

# Recurrence of Cardiovascular Events in Patients With Type 2 Diabetes

## Epidemiology and risk factors

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**OBJECTIVE** — The purpose of this study was to assess incidence of and risk factors for recurrent cardiovascular disease (CVD) in type 2 diabetes.

**RESEARCH DESIGN AND METHODS** — We estimated the incidence of recurrent cardiovascular events in type 2 diabetic patients, aged 40–97 years, followed by a network of diabetes clinics. The analysis was conducted separately for 2,788 patients with CVD at enrollment (cohort A) and for 844 patients developing the first episode during the observation period (cohort B).

**RESULTS** — During 4 years of follow-up, in cohort A the age-adjusted incidence of a recurrent event (per 1,000 person-years) was 72.7 (95% CI 58.3–87.1) in men and 32.5 (21.2–43.7) in women, whereas in cohort B it was 40.1 (17.4–62.9) in men and 22.4 (12.9–32.0) in women. After controls were included for potential predictors (familial CVD, obesity, smoking, diabetes duration, glycemic control, microvascular complications, geographic area, and antihypertensive and lipid-lowering treatment), male sex, older age, and insulin use were significant independent risk predictors (cohort A) and serum triglyceride levels  $\geq 1.69$  mmol/l emerged as the only metabolic (negative) prognostic factor (cohort B). In both cohorts, a prior CVD episode, especially myocardial infarction, was by far the strongest predictor of recurrent CVD.

**CONCLUSIONS** — Approximately 6% of unselected diabetic patients in secondary prevention develop recurrent major CVD every year. Those with long-standing previous CVD show a higher incidence of recurrence. Male sex, age, high triglyceride levels, and insulin use are additional predictors of recurrence.

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Preventing relapses of cardiovascular disease (CVD) in patients with previous CVD is a daunting task for clinicians. The clinical and socioeconomic impact of recurrence is such that many health care systems regard secondary prevention as worthy of free prescription of expensive medications. Nonetheless, relatively little is known of the natural

history of this manifestation of atherosclerotic cardiovascular disease. Although it is generally assumed that the pattern and risk factors for relapses are the same as for first CVD events, to the best of our knowledge, detailed analyses of this phenomenon are lacking.

Patients with type 2 diabetes have recurrent CVD disease with a high fre-

quency. Previous studies have concentrated on survival or recurrent CVD after a first myocardial infarction. Thus, the Framingham Study reported that the risk of recurrent myocardial infarction was higher in diabetic women than in diabetic men (1). In the Finnish contribution to the World Health Organization Multinational Monitoring of Trends and Determinants of Cardiovascular Disease (FINMONICA) study, the 1-year mortality in type 2 diabetic patients who had survived a previous myocardial infarction was 44% in men and 37% in women (2). In 169 diabetic patients with prior myocardial infarction, Haffner et al. (3) reported sex- and age-adjusted incidence rates (per 1,000 person-years) of 78 fatal or nonfatal myocardial infarctions, 34 strokes, and 73 cardiovascular deaths. In the largest observational cohort of type 2 diabetic patients with prior myocardial infarction reported thus far ( $n = 1,215$ ), i.e., the placebo arm of the Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive study) (4), the incidence of a recurrent composite end point, including nonfatal myocardial infarction, coronary revascularization, acute coronary syndrome, and cardiac death, was 6.5% per year. However, because this population consisted of patients selected with criteria typical of clinical trials, some caution is needed in generalizing the study's findings.

The objective of the present study was to describe incidence of and risk factors for recurrent CVD, including stroke and limb amputations, in a large, unselected cohort of diabetic patients receiving standard care who had previously had a CVD event.

## RESEARCH DESIGN AND METHODS

The present analysis was performed as part of the Diabetes and Informatics (DAI) study, a multicenter cohort study conducted by the DAI Study Group (DIAINF) together with the Italian Association of Clinical Diabetologists (AMD) and the Italian National Institute of Health (ISS) since September 1998. The aim of the DAI study was to evaluate the prevalence and incidence of CVD

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(myocardial infarction, ischemic heart disease [IHD], percutaneous coronary intervention angioplasty [PTCA], coronary artery bypass graft [CABG], stroke, and peripheral amputations) among type 2 diabetic patients regularly attending hospital-based diabetes clinics. In Italy, a public network of ~700 diabetes clinics provides care for up to 80% of patients with known diabetes, delivering diagnostic confirmation, therapy, prevention, and early diagnosis of acute and chronic complications through close patient follow-up by a team of specialists and the scheduling of regular checkups. Most patients are referred to these care units by their general practitioner, and care is free of charge. A detailed description of the DAI study methodology has been presented elsewhere (5). For the incidence study, 157 clinics participated, with a total of 14,432 patients: 11,644 patients free of CVD at enrollment and 2,788 patients who entered the study with a known prior CVD event. The recurrence of CVD events, described herein, was analyzed in the 2,788 patients with a prior CVD event (cohort A) and in the 844 of the 11,644 patients without events at enrollment who developed their first CVD event during the observation period (cohort B).

### Data collection and definitions

The data used in this analysis were collected in four waves of follow-up between 2000 and 2003. During the enrollment and follow-up visits, a standard questionnaire was used to collect, in addition to anthropometric data, information on lifestyle habits, drug therapy, laboratory measures (specified below), clinical history, microvascular complications (retinopathy, blindness, and foot ulcers), and cardiovascular complications. For patients who did not appear for the scheduled visits, information, including death, was obtained through telephone interviews with the patient, a relative, or the primary care physician.

The following tests were performed at enrollment and at each follow-up visit. Plasma glucose, A1C, and lipid profile were determined in the fasting state. A1C was measured at each clinic, not in a centralized laboratory; for this reason, glyce-mic control was estimated as the percent increment of the individual patient's A1C above the upper limit of the normal range of the local laboratory. Urinary albumin excretion (UAE) was obtained in a timed overnight collection; microalbuminuria

was defined as UAE of 30–300 mg/l in at least three successive measurements in the absence of other known causes of proteinuria. Hypertension was defined as systolic blood pressure  $\geq 140$  mmHg and/or diastolic blood pressure  $\geq 90$  mmHg and/or antihypertensive treatment. Retinopathy was assessed by a comprehensive dilated eye examination and by the acquisition of high-quality stereoscopic photographs assessed by an ophthalmologist. Familial CVD was identified when the patient had a first-degree relative (parent, sibling, or child) who had had a major cardiovascular event at age  $< 55$  years. Alcohol consumption was calculated in equivalent milliliters of wine and transformed to grams per week (0 g/week, no consumption; 1–225 g/week, moderate consumption; and  $\geq 226$  g/week, high consumption).

### CVD events

Study events were all major IHD events (myocardial infarction, PTCA, and CABG), minor IHD events (angina and other forms of IHD), stroke, and limb amputations. Patients were classified as having IHD if they had one of the following: 1) a history of hospital admission for either fatal or nonfatal myocardial infarction or an episode of angina; 2) a 12-lead electrocardiogram with positive results for prior myocardial infarction or angina by the Minnesota coding system (criteria I 1–3, IV 1–3, V 1–2, and VII 1); or 3) a history of CABG or PTCA. All patients had had at least one electrocardiogram in the 12 months preceding enrollment to exclude prior myocardial infarction. Stroke was defined according to World Health Organization criteria for confirmed and possible stroke (i.e., a clinical syndrome consisting of a rapidly developing neurological deficit persisting for  $> 24$  h or leading to death, in the absence of other diseases that could explain the symptoms). A hospital discharge record or a specialist visit was required to certify the event.

A CVD event was considered as recurrent if it occurred at least 28 days after the first event. A minor IHD event after another minor or a major IHD event was not counted as a bona fide recurrent event, i.e., a new episode. Similarly, a major IHD event after a minor IHD event was not considered as recurrent. Such episodes were collectively indicated as events not classifiable as recurrent, in contrast with the truly recurrent CVD events. This choice was made on the grounds that,

very often, angina and a subsequent myocardial infarction or revascularization are consequences of the same arterial lesion.

### Statistical analysis

The analysis was conducted separately in the two study cohorts (A and B). The variables considered in the analyses were those collected at enrollment for cohort A and those collected at the follow-up visit at which the first CVD event was reported for cohort B.

Data for the continuous variables are expressed as means  $\pm$  SD or median (interquartile range) for non-normal variables and as proportions for categorical variables. The incidence density of recurrent CVD events was standardized on the basis of the age distribution of the 1998 Italian population.

Univariate and multivariate Cox proportional hazards models were used to examine the risk factors for recurrent events. Preliminary data analysis was performed with univariate Cox models of all covariates: duration of diabetes, waist circumference, BMI, total cholesterol level, HDL cholesterol level, triglyceride level, A1C, blood pressure level, alcohol intake, smoke, familial CVD, microvascular complication, lipid-lowering treatment, antihypertensive treatment, and treatment of diabetes. The interaction between blood pressure level and antihypertensive treatment and between total cholesterol level and lipid-lowering therapy was evaluated. For cohort A, the overall model was also adjusted by the number of years from the first event to the enrollment to partially consider the patient's history of CVD preceding the beginning of the study. All covariates with  $P \leq 0.1$  ( $P \leq 0.05$  in cohort B, given the smaller sample size) were entered into the final multivariate models. All analyses were performed using the Stata 8.0 statistical package.

**RESULTS** — During the 4-year follow-up, in cohort A, 414 of 2,788 patients (who had entered the study with a known previous CVD event) developed at least an event that fulfilled the stipulated criteria of a recurrent event. In cohort B, 54 of 844 patients (who had had their first event during the study) had a recurrent event. With regard to multiple events, 38 patients in cohort A and 4 in cohort B had two recurrent events, and only 1 patient in cohort A had three recurrent events. Events occurring in 386 patients of cohort A and 46 patients of cohort B were not included in the analysis because they did

Table 1—Clinical characteristics of patients with type 2 diabetes in the two study cohorts by presence of recurrent events

Characteristics	Cohort A			Cohort B		
	No recurrent event	With event not classifiable as recurrent	With recurrent event	No recurrent event	With event not classifiable as recurrent	With recurrent event
n	1,988	386	414	744	46	54
Age (years)	68 ± 8	69 ± 8	69 ± 8	67 ± 8	66 ± 7	67 ± 9
BMI (kg/m <sup>2</sup> )	29 ± 5	28 ± 4	28 ± 4	29 ± 5	30 ± 5	29 ± 4
Waist circumference (cm)	99 ± 12	98 ± 11	99 ± 11	99 ± 11	99 ± 10	98 ± 10
Total cholesterol (mmol/l)	5.53 ± 1.11	5.56 ± 1.45	5.53 ± 1.06	5.40 ± 1.09	5.56 ± 1.03	5.69 ± 1.34
HDL cholesterol (mmol/l)	1.24 ± 0.34	1.24 ± 0.31	1.22 ± 0.36	1.29 ± 0.36	1.24 ± 0.28	1.27 ± 0.39
LDL cholesterol (mmol/l)	3.47 ± 0.96	3.47 ± 0.96	3.49 ± 0.91	3.36 ± 0.93	3.49 ± 0.85	3.41 ± 0.98
Diabetes duration (years)	10 (4–16)	11 (5–17)	11 (5–17)	11 (6–17)	11 (7–18)	14 (6–20)
Systolic blood pressure (mmHg)	145 (135–160)	145 (135–160)	135 (145–160)	140 (130–160)	150 (140–165)	140 (130–160)
Diastolic blood pressure (mmHg)	80 (80–90)	80 (80–90)	80 (80–90)	80 (80–90)	80 (80–90)	80 (80–90)
Plasma glucose (mmol/l)	9.0 (7.4–11.0)	8.8 (7.2–10.9)	8.6 (7.2–10.8)	8.8 (7.2–10.6)	8.9 (8.0–10.3)	8.7 (7.4–11.1)
Triglycerides (mmol/l)	1.63 (1.19–2.25)	1.54 (1.14–2.24)	1.63 (1.22–2.26)	1.52 (1.11–2.04)	1.32 (1.06–2.21)	1.73 (1.13–2.25)
Men	56.3	51.3	68.6	50.0	50.0	46.3
Hypertension*	91.2	91.2	92.8	89.1	95.7	92.5
A1C†	80.0	76.5	76.7	80.3	82.2	82.7
Alcohol intake	38.5	41.5	40.8	45.4	47.5	43.2
Smoking						
Current	10.2	12.4	10.9	11.6	13.0	3.7
Former	29.3	24.6	36.2	23.4	28.3	24.1
Familial CVD	39.0	38.9	43.5	28.0	23.9	22.2
Microvascular complications	45.3	44.0	52.9	49.5	58.7	61.1
Lipid-lowering treatment	24.0	27.2	31.2	32.8	43.9	38.5
Diabetes treatment						
Diet alone	11.9	12.7	7.7	8.3	4.3	4.0
Oral agents	64.7	59.3	58.7	60.1	67.4	56.0
Insulin + oral agents	9.8	12.7	13.1	9.6	8.7	12.0
Insulin	13.6	15.3	20.5	22.0	19.6	28.0
Geographic area						
Northern Italy	54.7	55.7	61.1	55.4	39.1	59.3
Central Italy	10.3	8.0	9.7	10.9	13.1	11.1
Southern Italy and Islands	35.0	36.3	29.2	33.7	47.8	29.6
Onset event						
Minor IHD event	41.3	58.8	10.4	58.3	84.8	31.5
Major IHD event	38.3	37.1	63.8	25.3	15.2	44.4
Stroke	12.9	—	15.0	9.9	—	11.1
Amputation	3.0	—	2.1	4.2	—	11.1
Other‡	4.5	4.1	8.7	2.3	0.0	1.9

Data are means ± SD, median (interquartile range), or %. \*Defined as systolic pressure ≥140 mmHg and/or diastolic pressure ≥90 mmHg and/or antihypertensive treatment. †Percentage of patients with values higher than the upper limit of the normal range. ‡Any combination of events.

not meet the required criteria for recurrent events (almost all IHD events).

As summarized in Table 1, the study population consisted of a high proportion of elderly patients with rather good glycaemic control. The most common CVD risk factor was hypertension, which was found in almost all patients. In cohort A, patients with recurrent events were older, were more often male with a previous history of microvascular complications, and had more use of insulin and lipid-lowering

medications. In cohort B, patients with recurrent events had higher total cholesterol and triglyceride levels, more often had a previous history of microvascular complications, myocardial infarction, or amputation, and had more use of insulin.

Of note, the age-standardized incidence rate of recurrent CVD was 40% lower in cohort B than in cohort A (Table 2). The average time between enrollment and the occurrence of the recurrent event in cohort A was 1.6 ± 1.04 years, whereas in cohort B

the average time between the first and recurrent event was 1.5 ± 0.8 years. The average time between the first and the recurrent event in cohort A was 1.6 ± 1.04 years, whereas the average time between the first and the recurrent event was 8.1 ± 6.9 years in cohort A and 1.5 ± 0.8 years in cohort B.

In cohort A, the standardized incidence of recurrent episodes was 89.2 per 1,000 person-years (95% CI 71.3–107.2) among patients with a major IHD event,

**Table 2—Crude and age-adjusted incidence rates of recurrent events in diabetic men and women with type 2 diabetes in the two study cohorts**

	No. patients	No. cases*	Person-years	Crude IR (95% CI)	Adjusted IR (95% CI)
<b>Cohort A</b>					
Men	1,602	284	3,847.8	73.8 (65.7–82.9)	72.7 (58.3–87.1)
Women	1,186	130	2,945.4	44.1 (37.2–52.4)	32.5 (21.2–43.7)
All	2,788	414	6,793.2	60.9 (55.3–67.1)	57.6 (47.3–67.8)
<b>Cohort B</b>					
Men	424	29	693.6	41.8 (29.1–60.2)	40.1 (17.4–62.9)
Women	420	25	724.1	34.5 (23.3–51.1)	22.4 (12.9–32.0)
All	844	54	1,417.8	38.1 (29.2–49.7)	33.0 (18.1–48.1)

Data are incidence rate (IR) per 1,000 person-years (95% CI). \*Patients with at least one recurrent event.

11.4 (3.6–19.2) among those with a minor IHD event, 49.2 (35.5–62.9) among those with a prior stroke, and 79.8 (36.0–123.5) among those with amputation or combined events. A multivariate Cox model for cohorts A and B is shown in Table 3. In cohort A, age, male sex, and use of insulin, alone or in combination with oral agents, were independent predictors of recurrence. However, having had a major IHD event as the first event was the strongest factor of all, with stroke and combined events also being powerful predictors, whereas time between first and recurrent events did not make a significant independent contribution. In cohort B, the risk factor pattern was similar to that of cohort A, with prior events carrying the highest risk. In this model, the only metabolic factor with an independent risk prediction was a serum triglyceride level  $\geq 1.69$  mmol/L. No interaction between blood pressure level and antihypertensive treatment or between total cholesterol level and lipid-lowering therapy was found in either cohort.

Given the dominant role of the first event as a predictor, the multivariate models were also run after excluding this variable. In cohort A, some difference emerged: receiving lipid-lowering therapy (hazard ratio [HR] 1.32 [95% CI 1.07–1.63]), number of years from first event (1.57, [1.21–2.03] for  $>6$  years), and living in Southern Italy (0.77 [0.62–0.96]) became significant. In cohort B no significant difference from the full model was found. Finally, given its value from the clinician point of view (although not considered in our analysis of recurrent events), we report the standardized incidence of a minor IHD event: 39.5 per 1,000 person-years (95% CI 30.3–48.7) in men and 57.1 (36.7–77.5) in women in cohort A and 21.3 (5.7–36.8) in men and 8.3 (2.4–14.3) in women in cohort B.

**CONCLUSIONS**— In our population of diabetic patients receiving usual care, we found that every year, 6.1% of the patients with a prior CVD event developed a new major atherosclerotic complication. This percentage compares very well with those (5.9–6.0% per year) of the cohorts of diabetic patients in secondary prevention analyzed in the PROactive (4) study and the Scandinavian Simvastatin Survival Study (4S) (7). A higher rate of 7.6% per year was reported in the Drugs and Evidence-Based Medicine in the Elderly (DEBATE) study (8), but that study was performed in subjects with a higher mean age (80 years).

The incidence rate of recurrent events in cohort B was almost half that of cohort A. Likely explanations of this difference are that among cohort B patients, there were more women, age was somewhat younger, familial CVD was less prevalent, and prior myocardial infarction was less frequent relative to prior stroke. Moreover, and more importantly, these patients had a shorter and more recent CVD history and were observed for only 1.7 year on average. The patients in cohort A, on the other hand, were “survivors” of a CVD event that preceded the recurrent event by a longer span of time; in fact, there was a remarkable difference in terms of number of years from first and recurrent event, which could be the explanation for this different outcome.

Our analysis highlighted features that can be useful in clinical practice. First, men had markedly higher rates of recurrent events than women. This result may be due to the greater predisposition to necrotic events of men than of postmenopausal women, who are more prone to nonmyocardial infarction IHD (angina) and, probably, heart failure (9–11). In the Framingham study, after the onset of angina, men had a twofold greater risk than

women for both myocardial infarction and coronary death after adjustment for age and IHD risk factors (1). We described this sex effect previously in the prevalence (5) and incidence analyses of the first IHD event (12) and stroke (13) in the DAI population. In the present study, on the other hand, the incidence of minor IHD in cohort A was higher in women than in men.

Second, in the search for risk factors specific to recurrent major CVD, we found that age played an important role, with a 10-year difference translating into a 26% risk increment. The impact of age as a CVD risk factor in the general population is well known (14–18), but the current findings document the fact that age is an independent risk factor for relapsing major CVD in a population of diabetic patients not selected for age.

The fact that use of insulin, alone or in combination with oral agents, was an independent risk factor for recurrence in cohort A should not be overlooked. This finding was also reported in the PROactive cohort of type 2 patients with prior myocardial infarction who developed a second fatal or nonfatal myocardial infarction (4) and in the Cardiovascular Health Study (19), in which insulin was found to be associated with greater CVD mortality compared with oral agents. The association was true also when serum insulin concentrations were measured (20). In the DAI study, insulin treatment was an independent risk factor for IHD (12) and stroke (13) in patients free of CVD at baseline as well. On the other hand, the adverse prognosis associated with insulin use may be regarded as the result of an “indication bias”: more severe, longer-standing diabetes is preferentially treated with insulin and has a worse cardiovascular prognosis (21,22). In fact, in clinical trials such as the Diabetes Control and Complications Trial in type 1 diabetic patients and the UK Prospective Diabetes Study (UKPDS) in type 2 diabetic patients (23,24), insulin treatment had a clear-cut antiatherogenic effect. Therefore, the possibility that prolonged use of insulin in these type 2 diabetic patients resulted in less cardioprotection than control of glycemia by other pharmacological means cannot be ruled out.

Dyslipidemia, as indicated by a higher frequency of lipid-lowering treatment in cohort A and higher serum triglyceride levels in cohort B, emerged as an independent risk predictor. This finding resonates with the previous observation

Table 3—Multivariate HRs for predictors of recurrent events among type 2 diabetic patients

Risk factor	HR (95%CI)	P value
Cohort A: patients with CVD at baseline		
Age (10-year increments)	1.26 (1.10–1.43)	<0.001
Sex		
Men	1	
Women	0.70 (0.55–0.88)	<0.001
Alcohol intake (g/week)		
No consumption	1	
Moderate	0.84 (0.65–1.07)	0.16
High	0.79 (0.60–1.05)	0.10
Microvascular complications		
No	1	
Yes	1.14 (0.93–1.39)	0.22
Antihypertensive therapy		
No	1	
Yes	1.21 (0.95–1.53)	0.13
Lipid-lowering therapy		
No	1	
Yes	1.16 (0.93–1.43)	0.18
Glycemic control		
Diet	1	
Oral agents	1.36 (0.94–1.97)	0.11
Insulin, insulin + oral	1.81 (1.21–2.69)	<0.001
First event		
IHD event	1	
Major IHD event	5.58 (3.98–7.82)	<0.001
Stroke	4.63 (3.12–6.88)	<0.001
Other*	4.59 (2.97–7.08)	<0.001
Geographic area		
North	1	
Center	1.00 (0.71–1.39)	0.98
South and islands	0.90 (0.72–1.12)	0.33
Years from first event		
<1.0	1	
1.0–2.0	0.98 (0.67–1.44)	0.93
2.1–6.0	1.13 (0.86–1.48)	0.38
>6.0	1.12 (0.86–1.46)	0.38
Cohort B: patients with the first CVD event during the study period		
Age (10-year increments)	1.20 (0.84–1.72)	0.32
Sex		
Men	1	
Women	0.90 (0.50–1.60)	0.71
Triglycerides (mmol/l)		
<1.69	1	
≥1.69	1.93 (1.10–3.40)	0.02
First event		
IHD event	1	
Major IHD event	3.64 (1.89–6.98)	<0.001
Stroke	3.23 (1.25–8.35)	0.02
Other*	6.21 (2.54–15.17)	<0.001

\*Amputations or combinations of events.

in the DAI study (12) that high triglyceride levels are a significant predictor of the first IHD event in women without prior CVD.

The dominant observation in the DAI

study seemed to be the strong impact of the type of the first CVD events on relapses—an observation that emerged from both study cohorts. Having had a major IHD event, alone or combined with an

other CVD event, was associated with the highest relative risk, possibly leaving little room for other modifiable factors.

A limitation of this study is the lack of centralized laboratory measurements. Also, given the fact that the observation period was relatively short, there may not have been time for other potentially significant factors to emerge. Finally, information on other potential risk predictors such as lipoprotein levels, postprandial glucose excursions, or genetic markers was lacking. The strength of this study, in addition to the large size, is that it provides a detailed description of the burden of secondary CVD prevention in diabetic patients under real-life conditions. Because in Italy the percentage of patients who seek care at the hospital-based diabetes clinics is very high (up to 80% of patients with known diabetes), our results can be confidently extrapolated to the entire type 2 diabetic population in the country.

In summary, this nationwide observational study outlines the natural history of recurrent events in type 2 diabetic patients managed by usual care. The observed risk profile has significant clinical implications. First, diabetic patients, especially elderly men, whose CVD onset is myocardial infarction or revascularization (or combined events) warrant close follow-up and intensive management. Second, patients using insulin show a higher frequency of recurrent events. Third, diabetic patients with high triglycerides levels may be targeted by aggressive treatment in secondary CVD prevention.

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