# Cardiac Events in 735 Type 2 Diabetic Patients Who Underwent Screening for Unknown Asymptomatic Coronary Heart Disease

## 5-year follow-up report from the Milan Study on Atherosclerosis and Diabetes (MiSAD)

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**OBJECTIVE** — To report the cardiac events in type 2 diabetic outpatients screened for unknown asymptomatic coronary heart disease (CHD) and followed for 5 years.

**RESEARCH DESIGN AND METHODS** — During 1993, 925 subjects aged 40–65 years underwent an exercise treadmill test (ETT). If it was abnormal, the subjects then underwent an exercise scintigraphy. Of the 925 subjects, 735 were followed for 5 years and cardiac events were recorded.

**RESULTS** — At the entry of the study, 638 of the 735 followed subjects had normal ETT, 45 had abnormal ETT with normal scintigraphy, and 52 had abnormal ETT and abnormal scintigraphy. The 52 subjects with abnormal scintigraphy and ETT underwent a cardiological and diabetological follow-up; the subjects with just abnormal ETT had a diabetological follow-up only. During the follow-ups, 42 cardiac events occurred: 1 fatal myocardial infarction (MI), 20 nonfatal MIs, and 10 cases of angina in the 638 subjects with normal ETT; 1 fatal MI in the 45 subjects with normal scintigraphy; and 1 fatal MI and 9 cases of angina in the 52 subjects with abnormal scintigraphy. In these 52 subjects all cardiac events were significantly more frequent ($\chi^2 = 21.40$, $P < 0.0001$) but the ratio of major (cardiac death and MI) to minor (angina) cardiac events was significantly lower ($P = 0.002$). Scintigraphy abnormality (hazard ratio 5.47; $P < 0.001$; 95% CI 2.43–12.29), diabetes duration (1.06; $P = 0.021$; 1.008–1.106), and diabetic retinopathy (2.371; $P = 0.036$; 1.059–5.307) were independent predictors of cardiac events on multivariate analysis.

**CONCLUSIONS** — The low ratio of major to minor cardiac events in the positive scintigraphy group may suggest, although it does not prove, that the screening program followed by appropriate management was effective for the reduction of risk of major cardiac events.

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**Abbreviations:** CHD, coronary heart disease; ECG, electrocardiogram; ETT, exercise treadmill test; MI, myocardial infarction; MiSAD, Milan Study on Atherosclerosis and Diabetes.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Many studies have investigated the presence of unknown asymptomatic coronary heart disease (CHD) among diabetic subjects (1–7). Each of these studies has shown, with different rates depending on the diagnostic methods and selection criteria used, increased prevalence rates compared with the general population. However, to our knowledge, none of these studies has followed screened patients prospectively. In 1993 we created the Milan Study on Atherosclerosis and Diabetes (MiSAD), and undertook a screening procedure for CHD detection in type 2 middle-aged diabetic outpatients, free from known and asymptomatic CHD (8). The aim of this article is to report on cardiac events in 735 screened subjects over a 5-year follow-up period.

## RESEARCH DESIGN AND METHODS

### Patient population

A total of 925 type 2 diabetic outpatients, aged 40–65 years, who were free from known and asymptomatic CHD were enrolled in seven Diabetology Centers during 1993. These patients did not have proliferative retinopathy, their serum creatinine was <1.5 mg/dl, peripheral or cerebral arteriopathy was absent, hypertension requiring more than two drugs was not present, and the patients were not poor-prognosis disease patients. CHD was screened by exercise treadmill test (ETT). When this test was abnormal, ex-

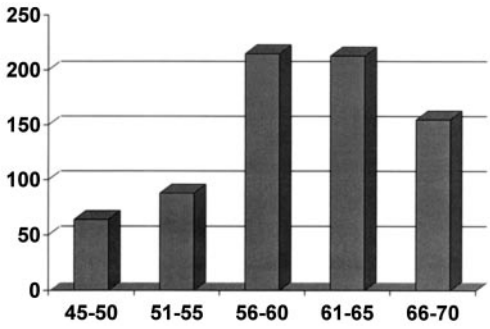


**Figure 1—***Age distribution of patients completing the 5-year follow-up period* (N = *735*).

ercise thallium-201 scintigraphy was performed. The ETT was considered positive in the presence of a horizontal or downsloping ST-segment depression ≥0.1 mV, or an upsloping ST-segment depression ≥0.2 mV, measured at 0.08 s after the *J* point. Exercise thallium-201 scintigraphy was classified as abnormal if perfusion defects were present. In the MiSAD article (8), patients with abnormal scintigraphy were defined as affected by asymptomatic unknown CHD.

One center was unable to participate in the follow-up study, and the 150 patients screened in this center did not participate in the follow-up. Of the patients referring to the remaining six centers participating in the follow-up, 40 moved to another city before completing the 5-year follow-up period and thus were completely removed from the follow-up analysis. At the time of removal from the study, these subjects did not show any events.

The study population of 735 patients (267 females and 468 males) were followed for 5 years. At the time of the screening, 638 of 735 presented normal ETT, 45 presented abnormal ETT but normal scintigraphy, and 52 had abnormal ETT and abnormal scintigraphy.

## Follow-up studies

At the end of the follow-up the mean age was 59.6 years and the mean diabetes duration was 12.4 ± 6.1 years. Figure 1 shows the age distribution. Table 1 shows the variables recorded in the study population in 1993 and the values at the end of the study of the variables monitored during the follow-up (Table 1).

On the basis of screening results in 1993, all 52 subjects with abnormal scintigraphy were placed on 100 mg daily of acetylsalicylic acid and underwent cardiological consultation. On the basis of the advice of a cardiologist, 22 subjects underwent coronary angiography. Stenoses >50% of vessel lumen were found in all cases. Five patients had three-vessel involvement; four of these subjects underwent coronary bypass. The remaining subject was considered not to be an appropriate candidate for surgical intervention. Six patients had two-vessel involvement, and four of these subjects underwent coronary angioplasty. Eleven had involvement that was limited to a single vessel, and none underwent a revascularization procedure. These 52 patients followed the cardiologist's follow-up protocol.

All of the subjects with normal ETT and abnormal ETT, but with normal scintigraphy, did not undergo any further cardiologic work-up (except for the annual resting electrocardiogram [ECG]) in the absence of any cardiac symptoms.

All 735 followed subjects underwent an average of four diabetological evaluations per year. Examination included determination of GHb ($HbA_{1c}$, Hb%, high-pressure liquid chromatography; normal value 4–6.4%), albuminuria (nefelometry), arterial blood pressure, and BMI measurement. The presence of diabetic retinopathy was assessed once a year by fundus oculi examination performed by an ophthalmologist, as well as total cholesterol (colorimetry), HDL cholesterol (Polyethylene Glycol 6000), triglycerides (colorimetry), and resting ECG. These data, together with drug therapy data, were recorded on a study form and sent to the coordinating center in charge of the central database. A special form was used to record all events—cardiac and noncardiac. Cardiac death, myocardial infarction, resting angina, and effort angina were considered cardiac events. Major events were defined as cardiac death and MI; minor events were defined as resting and effort angina. Each cardiac event was reported in this work by means of hospital admission chart or the cardiologist medical report.

## Statistical analysis

Cardiac events were the primary end points. Differences in event frequencies were evaluated by a $\chi^2$ test or an Fisher's exact test.

An incidence rate estimation with the CI of cardiac events was performed. The Cox model with the Stata statistical soft-

**Table 1—***Clinical parameters of study population* (N = *735*) *recorded in 1993 and values at the end of the study of the variables monitored during follow-up*

| Variables | 1993 | 1998 |
|---|---|---|
| Family history for CHD (*n*) | 198 | — |
| Fasting C-peptide (nmol/l) | 0.90 ± 0.40 | — |
| Postprandial C-peptide (nmol/l) | 2.10 ± 0.98 | — |
| GHb (% of Hb) | 7.3 ± 1.5 | 7.7 ± 1.6 |
| BMI (kg/m$^2$) | 27.4 ± 3.9 | 27.4 ± 4.0 |
| Total cholesterol (mmol/l) | 5.56 ± 0.99 | 5.58 ± 1.0 |
| HDL cholesterol (mmol/l) | 1.20 ± 0.3 | 1.23 ± 0.3 |
| Triglycerides (mmol/l) | 2.22 ± 1.26 | 2.11 ± 1.26 |
| Systolic blood pressure (mmHg) | 142.4 ± 18.7 | 141.6 ± 17.7 |
| Diastolic blood pressure (mmHg) | 84.3 ± 8.8 | 81.9 ± 7.9 |
| Smokers | 198 (26.9) | 126 (17.1) |
| Autonomic neuropathy | 162 (22.0) | — |
| Retinopathy | 39 (5.3) | 39 (5.3) |
| Microalbuminuria (>20 and <200 μg/min) | 162 (22.0) | 166 (22.6) |
| Proteinuria (≥200 μg/min) | 10 (1.4) | 10 (1.4) |

Data are *n* (%) or means ± SD.

**Table 2—*Univariate analysis results of the association with the variables considered and cardiac events* (n = 42) *in study population* (N = 735)**

| Variables | Hazard ratio | *P* | 95% CI |
|---|---|---|---|
| Age (years) | 1.06 | 0.03 | 1.01–1.12 |
| Women | 0.39 | 0.02 | 0.18–0.85 |
| Family history for CHD (no/yes) | 2.99 | 0.11 | 0.77–11.56 |
| Diabetes duration (years) | 1.10 | 0.02 | 1.01–1.18 |
| GHb (% of Hb) | 1.16 | 0.18 | 0.93–1.45 |
| BMI (kg/m$^2$) | 1.05 | 0.24 | 0.96–1.15 |
| Fasting C-peptide (nmol/l) | 0.99 | 0.83 | 0.96–1.04 |
| Postprandial C-peptide (nmol/l) | 0.99 | 0.73 | 0.98–1.01 |
| Total cholesterol (mmol/l) | 1.00 | 0.79 | 0.99–1.01 |
| HDL cholesterol (mmol/l) | 0.98 | 0.29 | 0.95–1.02 |
| Triglycerides (mmol/l) | 1.00 | 0.67 | 0.99–1.00 |
| Systolic blood pressure (mmHg) | 0.99 | 0.99 | 0.98–1.02 |
| Diastolic blood pressure (mmHg) | 1.00 | 0.88 | 0.95–1.06 |
| Smokers (no/yes) | 1.08 | 0.83 | 0.52–2.28 |
| Autonomic neuropathy (no/yes) | 0.98 | 0.77 | 0.84–1.14 |
| Retinopathy (no/yes) | 2.07 | 0.02 | 1.14–3.78 |
| Microalbuminuria (<20 and >200 μg/min) (no/yes) | 1.06 | 0.20 | 0.97–1.17 |
| Proteinuria (≥ 200 μg/min) (no/yes) | 1.00 | 1.00 | — |
| Abnormal scintigraphy | 4.57 | 0.00 | 2.00–9.52 |

ware (Statistics/Data Analysis; Stata, College Station, TX) was used to accomplish the survival analysis, to estimate relative risk and 95% CI limit, and to assess the relationship between clinical features of the 735 followed subjects and time at onset of all cardiac events. For each continuous variable considered, mean and SDs are reported.

**RESULTS** — During follow-up, nine patients died of noncardiac events: seven from malignancies, one from a stroke, and one from gastrointestinal bleeding. A total of 42 cardiac events occurred; 3 were fatal.

In the group of 638 subjects with normal ETT, there was 1 fatal MI, 20 nonfatal MIs (3 of which were silent), 5 cases of resting angina, and 5 cases of effort angina. The fatal MI occurred in a hospital setting. Of the 20 subjects with nonfatal MIs, 18 were admitted to the hospital and underwent coronary angiography. Two of the three patients with silent nonfatal MI, which was discovered during a routine annual ECG and confirmed by an echocardiogram and scintigraphy, were not admitted. Of the 18 subjects who underwent coronary angiography, 5 underwent coronary angioplasty and 3 coronary bypass. All five subjects with resting angina were admitted to the hospital; four underwent coronary angiography and one underwent coronary bypass. Of the five patients with effort angina, two were admitted to the hospital and one underwent coronary bypass; three patients were diagnosed in an outpatient setting by means of ETT and scintigraphy.

In the group of 45 patients with abnormal ETT but normal scintigraphy 1 fatal MI occurred in the hospital.

In the group of 52 patients with abnormal ETT and scintigraphy, 1 case of fatal MI, 6 cases of resting angina, and 3 cases of effort angina occurred. The patient with inoperable three-vessel disease had the fatal MI in the hospital. All six subjects with resting angina were admitted to the hospital; three underwent coronary angiography and one underwent a coronary bypass. The three subjects who underwent coronary angiography at the moment of the event were subjects who did not undergo coronary angiography in 1993, and the three subjects who did not undergo coronary angiography at the moment of the event were subjects who underwent coronary angiography in 1993. Of the three patients with effort angina, only one was hospitalized, and none had coronary angiography in 1993 or at the time of the event. In all three patients, the diagnosis was made by means of ETT, echocardiogram, and scintigraphy. Two of the six subjects who presented resting angina underwent myocardial revascularization in 1993, by means of coronary bypass in one and coronary angioplasty in the other. No cardiac events occurred in the remaining patients having undergone a myocardial revascularization.

The incidence of cardiac events is 3.85/100 persons/year (95% CI1.84–7.07) in subjects with abnormal scintigraphy, 0.44/100 persons/year (0.01–2.47) in subjects with abnormal ETT but normal scintigraphy, and 0.97/100 persons/year (0.66–1.38) in subjects with normal ETT. The number of cardiac events was significantly higher in patients with abnormal scintigraphy: $\chi^2 = 21.40$, $P < 0.0001$. The proportion between major and minor events is significantly lower in subjects with abnormal scintigraphy compared with subjects who had normal ETT or abnormal ETT but normal scintigraphy at the screening in 1993 ($P = 0.002$). The incidence of all cardiac events between subjects with normal ETT and subjects with abnormal ETT but with normal scintigraphy was not statistically significant ($P = 0.715$).

Univariate analysis results of the association with the variables considered and cardiac events are summarized in Table 2 .

Of the variables found to be associated in the univariate analysis, the following maintained independent prognostic significance for cardiac events on multivariate analysis: scintigraphy abnormality (hazard ratio 5.47; $P < 0.0001$; CI 2.43–12.27), diabetes duration (1.06; $P = 0.021$; 1.01–1.12), presence of diabetic retinopathy (2.37; $P = 0.036$; 1.06–5.31).

**CONCLUSIONS** — There is a significantly different rate of all cardiac events in subjects with abnormal scintigraphy with respect to subjects with normal ETT or abnormal ETT but normal scintigraphy. These data suggest that our screening algorithm may effectively identify middle-aged type 2 diabetic subjects with preclinical CHD (9). For this purpose, thallium scintigraphy is the most accurate diagnostic test (10). However, it is costly and not widely available and therefore not suitable as a first-line screening procedure. Thus, a more realistic approach is the use of an initial test such as ETT, which may not be very specific but is inexpensive and widely available. Patients

with abnormal ETT can then be more accurately assessed by a more specific test that will highlight false positives (11). In patients with a positive ETT but a normal scintigraphy the incidence of cardiac events is not significantly different from that of patients with a normal ETT. Nonetheless, we have to note that the CI in the group with positive ETT but normal scintigraphy is very large.

We believe that the most relevant data emerging from the study is the low incidence of fatal cardiac events in subjects with abnormal scintigraphy (0.38/100 persons/year). The only death that occurred in this group was in a patient with inoperable three-vessel disease. The incidence of cardiac deaths among patients identified as coronaropathic in the MiSAD screening is superimposable to that of nondiabetic, noncoronaropathic subjects reported in the Kuopio Study, which followed over a 7-year period both type 2 diabetic and nondiabetic subjects aged 45–64 years with or without a history of MI (12).

The proportion between major and minor cardiac events is significantly less in subjects with an abnormal scintigraphy, and only two patients who underwent a myocardial revascularization after screening have presented cardiac events, both being minor, in the5-year follow-up. This ratio may indicate that preclinical diagnosis of CHD and the consequent early institution of appropriate management might be a relevant factor in the prevention of major cardiac events in the subset of patients with CHD detected at screening (13). These patients were treated with acetylsalicylic acid (14), and in some instances revascularization procedures were performed and appropriate cardiologic therapy and follow-up were instituted (15). It is probable that these interventions have had an influence on the low rate of major cardiac events. These data are enchanting, but without a control study in our population, it is not possible to assess the impact of these interventions on the rate of major cardiac events. Nevertheless, we could not observe any danger of the screening (16).

Another interesting finding from our entire patient population is that the incidence of all cardiac events, 1.14/100 persons/year, and the incidence of fatal cardiac events, 0.08/100 persons/year, are low. This low incidence is in contrast with the data generally reported in the literature concerning diabetic people (12,17–19). This discrepancy may be explained on the basis of the CHD risk category of our study population. In fact, the MiSAD excluded patients with advanced age, known peripheral or cerebral arteriopathy, renal insufficiency, and severe hypertension. These selection criteria resulted in the inclusion of a diabetic subset with low-risk features. In addition, in the MiSAD the most relevant modifiable cardiovascular risk factors, such as total and HDL cholesterol, triglycerides, and hypertension, were optimal at enrollment and remained such throughout follow-up (20). We do not believe that variations, even if statistically significant, of the clinical modifiable variables monitored during the course of the follow-up are clinically relevant (21). We believe that the exclusion criteria used in our study population and the optimal status of CHD-modifiable major risk factors resulted in the low frequency of cardiac events in our study.

In conclusion, the low ratio of major to minor cardiac events in patients identified as coronaropathic in the MiSAD study suggests but does not prove that the screening program was effective probably because interventions were possible and, thus, were carried out. However, it also suggests that ETT may be inadequate as an initial screening test because in the larger group, patients with coronary artery disease were not pinpointed; subsequently, no intervention was performed, and the risk of a major event was therefore higher. So our data can be interpreted to understand that routine scintigraphy is probably best but, if for financial reasons this is not possible, methods should be found to improve accuracy of low-cost screening procedures such as the ETT. However, the MiSAD follow-up data suggest that in middle-aged type 2 diabetic subjects the preclinical diagnosis of CHD, followed by appropriate management, may be advantageous.

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