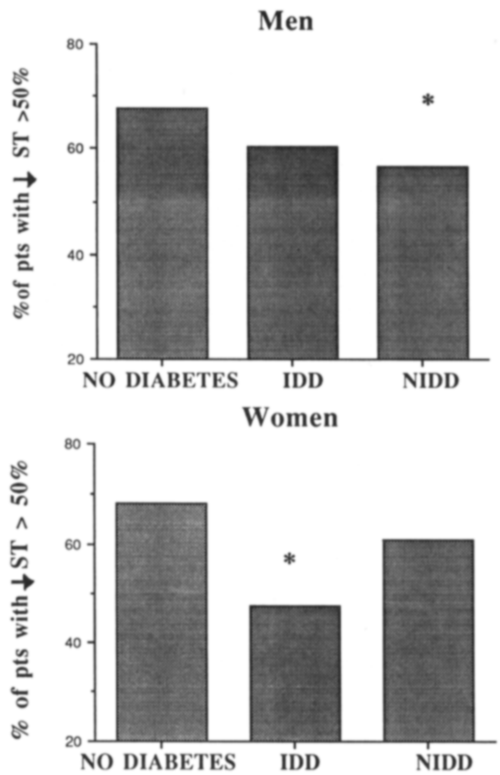

Figure 1. Bar graph showing percent of patients whose electrocardiogram taken 4 h after randomization showed a >50% decrease of ST (↓ST) elevation in the groups without diabetes and with insulin-dependent (IDD) and noninsulin-dependent diabetes (NIDD). *$p < 0.05$.

Six-month and total mortality rates. Six-month follow-up data were available for 98.5% of patients discharged alive from the hospital. The mortality rate after discharge up to 6 months of follow-up (Table 3) showed a dependence on gender and type of diabetes that was similar to that observed for the in-hospital mortality rate. Again, noninsulin-dependent diabetes was most detrimental in men and insulin-dependent diabetes was most detrimental in women.

Sudden cardiac death accounted for a similar proportion of deaths among men. Twenty-nine percent of nondiabetic men and 33% of insulin-dependent and 30% of noninsulin-dependent diabetic men died suddenly; among women, sudden death was slightly higher in those with diabetes: 20% of nondiabetic women and 31% of those with insulin-dependent and 32% of those with noninsulin-dependent diabetes died suddenly.

Because both left ventricular dysfunction and electrical instability are associated with a higher mortality rate after hospital discharge, we evaluated the role of these variables in affecting survival in each group. The prevalence of frequent arrhythmias (>10 premature ventricular complexes/h) and its prognostic significance was similar for men and women irrespective of diabetic status. In general, women were more prone to develop congestive heart failure than men. Overall, 7.9% of men and 12.1% of women developed late left ventricular dysfunction. Within each gender, a higher proportion of diabetic than of nondiabetic patients showed signs or symptoms of congestive heart failure (7.3% in nondiabetic men, 19.7% and 11.6%, respectively, in men with insulin-dependent and noninsulin-dependent diabetes; 11.3% in nondiabetic women and 15.4% and 14.2%, respectively, in women with insulin-dependent and noninsulin-dependent diabetes). As expected, the presence of late congestive heart failure was linked to increased mortality in all groups of patients, with a two- to eight-fold increase in 6-month mortality in each group of patients. However, the prognosis of insulin-dependent diabetic women was ominous, even in the absence of signs of congestive heart failure (the postdischarge mortality rate in insulin-dependent diabetic women up to 6 months of follow-up evaluation was 13.1% in the absence and 16.7% in the presence of congestive heart failure). Thus, as shown by the survival curves for patients with and without diabetes stratified by gender (Fig. 2) a history of insulin-dependent diabetes in women itself identifies a subgroup of postmyocardial infarction patients at high risk of in-hospital and postdischarge death.

Table 3. Mortality Rates: Unadjusted Analysis

	In the Hospital			After Discharge		
	Mortality (%)	Odds Ratio (95% CI)	p Value	Mortality (%)	Odds Ratio (95% CI)	p Value
Men						
No diabetes	5.8	1		3.1	1	
Diabetes						
Insulin-dependent	8.7	1.7 (0.8–3.3)	NS	2.2	0.7 (0.3–2.4)	NS
Noninsulin-dependent	10.1	2.0 (1.6–2.6)	< 0.001	4.4	1.5 (1.0–2.2)	< 0.05
Women						
No diabetes	13.9	1		4.3	1	
Diabetes						
Insulin-dependent	24.0	2.2 (1.4–3.5)	< 0.001	13.7	7.3 (3.1–17.4)	< 0.001
Noninsulin-dependent	15.8	1.2 (0.9–1.6)	NS	5.5	1.3 (0.8–2.4)	NS

p values are in comparison with values in nondiabetic patients. CI = confidence interval.

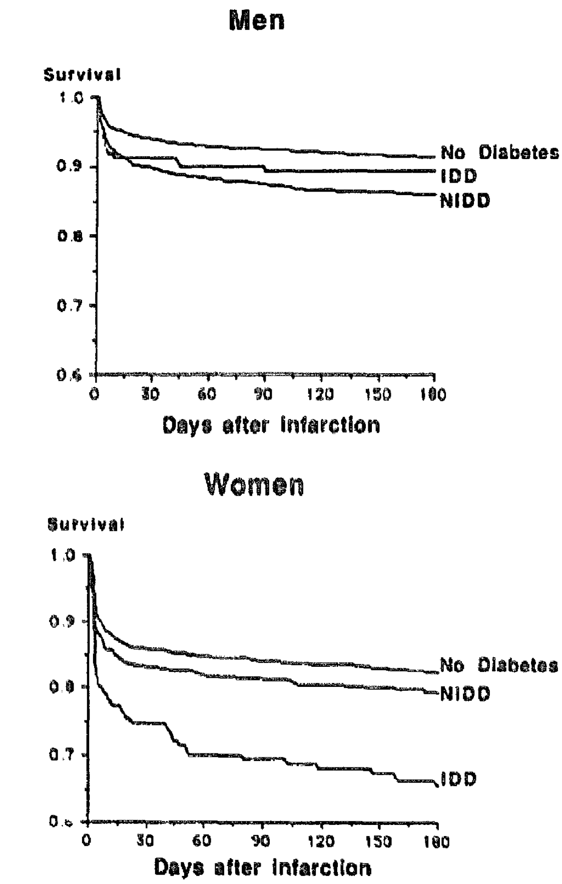

Figure 2. Survival curves from randomization up to 6 months of follow-up for nondiabetic patients and patients with insulin-dependent (IDD) and noninsulin-dependent (NIDD) diabetes.

Discussion

Three major observations can be derived from the results of this study: 1) history of diabetes still exerts a significant and independent role in in-hospital death in patients after myocardial infarction, even when they are treated with fibrinolysis during the acute phase; 2) there is a gender difference in the prognostic significance of diabetes, with the worst prognoses observed for noninsulin-dependent diabetes in men and insulin-dependent diabetes in women; and 3) women with insulin-dependent diabetes may be considered to be at particularly high risk of death after myocardial infarction, irrespective of other clinical variables.

Limitations of the present study. This is a retrospective analysis of data collected for different purposes. Although the stratification by gender and type of diabetes was predefined, the results should be interpreted with caution and need to be confirmed by prospective studies. Also, because the main objective was to assess the prognostic significance of the two types of diabetes in men and women, analysis of mortality was performed on several subgroups so that further stratification for other risk variables may not be meaningful. Finally, a careful definition of the extent of coronary artery disease by invasive techniques such as coronary angiography was not available.

Despite these limitations, the results from this study may have some important implications for understanding the role of concomitant diseases such as diabetes in the prognosis of patients after myocardial infarction and for optimizing their management. Indeed, the possibility to analyze a large group of patients with acute myocardial infarction in which information on type of diabetes was available allowed us to carefully evaluate for each gender, the effect on mortality of noninsulin-dependent and insulin-dependent diabetes. The presence and type of diabetes were assessed by the attending physician on the basis of current definitions (12); thus, these data may well reflect the exact prevalence of diabetes in postinfarction patients. In addition, because no age limits were imposed for enrollment and all patients underwent fibrinolytic treatment during the acute phase of infarction, we believe it is possible to extrapolate with confidence the results of our study to postinfarction patients in the current era.

Prognosis of diabetic patients after myocardial infarction. Our results confirm and extend the results of several studies performed before the advent of fibrinolysis in smaller groups of patients. These studies have consistently shown that diabetic postinfarction patients have a higher mortality rate in the hospital (2–4,13) and after discharge (1). However, our data are in contrast to the recent suggestion (14) that the widespread use of fibrinolysis might have had a greater effect on diabetic patients and therefore minimized the difference between the prognoses of patients with and without diabetes.

In our analysis, diabetic patients were generally more prone to develop in-hospital cardiovascular complications; their mortality rate was 1.5 to 2.5 times higher than that of nondiabetic patients. It is extremely difficult to assess the independent prognostic significance of diabetes in acute myocardial infarction; for example, it is not possible to establish whether the development of acute congestive heart failure after myocardial infarction is independent or is somehow dependent on a previous history of diabetes. Thus, for our multivariate analysis, we selected those variables that were possibly linked, but not consequent to, the acute event, such as age, previous myocardial infarction, history of hypertension, angina, hypercholesterolemia, Killip class and infarct size at admission estimated from the number of ECG leads showing ST segment elevation. The multivariate analysis taking into account those variables confirmed the independent negative prognostic significance of diabetes and particularly of noninsulin-dependent diabetes in men and insulin-dependent diabetes in women.

Several mechanisms may underlie the increased in-hospital mortality rate in diabetic patients. Among them, extensive coronary atherosclerosis and clinical or subclinical diabetic cardiomyopathy appear to be most important (5). Indeed, several studies (15) have shown that extent of coronary atherosclerosis is greater in diabetic than in nondiabetic patients, and in our study, a history of ischemic heart disease was more frequent in diabetic patients (Table 1). However, the increased mortality rate in diabetic patients remained significant, even after adjusting for these important risk factors. A novel and interesting aspect of the pathophysiology of myocardial infarction in diabetic patients was revealed in the present study by the rate of reperfusion assessed noninvasively. Indeed, diabetic patients had a lower rate of reperfusion than did nondiabetic patients, and this difference was most evident for insulin-dependent diabetic women. The several alterations in the fibrinolytic system of diabetic patients (5) that appear at least in part to explain their higher incidence of primary cardiovascular events, may also play a major role in affecting rates of reperfusion and reocclusion after fibrinolysis. This point clearly deserves studies targeted to address it with more specific invasive indexes of reperfusion, because of the obvious limitations of a noninvasive index, but it may be an important clue to interpreting the prognosis of diabetic patients after myocardial infarction in the fibrinolytic era.

Mechanisms of death in diabetic patients. There were no major differences in the cause of death in diabetic versus nondiabetic patients. During the acute and subacute phases of infarction, acute cardiac insufficiency evolving in cardiogenic shock or acute pulmonary edema was the most common cause of death. After hospital discharge, sudden death was responsible for a slightly higher proportion of deaths in diabetic patients, especially among women. These data indicate that not only the absolute risk of death but also the absolute risk of sudden death is higher in diabetic patients, perhaps because of an autonomic imbalance consequent to diabetic neuropathy (16) and responsible for a decreased electrical stability (17).

Gender difference. One of the most intriguing findings of this study was the differential significance of the type of diabetes in relation to gender. Men with both insulin-dependent and noninsulin-dependent diabetes had a moderately higher mortality rate than that of nondiabetic patients during their in-hospital stay. After discharge, the mortality rate in these men was higher only for those with noninsulin-dependent diabetes. In contrast, in women, the prognosis of those with noninsulin-dependent diabetes was only slightly worse than that of nondiabetic patients, whereas insulin-dependent diabetes was associated with a dramatic decrease in survival both in the hospital and after discharge. This was evident even when the main epidemiologic characteristics of insulin-dependent diabetic women and men were largely similar (Table 1).

The possibility cannot be excluded that this result merely represents a chance phenomenon due to the post-hoc subgroup analysis, and the data may vary for different groups of patients because of the wide confidence intervals for the group with insulin-dependent diabetes and the low prevalence of this disease in men. However, the differences observed for in-hospital mortality were confirmed after correcting for several epidemiologic and clinical variables available at admission to the coronary care unit, thus rendering the "chance phenomenon" an improbable explanation. Indeed, a careful analysis of previously published data (2,13) suggests that a major gender difference in the significance of diabetes may be relevant. For example, in the study by Singer et al. (2), which included only patients with noninsulin-dependent diabetes, the mortality rate was identical (26%) for women with or without diabetes, whereas it was much higher in diabetic than in nondiabetic men (27% vs. 13%). Conversely, in the study from the Framingham (13), which included a much higher proportion of women than men taking insulin (27% vs. 14.5%), the relative risk of fatal coronary artery disease was higher for women.

It may be possible that in men, the presence of diabetes leads to an overall decreased survival rate independent from the type of diabetes, whereas in women, insulin-dependent diabetes is uniquely associated with major alterations in cardiovascular function that have a strong impact on mortality after myocardial infarction. Several epidemiologic studies (18) have shown that differences exist in the long-term prognosis of diabetic men and women and that insulin-dependence may play an important role in altering the course of cardiovascular disease. In the study by Savage et al. (4), which compared the prognosis of diabetic men and women after myocardial infarction, the in-hospital mortality rate was almost twice as high in women as in men (37% vs. 19%) and the excess mortality rate in women was attributed to an increased risk of severe congestive heart failure.

The scarcity of data on the type of diabetes in previous studies in patients after acute myocardial infarction does not allow any comparison of data with previous studies. However, the wide difference in the relative risk of death in diabetic compared with nondiabetic patients in previous studies may be at least in part due to the inclusion of a different proportion of patients with insulin-dependent and noninsulin-dependent diabetes in those defined as "diabetic."

Overall, our data indicate that even after the introduction of fibrinolysis, the mortality rate in diabetic patients remains high. An aggressive diagnostic and therapeutic approach may be required in these patients.

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