

MORTALITY FROM CORONARY HEART DISEASE IN SUBJECTS WITH TYPE 2 DIABETES AND IN NONDIABETIC SUBJECTS WITH AND WITHOUT PRIOR MYOCARDIAL INFARCTION

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ABSTRACT

Background Type 2 (non-insulin-dependent) diabetes is associated with a marked increase in the risk of coronary heart disease. It has been debated whether patients with diabetes who have not had myocardial infarctions should be treated as aggressively for cardiovascular risk factors as patients who have had myocardial infarctions.

Methods To address this issue, we compared the seven-year incidence of myocardial infarction (fatal and nonfatal) among 1373 nondiabetic subjects with the incidence among 1059 diabetic subjects, all from a Finnish population-based study.

Results The seven-year incidence rates of myocardial infarction in nondiabetic subjects with and without prior myocardial infarction at base line were 18.8 percent and 3.5 percent, respectively ($P < 0.001$). The seven-year incidence rates of myocardial infarction in diabetic subjects with and without prior myocardial infarction at base line were 45.0 percent and 20.2 percent, respectively ($P < 0.001$). The hazard ratio for death from coronary heart disease for diabetic subjects without prior myocardial infarction as compared with nondiabetic subjects with prior myocardial infarction was not significantly different from 1.0 (hazard ratio, 1.4; 95 percent confidence interval, 0.7 to 2.6) after adjustment for age and sex, suggesting similar risks of infarction in the two groups. After further adjustment for total cholesterol, hypertension, and smoking, this hazard ratio remained close to 1.0 (hazard ratio, 1.2; 95 percent confidence interval, 0.6 to 2.4).

Conclusions Our data suggest that diabetic patients without previous myocardial infarction have as high a risk of myocardial infarction as nondiabetic patients with previous myocardial infarction. These data provide a rationale for treating cardiovascular risk factors in diabetic patients as aggressively as in nondiabetic patients with prior myocardial infarction. (N Engl J Med 1998;339:229-34.)

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DIABETES is associated with a marked increase (by a factor of two to four) in the risk of coronary heart disease.¹⁻⁴ Clinically established coronary heart disease itself is associated with an increase in mortality from coronary heart disease by a factor of three to seven, depending on the mode of presentation.^{5,6} The plasma cholesterol level is a strong predictor of the risk of cardiovascular events both in patients with diabetes^{4,7}

and in patients with coronary heart disease.^{5,6} The high-risk status of these groups of patients and their need for more aggressive lipid-lowering therapy have been recognized by both the National Cholesterol Education Program⁸ and the American Diabetes Association.⁹

The reduction in plasma lipids recommended by the National Cholesterol Education Program is greater for patients with coronary heart disease than for patients with diabetes. However, there were differing opinions among members of the National Cholesterol Education Program panel, with some suggesting that diabetic patients should have the same intensity of cholesterol-lowering therapy as patients with coronary heart disease. Thus, there is controversy about how aggressively to treat cardiovascular risk factors in patients with diabetes. It has been suggested that such patients should be treated as if they had established coronary heart disease.¹⁰

Additional interest has focused on the role of lipid-lowering therapy in reducing coronary heart disease in patients with diabetes since data on the efficacy of lipid-lowering therapy with simvastatin and pravastatin in patients with both diabetes and pre-existing coronary heart disease were published by the Scandinavian Simvastatin Survival Study^{11,12} and the Cholesterol and Recurrent Events study.¹³ In the Scandinavian Simvastatin Survival Study,¹² lipid-lowering therapy produced a greater reduction in the rate of coronary events in diabetic subjects than in nondiabetic subjects (55 percent vs. 32 percent). However, in the Cholesterol and Recurrent Events study,¹³ there were similar reductions in diabetic and nondiabetic subjects (27 percent and 25 percent, respectively).

One way to assess whether patients with diabetes and patients who already have clinical coronary heart disease have a similar risk of cardiovascular events is to compare the risk of such events in diabetic subjects with and without prior coronary heart disease with that in nondiabetic subjects with and without

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prior coronary heart disease. In previous reports, the excess risk of coronary events in patients with prior myocardial infarction (a six-to-sevenfold difference)^{5,6} was higher than the excess risk in diabetic patients (a two-to-fourfold difference).¹⁻⁴ However, comparisons across populations are difficult. Furthermore, diabetic patients are overrepresented among patients with myocardial infarction,¹⁻⁴ and diabetic patients with myocardial infarction have a worse prognosis than nondiabetic patients with myocardial infarction.¹⁴⁻¹⁶ Little information is available on mortality from coronary heart disease in diabetic patients without prior myocardial infarction as compared with nondiabetic patients with prior myocardial infarction. We examined this issue in a well-characterized Finnish population-based cohort using standardized criteria for both type 2 diabetes and myocardial infarction.¹⁷

METHODS

The study was approved by the ethics committees of Kuopio University Hospital and the Turku University Central Hospital. All subjects gave informed consent.

Cross-Sectional Study

Subjects with Type 2 Diabetes

The Finnish Social Insurance Institution maintains a central register of all patients with diabetes who receive reimbursement for drugs. On the basis of information from this register, we identified all diabetic patients 45 to 64 years of age born and living in the Kuopio University Hospital district in eastern Finland or the Turku University Central Hospital district in western Finland. The formation of the final patient population, consisting of 510 diabetic subjects from eastern Finland and 549 from western Finland who participated in the study from 1982 to 1984 (participation rates, 83 and 79 percent, respectively) has been previously described.¹⁸ One hundred twenty-eight subjects with insulin-dependent diabetes had previously been excluded on the basis of C-peptide measurements. None of the subjects who were classified as having type 2 diabetes according to World Health Organization (WHO) criteria¹⁹ and who were included in the final study population had a history of ketoacidosis. Only nine subjects (seven men and two women) with type 2 diabetes were receiving hypolipidemic drugs at base line.

Nondiabetic Subjects

A random control sample of subjects born and living in the Kuopio University Hospital district or the Turku University Central Hospital district was taken from the population register that listed all persons 45 to 64 years of age living in these districts.¹⁸ The participation rates were 79 percent in the Kuopio district and 85 percent in the Turku district.

The study protocol was carried out during one outpatient visit at the Clinical Research Unit of the University of Kuopio or the Rehabilitation Research Center of the Social Insurance Institution in Turku. These methods have been previously described in detail.¹⁸ The visit included an interview concerning smoking, alcohol intake, physical activity, the use of drugs, and any history of chest pain suggestive of coronary heart disease. All medical records of subjects who reported that they had been admitted to the hospital for chest pain were reviewed. Review of the medical records was performed by two investigators after a careful standardization of the methods. The WHO criteria for verified definite or possible myocardial infarction, based on chest-pain symptoms, elec-

trocardiographic changes, and enzyme determinations, were used to define previous myocardial infarction.²⁰

The WHO criteria for verified definite or possible stroke were used in the ascertainment of the diagnosis of previous stroke, which was defined as a clinical syndrome consisting of neurologic symptoms persisting for more than 24 hours.²¹ Thromboembolic and hemorrhagic strokes, but not subarachnoid hemorrhage, were included in the diagnosis of stroke.

Smoking status was based on an interview. In all statistical analyses, subjects were classified as nonsmokers, former smokers, or current smokers.

Blood pressure was measured to the nearest 2 mm Hg with a mercury sphygmomanometer with the subject in the sitting position after a five-minute rest. Subjects were classified as having hypertension if they were receiving drug treatment for hypertension or if they had a systolic pressure of at least 160 mm Hg or a diastolic pressure of at least 95 mm Hg. Hypertension was treated as a dichotomous variable in our statistical analyses.

Blood specimens were drawn at 8 a.m. after a 12-hour fast. Fasting plasma glucose was determined by the glucose oxidase method (Boehringer Mannheim, Mannheim, Germany). Serum lipids and lipoproteins were measured in fresh serum samples.¹⁸ Lipids and lipoproteins were treated as continuous variables in the statistical analyses.

Follow-up Study

In 1990, a questionnaire about hospitalization for acute chest pain and symptoms suggestive of stroke was sent to every surviving member of the original study cohort. All medical records of the subjects who died between the base-line examination and December 31, 1989, or who reported on the questionnaire that they had been admitted to the hospital because of chest pain or symptoms suggestive of stroke between the base-line examination and December 31, 1989, were reviewed by one of the investigators. The modified WHO criteria for definite or possible myocardial infarction, which are based on chest pain, electrocardiographic changes, and enzyme determinations, were used in the ascertainment of the diagnosis of myocardial infarction, as was done in the base-line study.²⁰ In the final classification of the causes of death, hospital records and autopsy records were used, if available. To ensure that the data collection was complete, a computerized hospital-discharge register was used to check for hospital admissions of all participants in the base-line study; in cases of symptoms of myocardial infarction or stroke, medical records were also checked. Copies of death certificates of the subjects who had died were obtained from the Central Statistical Office of Finland.

The WHO definition of definite and possible stroke used in the ascertainment of a new stroke event was similar to that used in the base-line study — that is, a clinical syndrome consisting of a neurologic deficit persisting for more than 24 hours (nonfatal stroke), without the presence of other diseases that explained the symptoms.²¹ The causes of death from stroke included codes 431 through 434 of the *International Classification of Diseases, Ninth Revision*.

Statistical Analysis

Data analyses were performed with the SPSSX and SPSS/PC programs (SPSS, Chicago). The results for continuous variables are given as means (\pm SE) or percentages. The differences among the groups were assessed by logistic regression (for dichotomous data) or Student's two-tailed t-test (for continuous data) for independent samples, when appropriate. Univariate and multivariate Cox regression models²² were used to investigate the association of cardiovascular risk factors with the incidence of cardiovascular events. Kaplan-Meier survival curves were used to construct figures for mortality from coronary heart disease. The numbers of subjects at risk for cardiovascular events during the follow-up period were as follows. Of nondiabetic subjects without prior myocardial infarction at base line, 1278 were at risk at two years, 1266 at four years, 1246 at six years, and 681 at seven

years. Of nondiabetic subjects with prior myocardial infarction at base line, 64 were at risk at two years, 58 at four years, 56 at six years, and 27 at seven years. Of subjects with type 2 diabetes without prior myocardial infarction at base line, 819 were at risk at two years, 762 at four years, 691 at six years, and 455 at seven years. Of subjects with type 2 diabetes with myocardial infarction at base line, 155 were at risk at two years, 138 at four years, 105 at six years, and 731 at seven years. Since the maximal follow-up period was 7.93 years, no subjects were at risk at 8 years. All P values are two-sided.

RESULTS

Table 1 shows the clinical characteristics of the subjects according to diabetic status and history of myocardial infarction at base line. In the overall population, type 2 diabetes was associated with older age, higher body-mass index, a greater prevalence of hypertension, higher triglyceride levels, and lower levels of low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol. In the overall population, prior myocardial infarction was associated with male sex, smoking, older age, hypertension, obesity, higher total and LDL cholesterol and triglyceride levels, and lower HDL cholesterol levels.

Table 2 shows the seven-year incidence of cardiovascular events in relation to diabetic status and history of myocardial infarction at base line. In both diabetic and nondiabetic subjects, a history of myocardial infarction at base line was significantly associated with an increased incidence of myocardial infarction (fatal and nonfatal), stroke (fatal and nonfatal), and death

from cardiovascular causes. The incidence of myocardial infarction among nondiabetic subjects was 18.8 percent in those with prior myocardial infarction and 3.5 percent in those without prior myocardial infarction. Among diabetic subjects, the incidence of myocardial infarction was 45.0 percent in those with prior myocardial infarction and 20.2 percent in those without prior myocardial infarction. In the overall population, both diabetes and the prevalence of myocardial infarction were associated with an increased incidence of cardiovascular events.

Figure 1 shows the Kaplan–Meier estimates of the probability of death from coronary heart disease. Diabetic subjects with prior myocardial infarction had the worst prognosis, whereas nondiabetic subjects without prior myocardial infarction had the best prognosis. Diabetic subjects without prior myocardial infarction and nondiabetic subjects with prior myocardial infarction had an intermediate survival rate, and these two groups had similar outcomes.

Table 3 shows the results of a Cox proportional-hazards model comparing diabetic subjects without prior myocardial infarction with nondiabetic subjects with prior myocardial infarction. The age- and sex-adjusted hazard ratio was not significantly different from 1.0 (hazard ratio, 1.4; 95 percent confidence interval, 0.7 to 2.6), suggesting that these groups have similar mortality rates. Further adjustment for LDL cholesterol, HDL cholesterol, triglyc-

TABLE 1. RISK FACTORS FOR CORONARY HEART DISEASE AT BASE LINE IN RELATION TO THE HISTORY OF MYOCARDIAL INFARCTION IN SUBJECTS WITH TYPE 2 DIABETES AND IN NONDIABETIC SUBJECTS.*

VARIABLE†	NONDIABETIC SUBJECTS			SUBJECTS WITH TYPE 2 DIABETES			ALL SUBJECTS	
	PRIOR MI (N=69)	NO PRIOR MI (N=1304)	P VALUE	PRIOR MI (N=169)	NO PRIOR MI (N=890)	P VALUE	P VALUE FOR PRIOR MI VS. NO PRIOR MI	P VALUE FOR DIABETES VS. NO DIABETES
Sex (M/F)	51/18	587/717	<0.001	115/54	466/424	<0.001	<0.001	0.1
Age (yr)	56.2±0.2	54.6±0.6	0.02	59.1±0.3	57.9±0.2	0.007	<0.001	<0.001
Body-mass index	27.3±0.5	26.5±0.1	0.12	29.3±0.3	29.2±0.2	0.922	0.001	<0.001
Hypertension (%)	43.5	31.9	0.05	66.9	62.2	0.3	<0.001	<0.001
Total cholesterol (mmol/liter)	7.07±0.16	6.80±0.04	0.1	7.04±0.12	6.68±0.06	0.01	0.01	0.2
HDL cholesterol (mmol/liter)	1.32±0.05	1.50±0.01	<0.001	1.08±0.02	1.23±0.01	<0.001	<0.001	<0.001
LDL cholesterol (mmol/liter)	4.93±0.14	4.71±0.03	0.2	4.68±0.02	4.39±0.04	0.003	0.06	<0.001
Triglycerides (mmol/liter)	2.00±0.15	1.40±0.02	<0.001	3.07±0.14	2.52±0.03	0.001	<0.001	<0.001
Smoking status (%)								
Never smoked	33.3	59.2	0.02	46.7	66.8	0.8	0.01	0.3
Former smoker	36.2	21.6		37.3	16.6			
Current smoker	30.4	19.2		16.0	16.6			
Duration of diabetes (yr)	—	—	—	8.05±0.83	8.06±0.14	1.0	1.0	1.0
Fasting plasma glucose (mmol/liter)	5.40±0.08	5.43±0.02	0.8	11.89±0.31	11.67±0.13	0.5	<0.001	<0.001

*Two-way analysis of variance was performed for continuous variables, and logistic regression was performed for noncontinuous variables. MI denotes myocardial infarction, HDL high-density lipoprotein, and LDL low-density lipoprotein. Plus–minus values are means ±SE.

†The body-mass index was calculated as the weight in kilograms divided by the square of the height in meters. To convert values for cholesterol to milligrams per deciliter, divide by 0.02586. To convert values for triglycerides to milligrams per deciliter, divide by 0.01129. To convert values for glucose to milligrams per deciliter, divide by 0.05551.

TABLE 2. INCIDENCE OF CARDIOVASCULAR EVENTS DURING A SEVEN-YEAR FOLLOW-UP IN RELATION TO HISTORY OF MYOCARDIAL INFARCTION IN SUBJECTS WITH TYPE 2 DIABETES AND IN NONDIABETIC SUBJECTS.*

EVENT	NONDIABETIC SUBJECTS			SUBJECTS WITH TYPE 2 DIABETES			ALL SUBJECTS	
	PRIOR MI (N=69)	NO PRIOR MI (N=1304)	P VALUE	PRIOR MI (N=169)	NO PRIOR MI (N=890)	P VALUE	P VALUE FOR PRIOR MI VS. NO PRIOR MI	P VALUE FOR DIABETES VS. NO DIABETES
Fatal or nonfatal MI								
Incidence during follow-up	18.8	3.5	<0.001	45.0	20.2	<0.001	<0.001	<0.001
Events/100 person-yr	3.0	0.5		7.8	3.2			
Fatal or nonfatal stroke								
Incidence during follow-up	7.2	1.9	0.01	19.5	10.3	<0.001	<0.001	<0.001
Events/100 person-yr	1.2	0.3		3.4	1.6			
Death from cardiovascular causes								
Incidence during follow-up	15.9	2.1	<0.001	42.0	15.4	<0.001	<0.001	<0.001
Events/100 person-yr	2.6	0.3		7.3	2.5			

*P values were calculated with Cox proportional-hazards models. The Cox models were adjusted for age and sex. MI denotes myocardial infarction.

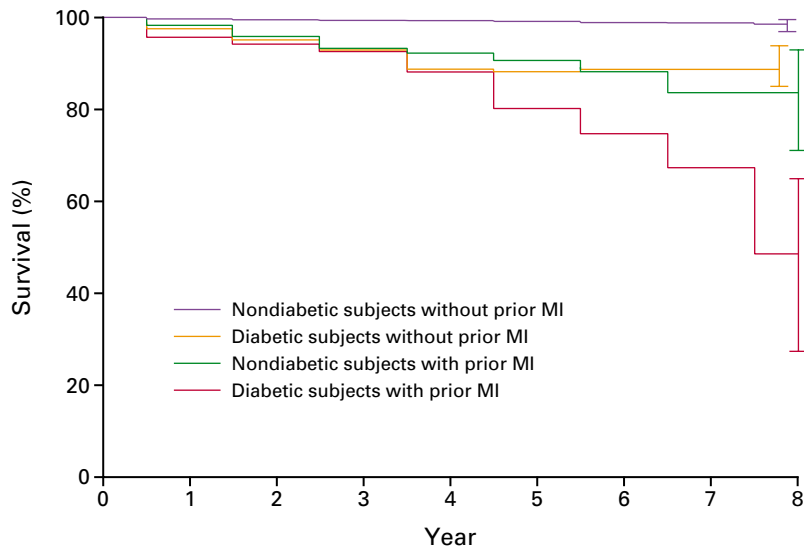


Figure 1. Kaplan–Meier Estimates of the Probability of Death from Coronary Heart Disease in 1059 Subjects with Type 2 Diabetes and 1378 Nondiabetic Subjects with and without Prior Myocardial Infarction. MI denotes myocardial infarction. I bars indicate 95 percent confidence intervals.

eride, smoking, and hypertension did not significantly change the results.

DISCUSSION

We confirmed earlier reports¹⁴⁻¹⁶ that both diabetic and nondiabetic subjects with prior myocardial infarction have an increased incidence of cardiovascular events. The seven-year rate of major cardiovascular events for diabetic subjects with previous myocardial infarction in this study was similar to that reported for diabetic subjects in the Scandinavian Simvastatin Survival Study (45 percent)¹² over a period of 5.4

years, a somewhat shorter period of follow-up. As expected, diabetic subjects had much higher mortality from coronary heart disease than nondiabetic subjects, confirming previous results.¹⁻⁴

The more critical issue is whether diabetic subjects without prior myocardial infarction have a risk of infarction similar to that of nondiabetic subjects with prior myocardial infarction. If this is true, it suggests a similar base-line risk of cardiovascular disease, and perhaps that similar management of cardiovascular risk factors in these groups is indicated. Our data indicate a similar incidence of cardiovascu-

TABLE 3. RESULTS OF COX PROPORTIONAL-HAZARDS MODEL COMPARING MORTALITY FROM CORONARY HEART DISEASE IN 890 SUBJECTS WITH TYPE 2 DIABETES WITHOUT PRIOR MYOCARDIAL INFARCTION WITH THAT IN 69 NONDIABETIC SUBJECTS WITH PRIOR MYOCARDIAL INFARCTION DURING A SEVEN-YEAR FOLLOW-UP.*

VARIABLE	HAZARD RATIO FOR DIABETIC SUBJECTS (95% CI)	P VALUE
Adjusted for age, sex	1.4 (0.7–2.6)	0.4
Adjusted for age, sex, smoking status, hypertension, LDL cholesterol, HDL cholesterol, and triglycerides	1.2 (0.6–2.4)	0.5

*CI denotes confidence interval, LDL low-density lipoprotein, and HDL high-density lipoprotein.

lar disease in these groups, both after adjustment for demographic variables (age and sex) and after further adjustment for other cardiovascular risk factors (smoking, hypertension, and LDL cholesterol, HDL cholesterol, total cholesterol, and triglyceride levels). The number of diabetic subjects in this report was large, and the samples of subjects with diabetes and without diabetes were population-based, suggesting that these results may be generalizable. However, the confidence intervals around the risk ratios were wide, indicating that the power of the study to detect differences between the two groups was limited.

It was recently shown that the one-year case fatality rate for a first myocardial infarction (from the onset of symptoms, thus including prehospitalization mortality) in the population studied in the Finnish Monitoring International Cardiovascular Disease (FINMONICA) trial¹⁶ was 45 percent in diabetic men and 39 percent in diabetic women. These case fatality rates were significantly higher than the rates in nondiabetic subjects (38 percent for men and 25 percent for women). Of the diabetic subjects who died, 50 percent of men and 25 percent of women died before hospitalization. These patients, by definition, could not benefit from secondary prevention strategies, indicating (especially in diabetic men) that aggressive management of cardiovascular risk factors in diabetic subjects should precede the onset of clinical coronary heart disease.

Several clinical trials have shown that 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor therapy reduces the incidence of cardiovascular events in diabetic patients with prior coronary heart disease. In the Scandinavian Simvastatin Survival Study, simvastatin reduced the incidence of coronary heart disease events in diabetic subjects by 55 percent.¹² In the Cholesterol and Recurrent Events study, pravastatin reduced the incidence of cardiovascular events in diabetic subjects by 27 percent.¹³ Unfortunately, there are no results from clinical trials of

lipid-lowering therapy with HMG-CoA reductase inhibitors in diabetic patients without prior coronary heart disease. Such trials are currently under way.

One potential limitation of the current study is that the rates of mortality from coronary heart disease in Finland are among the highest in the world.²³ However, for a number of reasons, we believe our data are likely to be generalizable to countries with lower rates of coronary heart disease. Within Finland, rates of coronary heart disease vary widely,²³ ranging from very high in eastern Finland (Kuopio) to lower in western Finland (Turku). In Turku, the rate of coronary heart disease in men is somewhat higher than that in men in the United States, whereas the rate of coronary heart disease in women in Turku is actually lower than that in women in the United States.²³ Furthermore, in this population, the relation between type 2 diabetes and both the prevalence¹⁸ and incidence²⁴ of coronary heart disease is similar in both high-risk areas (eastern Finland) and moderate-risk areas (western Finland).

Finally, we completed a preliminary analysis of atherosclerosis (indicated by intimal-wall thickness as assessed by B-mode ultrasonography of the common and internal carotid arteries) in the Insulin Resistance Atherosclerosis Study, a multiethnic study involving Hispanics, non-Hispanic whites, and African Americans in the United States.²⁵ Carotid-artery intimal-wall thickness was very similar in diabetic subjects without clinical coronary artery disease and nondiabetic subjects with clinical coronary artery disease. Diabetic subjects with coronary artery disease had the greatest intimal-wall thickness, and nondiabetic subjects without coronary artery disease had the lowest. These results support the current findings and, furthermore, suggest that the high rate of coronary heart disease in diabetic patients without vascular disease at base line may be due to accelerated atherosclerosis.

In conclusion, we have shown that patients with type 2 diabetes who have not had a myocardial infarction have a risk of infarction similar to that among nondiabetic patients who have had a prior myocardial infarction. This observation, combined with the results of previous studies showing the efficacy of lipid-lowering therapy in diabetic patients with coronary heart disease^{12,13} and the high mortality (including prehospital mortality) after myocardial infarction,¹⁴⁻¹⁶ suggests that all persons with diabetes could be treated as if they had prior coronary heart disease. The best way to answer this question more definitively would be to conduct a clinical trial comparing the effect of different levels of lipid-lowering therapy on coronary heart disease in diabetic subjects. Clinical trials, however, are very expensive and take many years to complete. In the short term, further confirmation of our findings may come from other observational studies.

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