Long-Term Prognosis After Myocardial Infarction in Men with Diabetes

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SUMMARY

Men (1306) who survived a first myocardial infarction (MI) were studied. The mean follow-up time was 6.5 yr, and at the end of the follow-up period survival status was known for all patients. By the time of the MI the prevalence of diabetes was 5.6%. Patients with and without diabetes were compared. There were no differences in the estimated primary or secondary risk. The cumulative survival rate 1, 2, and 5 yr after the MI was 82, 78, and 58% among the diabetic subjects compared with 94, 92, and 82% among the nondiabetic subjects ($P < 0.001$). The difference remained even after allowance for age and estimated secondary risk in a multivariate regression analysis. There were no differences in mortality rates among patients with type I diabetes compared with type II diabetes, nor among patients treated with diet alone, sulfonylurea, or insulin, but the numbers were small. The cumulative rate of reinfarctions after 1, 2, and 5 yr was 18, 28, and 46% in diabetic subjects and 12, 17, and 27% in nondiabetic subjects ($P = 0.004$).

A history of diabetes was an independent secondary risk factor among male survivors of a first MI with respect to deaths and reinfarctions. DIABETES 1985; 34:787–92.

The incidence of myocardial infarction (MI) and other manifestations of atherosclerosis is increased in diabetes.[1–4] The mortality rate in diabetic patients who have suffered an MI has been reported high in hospital as well as during long-term follow-up compared with nondiabetic patients[5–9] even after allowance for other prognostically important variables.[10] However, because of differences in sampling and selection of patients and differences in diagnostic criteria, direct comparisons between earlier studies are often not relevant.

Reinfarction among diabetic compared with nondiabetic subjects has been sparsely addressed in previous studies and large variations in the rates of reinfarctions have been described.[11,12]

Reliable recording of deaths and reinfarctions during a long period of time requires special efforts. In Göteborg, Sweden, community-wide registration and follow-up of patients with MI have been in operation since 1968, and all methods have been unchanged.[13,14]

The aim of the present study was to compare men with and without diabetes at the time of their first MI with regard to, first, prognostically and clinically important variables and, second, mortality and recurrent MI during long-term follow-up.

PATIENTS AND METHODS

Göteborg is an industrial and merchant city situated on the Swedish west coast, with a population of about 450,000 (220,000 males). Registration of all cases of MI occurring in Göteborg has been in operation since January 1968.[13] All middle-aged patients discharged from hospital with a diagnosis of MI were systematically followed-up at a special Post-MI Clinic—an institution providing outpatient medical care to post-MI patients by trained internists.[14] For administrative reasons, the upper age limit for admission to the Post-MI Clinic was changed a few times.[15] The present study comprised 1306 men who suffered a first MI between January 1968 and December 1977. For all interviews and physical examinations, identical questionnaires were used by the same group of physicians. The patients were treated according to uniform rules established and maintained by means of regular staff meetings. Examinations and interviews took place at intervals required by the clinical situation and always 1, 3, 12, 24, 60, and 120 mo after the MI. The mean drop-out frequency at any of the predetermined outpatient visits was 6%.

Among secondary preventive measures, antismoking in-

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TABLE 1
Treatment of diabetes at discharge from hospital

	N	%
Diet alone	21	28.8
Sulfonylurea, biguanide	37	50.7
Insulin	15	20.5
Total	73	100.0

formation, treatment of hypertension, and prophylactic beta blockade after the MI were emphasized in the annual cohorts 1975 to 1977. Patients with cholesterol levels above 7.8 mmol/L (300 mg/dl) 3 mo after the MI were given general dietary advice. When raised cholesterol levels persisted, lipid-lowering drugs were added at the discretion of the physician. Drug treatment was never given to more than 8% of the patients in the highest cholesterol quintile. Angina pectoris was treated with sublingual and long-acting nitroglycerine and possibly with a beta blocker. Only exceptional patients with disabling angina were brought to coronary bypass surgery.

Patients with a diagnosis of diabetes were always offered systematic follow-up and treatment also for their metabolic disease at the Post-MI Clinic. Regular physical activity until symptoms such as dyspnea or angina appeared was encouraged in all patients. In type II diabetes, if metabolic control was not achieved by diet alone, a sulfonylurea preparation was added, sometimes in combination with a biguanide. If this failed to achieve control, insulin treatment was started. Laboratory control was based on measurement of urine glucose, with glucose-free urine the goal. The diabetic subjects routinely visited the clinic 3–4 times a year. Thus, the diabetic patients were seen more frequently at the Post-MI Clinic than were nondiabetic patients.

Deaths and nonfatal reinfarctions were verified by the MI Register by means of continuous checking of all death certificates and hospital records of all patients admitted with symptoms suggestive of an MI. At the end of the follow-up period, the survival status of all patients was known.

Autopsy was routinely performed in all patients who died outside hospital and in the majority of patients who died in hospital. The total autopsy rate was 80%. Autopsy protocols were always collected.

The patients were followed to December 31, 1979. Thus, the maximum possible observation period was 12 yr. The mean follow-up time was 6.5 yr.

DEFINITIONS

Myocardial infarction. The diagnosis of MI was based on at least two of the following three criteria (A, B, and C):

(A) Central chest pain of more than 15-min duration and with onset within the last 48 h, or pulmonary edema without previously known valvular disorder, syncope or shock without suspicion of acute hypovolemia or intoxication.

(B) Transient rise of S-GOT (S-ASAT: serum aspartate-aminotransferase) with two values above the normal limits supplied by the laboratory and a maximum approximately 24 h after the calculated onset of infarction, combined with a less pronounced increase or lack of increase of S-GPT (S-ALAT: serum alanine-aminotransferase) or two values of S-LD (serum lactate dehydrogenase) above the normal limits with a maximum about 60 h after the calculated onset of infarction, or one raised S-GOT (S-ASAT) value in combination with one raised S-LD value.

(C) EKG series with occurrence of pathologic Q-waves and/or the occurrence or disappearance of localized ST-segment elevations in combination with the development of T-wave inversion in at least two of the 11 routinely recorded standard leads I, II, III, aVR, aVL, aVF, CR_1, CR_2, CR_4, CR_5, and CR_7 (during the latter part of the follow-up period the CR leads were exchanged for V leads).

Reinfarctions. Criteria for a nonfatal reinfarction were identical to those of the primary infarction. A reinfarction was considered nonfatal if the patient was discharged from hospital or alive in hospital 4 wk after onset of the attack.

A reinfarction was defined as fatal: (1) If the patient died when still in hospital within 4 wk from the onset and having fulfilled the conventional criteria defining a clinical diagnosis above. (2) A fatal reinfarction was further suspected in survivors from a primary MI who: (a) were readmitted to hospital with chest pain, pulmonary edema, syncope, or shock and died before enzyme rise or EKG changes developed; (b) died before arrival in hospital; or (c) were found dead outside hospital when no other cause of death such as trauma or suicide was suspected. The diagnosis of a fatal reinfarction was then confirmed for the purpose of the study when among

TABLE 2
Preinfarction characteristics

Variable	Nondiabetic subjects (N = 1229)	Diabetic subjects (N = 73)	P
Age (yr)	53.2 ± 6.5*	54.6 ± 6.2*	0.073
BMI (kg/m^2)	25.0 ± 3.2*	25.3 ± 3.6*	>0.20
Smokers (%)	79.2	69.9	>0.20
Hypertension (%)	22.0	31.5	0.088
Cerebrovascular disease (%)	2.4	6.9	0.070
Intermittent claudication (%)	8.6	7.4	>0.20
Angina pectoris (%)	38.2	45.8	>0.20
Dyspnea (%)	30.6	46.4	0.011
Digitalis (%)	4.7	13.9	0.007
Estimated relative primary risk	1.0	0.96	0.138

*Mean ± SD.

TABLE 3
Characteristics during admission to hospital

Variable	Nondiabetic subjects (N = 1229)	Diabetic subjects (N = 73)	P
Left ventricular failure (%)	21.5	27.4	>0.20
Q-wave infarction (%)	65.7	78.6	0.033
Mean S-ASAT max (μkat/L)	2.9 ± 2.5*	2.8 ± 2.2	>0.20
Mean relative cardiac volume (ml/m² BSA)	469 ± 95*	480 ± 107	>0.20
VF/treated VT (%)	20.5	18.1	>0.20
Atrial fibrillation (%)	4.8	8.3	>0.20
Estimated relative secondary risk	1.0	0.96	>0.20

*Mean ± SD.

categories a–c an autopsy protocol stated the presence of a fresh thrombus occluding a coronary artery, myocardial necrosis, or recent myocardial necrosis in organization.

Some infarctions of very recent onset cannot be detected macroscopically. Microscopic or chemical analysis of the myocardium was not routinely performed in the autopsied patients. The distinction between "myocardial necrosis," "necrosis in organization," and "recent MI" is not clearcut and varies between pathologists, but were all used to describe lesions not older than 1–2 wk, in contrast to "myocardial scar," which denoted an old infarction. The formulation of the present definition of a fatal reinfarction has been discussed elsewhere.[16]

Mortality. All causes of death were considered.

Diabetes diagnosed before MI. A history of diabetes before the MI was recorded if the patient had previously been informed by a physician that he was suffering from diabetes. Type I was defined as diabetes with ketoacidosis that required substitution with insulin. Type II diabetes was defined in patients without ketoacidosis who were treated with diet and/or sulfonylurea.

Diabetes diagnosed during follow-up. Urine was routinely checked for presence of glucose at the visits to the Post-MI Clinic with a qualitative dip slide test. A positive test combined with a fasting serum glucose >6.7 mmol/L (120 mg/dl) were required for a diagnosis of diabetes.

Relative body weight was calculated as body mass index (BMI) according to the following formula: BMI (kg/m²) = (wt [kg]/ht [m²]).

Relative cardiac volume was calculated from biplane chest roentgenograms.[17] The x-ray and measurements of weight and height were performed during one of the last days in hospital.

Definitions of other clinical variables have been published previously.[14]

STATISTICAL METHODS

Fisher's permutation test was used to test differences in continuous and binary variables between diabetic and nondiabetic subjects. For binary variables, this test is equivalent to Fisher's test in a fourfold table.[18] The estimated primary risk was calculated according to a multiple logistic model based on hypertension, serum cholesterol, and smoking habits before MI.[19] This model has been adjusted to be used retrospectively after MI.[20] The estimated secondary risk was calculated according to another multiple logistic model derived in a subsample of the patients in the present study based on hypertension before MI, dyspnea on infarction, maximum A-ASAT, left heart failure, atrial fibrillation, and relative cardiac volume during stay in hospital.[21]

Fisher's exact test was used to test differences in crude mortality and reinfarction rates.

To make use of all information, the Kaplan-Meier estimate was used to produce survival curves.[22] The log rank procedure was used to test differences between survival curves.[23]

The Cox proportional hazard model was used for multivariate comparison.[24]

Conventional methods were used for calculation of means

TABLE 4
Characteristics 3 mo post-MI

Variable	Nondiabetic subjects (N = 1229)	Diabetic subjects (N = 73)	P
Mean S-cholesterol (mmol/L)	7.1 ± 1.2*	6.6 ± 1.4	0.002
Mean SBP (mm Hg)	144 ± 22*	151 ± 26	0.013
Mean DBP (mm Hg)	90 ± 12*	90 ± 13	>0.20
Stopped smoking (%)	45.1	41.7	>0.20
Angina pectoris (%)	53.0	62.1	0.183
Dyspnea (%)	46.3	62.1	0.017
Digitalis (%)	33.4	56.1	>0.001
Beta-blockers (%)	29.4	26.9	>0.20
Other antihypertensive treatment (%)	9.3	16.4	0.100

*Mean ± SD.

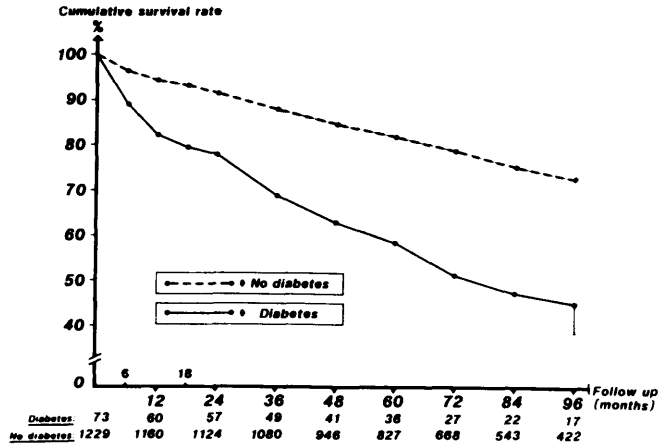

FIGURE 1. Cumulative survival rate in patients with and without diabetes.

and standard deviations. Two-tailed tests were used and P-values <0.05 were considered significant.

RESULTS

The total number of men with a first MI was 1306. By the time of the infarction, the mean age of all patients was 53 yr (range 27–67 yr) and 73 patients (5.6%) had diabetes (mean age 55 yr, range 31–67 yr). Diabetic status was unknown in four patients. Eighty percent of the diabetic patients had type II diabetes. Diabetic treatment at discharge from hospital is presented in Table 1.

Variables of clinical or prognostic importance among diabetic and nondiabetic subjects are compared in Tables 2–4. The diabetic subjects were older at the time of MI. The primary risk factors, tobacco smoking, hypertension, and serum cholesterol, differed significantly between the groups only regarding serum cholesterol (measured 3 mo post-MI, Table 4), but there was a trend toward a higher prevalence of hypertension among the diabetic subjects. However, the estimated primary risk was similar in the two groups. Dyspnea on effort and treatment with digitalis before MI were more common among the diabetic subjects (Table 2).

There was no difference in prevalence of congestive heart failure or arrhythmias during the acute hospital phase and no difference in maximal enzyme release. Pathologic Q-waves on EKG developed more commonly among the diabetic subjects. There was no difference in the estimated secondary risk (Table 3). The mean systolic blood pressure and the prevalence of antihypertensive treatment 3 mo after the MI was higher in the diabetic subjects. Dyspnea on effort and treatment with digitalis were also more common among the diabetic subjects (Table 4).

During the follow-up, 38 deaths (52%) occurred among the patients with diabetes as compared with 307 deaths (25%) among the nondiabetic subjects. Survival curves are presented in Figure 1. The cumulative survival rate 1, 2, and 5 yr after the MI was 82, 78, and 58% among the diabetic subjects as compared with 94, 92, and 82% among the nondiabetic subjects (P < 0.001). The difference remained after allowance for age and estimated secondary risk in a multivariate regression analysis.

The crude mortality rates in the different treatment groups are presented in Table 5. There was a trend toward a higher

TABLE 5
Crude mortality in different treatment groups

	Deaths	
	N	%
Diet alone (N = 21)	9	42.9
Sulfonylurea, biguanide (N = 37)	24	64.9
Insulin (N = 15)	5	33.3

mortality among patients treated with sulfonylureas compared with those on insulin treatment (P = 0.077).

In patients with diabetes, 13% of the deaths were due to diseases other than coronary heart disease, as compared with 21% of the deaths in nondiabetic subjects. The cause of death in the five diabetic subjects who did not die from coronary heart disease was cancer in three, cerebrovascular disease in one, and a traffic accident in one.

The autopsy rate was 81.6% among diabetic subjects and 80.5% among nondiabetic subjects. The extension of coronary arteriosclerosis and the prevalence of scattered myocardial fibrosis, fresh occluding thrombosis, and left ventricular aneurysms were similar in the two groups.

During the follow-up period, 31 diabetic patients (42%) suffered from a reinfarction (fatal and nonfatal) compared with 371 (30%) among nondiabetic subjects. The cumulative rate of reinfarctions after 1, 2, and 5 yr was 18, 28, and 46% in diabetic subjects and 12, 17, and 27% in nondiabetic subjects (Figure 2; P = 0.004). Adjustments for age did not affect the difference between the groups.

In the present series, only two patients had maximum serum creatinine values >2.5 mg/dl (220 μmol/L).

Diabetes was diagnosed in 59 patients during the follow-up. Because of differences in the follow-up time, the mortality and reinfarction rates in the different groups were only crudely comparable, but no great differences emerged (Table 6), nor were mortality or reinfarction rates related to treatment with diet alone, sulfonylurea, or insulin (Table 7).

DISCUSSION

The patients were representative of the middle-aged, male population in Göteborg. During the study period there was only one hospital that admitted patients with suspected MI, and patients with symptoms suggestive of MI were not treated

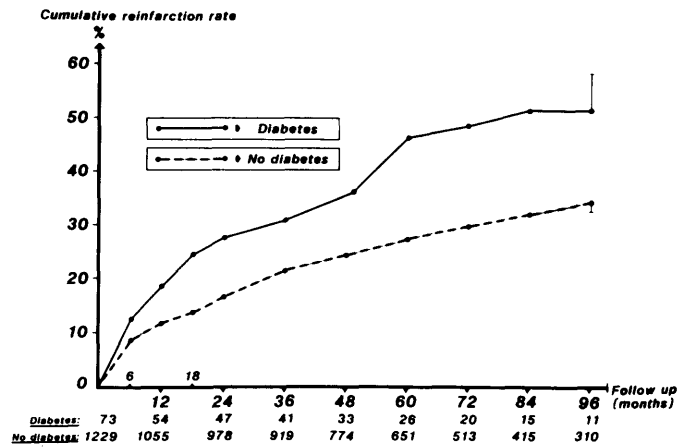

FIGURE 2. Cumulative reinfarction rate in patients with and without diabetes.

TABLE 6
Deaths and nonfatal reinfarctions in relation to time from MI in patients with diabetes diagnosed during the follow-up

Interval (mo after MI)	Patients N	Deaths N	Deaths %	Nonfatal reinfarctions N	Nonfatal reinfarctions %
0–3	20	8	40.0	6	30.0
4–12	16	4	25.0	5	31.3
13–24	8	3	37.5	2	25.0
25–60	15	3	20.0	3	20.0
Total	59	18	30.5	16	27.1

in their homes. An evaluation of the methods for continuous registration of MI revealed that 90% of survivors of MI (by the given criteria) were in fact registered.[13] Thus, only a small number of diabetic subjects surviving an MI may have been missed in this study. On the other hand, the conclusions of the present study cannot be immediately expanded to patients dying before admission and during hospitalization for their first MI.

As the patients were recruited from the entire population, the drawbacks of patient selection were not encountered. Clinics specifically involved in the treatment and control of diabetes often report high mortality rates among those of their patients who suffer from MI.[5,6] Under these circumstances, a selection due to referral of diabetic subjects with secondary complications can be suspected. This subset of diabetic patients probably has a particularly poor prognosis.

The ischemic pain in MI may be distorted in some diabetic subjects, perhaps due to autonomic neuropathy.[25] Among such patients, the presenting symptom of MI may be dyspnea instead of chest pain. The prevalence of painless MI among diabetic subjects in the Göteborg population is unknown, but may present a source of bias, as these patients may not meet the diagnostic criteria for MI. However, it is unlikely that the frequency of so-called silent MI in this age group of diabetic subjects is widely different from the corresponding rate of 20–25% in the general population.[13]

Treatment with digitalis was frequent in the diabetic subjects before as well as after the MI. This may reflect the high prevalence of congestive heart failure that has been reported among diabetic subjects and parallels the observed high frequency of dyspnea before MI. The diabetic cardiomyopathy may be caused by metabolic decompensation or by microangiopathy of the coronary vessels.[26]

The autopsy findings were similar, supporting the view that the difference between diabetic and nondiabetic coronary atherosclerosis is quantitative rather than qualitative.[27] The autopsy technique used in the present series does not allow for any conclusions about differences in the small vessels or in the myocardium.

Although there was an increased prevalence of diabetes among survivors of MI compared with the prevalence in the population, the number of patients was small. In Göteborg, the prevalence of diabetes measured by questionnaire was 1.8–1.9% among middle-aged men in two independent population surveys.[28,29] Prospective collection of a sufficiently large number of patients for valid statistical analysis is very time consuming and thus many of the studies of the prognosis in diabetic subjects after MI have been retrospective, with the disadvantages inherent in such studies.[5–7,30] In a large postinfarction study involving 1591 male patients under age 70 yr with a first MI between 1935 and 1954, there were only 42 survivors with a history of diabetes or a diagnosis of diabetes during the hospital stay.[7] In other studies, because of difficulties in recruiting sufficient numbers of patients, those with history of several earlier infarcts,[9,31] both sexes,[9,31] and wide age ranges[6] were analyzed together.

Patients who survive an MI are subject to selection, since a large proportion of the deaths from MI occur before or during the hospital admission. According to some studies, deaths early during MI were more common among diabetic than among nondiabetic subjects,[6,8,9,32] although this has been disputed by others.[31]

The present study was confined to patients who survived an MI, and data concerning early deaths in relation to diabetic status were not available.

The diagnostic criteria for diabetes vary between different studies. A medical history of diabetes treated with drugs or insulin has been a diagnostic criterion in all studies. In addition, a number of previous studies have used the presence of glucosuria,[1,8,31] blood glucose exceeding preset limits,[1,3,4,31] or a pathologic glucose tolerance test.[3,4,8] Extrapolation of results from studies with different diagnostic criteria must be done with caution. Various degrees of impaired glucose tolerance is not the same as clinical diabetes, although it may aggravate coronary atherosclerosis.[33]

The existence of nondiagnosed diabetes at the time of MI, or diabetes triggered by the acute MI, may be reflected in the somewhat high rate of new diabetic subjects diagnosed at the check-up 3 mo after the MI. Thus, the true prevalence of diabetes at the time of infarction in the present study was probably underestimated, which would tend to decrease prognostic differences between the groups. In the present study, conclusions about the prognostic impact of diabetes will thus tend to be overly modest.

To analyze whether diabetes had an independent influence on prognosis after MI, adjustments had to be made for possible confounders. In the present study, adjustments have been made for age and estimated 2-yr prognosis. A few authors have used mathematical procedures to adjust for differences in the prevalence of risk factors. The Health Insurance Plan of New York Study (HIP) found no significant difference in total deaths, cardiac deaths, or nonfatal recurrences over 4.5 yr among diabetic compared with nondiabetic subjects. All patients were men, discharged from hospital after a first MI, and adjustments were made for differences in age.[12] In the Swedish CCU Study, in which the short-term prognosis after MI was investigated, the mortality rate was increased in patients with a history of diabetes. After multivariate analysis, diabetes made an independent contri-

TABLE 7
Deaths and nonfatal reinfarctions in different treatment groups in patients with diabetes diagnosed during the follow-up

Treatment	Patients N	Deaths N	Deaths %	Nonfatal reinfarctions N	Nonfatal reinfarctions %
Diet	22	7	31.8	5	22.7
Sulfonylurea	33	10	30.3	9	27.3
Insulin	4	1	25.0	2	50.0
Total	59	18	30.5	16	27.1

bution to prognosis, but later was not included in the prognostic index because of inability to reach a predetermined level of significance.[10] In another post-MI study from Stockholm, a history of diabetes on MI was independently related to reinfarctions during 1 yr follow-up.[34] Among long-term studies of prognosis after MI, subjects with impaired glucose tolerance from the placebo group of the Coronary Drug Project had a worse prognosis than those with normal glucose tolerance. Multivariate analysis revealed an independent prognostic significance.[35] Similar results among patients with a history of diabetes were recently reported from the Perth Coronary Register.[36]

So far, no controlled study has demonstrated what kind of treatment should be preferred in diabetic subjects who survive an MI. The high mortality rate among patients on oral antidiabetic drugs demonstrated in the present study as well as in earlier studies may be explained by differences in age and other risk factors between the different treatment groups. This issue has been reviewed.[27] The present findings do not represent outcome in a randomized prospective trial and must be interpreted with caution.

In conclusion, among unselected, middle-aged men who had survived a first MI, a history of diabetes was associated with a high rate of deaths and reinfarctions during long-term follow-up, even after adjustment for other risk factors.

New studies on secondary prevention in diabetic subjects are needed to demonstrate whether specific antidiabetic treatment may have a more favorable effect on prognosis. Until then, optimal metabolic control should be aimed at among these patients. Other well-documented secondary preventive measures such as cessation of smoking[15,37] and treatment with beta blockers[38–41] should be vigorously applied to these patients with a high secondary risk. It is important to note that this applies also to diabetic subjects.[42]

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