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Rapid communication

Coronary atherosclerosis in Type II diabetes: angiographic findings and clinical outcome

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Abstract

Aims/hypothesis. Prevalence and incidence of coronary heart disease (CHD) are increased in patients with Type II (non-insulin-dependent) diabetes mellitus; whether this is entirely due to more extensive coronary atherosclerosis is, however, controversial.
Methods. We analysed the clinical, angiographic and follow-up data of 2253 consecutive patients undergoing coronary angiography over the decade 1983–1992.
Results. Abnormal coronary arteries (≥ 50 % stenosis) were found more frequently in diabetic than in non-diabetic subjects (85 vs 67 %, $p < 0.0001$), the excess being explained by a higher prevalence of three-vessel disease (36 vs 17 %, $p < 0.0001$). The sum of all angiographically detectable lumen stenoses (atherosclerosis score, ATS) was higher in diabetic than in non-diabetic subjects (352 ± 232 vs 211 ± 201 units, $p < 0.0001$). After adjusting for measured cardiovascular risk factors, diabetes was still associated with an excess ATS (114 units in men and 187 units in women, $p < 0.0001$ for both, $p < 0.03$ for the interaction ATS x sex). Within the diabetic group, the only variable that was independently (of sex and age) associated with ATS was serum cholesterol, whereas plasma glucose concentration, disease duration and type of treatment were not correlated with the severity of coronary atherosclerosis. In contrast, clinical grade proteinuria was not associated with a more diffuse coronary atherosclerosis either in diabetic (366 ± 243 vs 354 ± 233 units) or non-diabetic subjects (231 ± 201 vs 207 ± 197 units). Over a mean follow-up period of 88 months, 19 % of diabetic patients compared with 10 % of non-diabetic patients died of a cardiac cause (age and sex-adjusted odds ratio OR = 1.34 [1.14–1.57]). In a Cox model adjusting for age, sex and all major risk factors, diabetes was still associated with a significant excess risk of dying of a cardiac cause (OR = 1.37 [1.14–1.60]); this excess was similar to, and independent of, that carried by the presence of prior myocardial infarction in the whole population (OR = 1.42 [1.25–1.62]). Proteinuria was associated with a higher risk of cardiac death, particularly in diabetic patients, independently of coronary atherosclerosis (adjusted OR = 1.46 [1.03–1.99]).
Conclusion/interpretation. In patients undergoing angiography, diabetes, especially in women, is associated with more severe and diffuse coronary atherosclerosis which is not explained by either the traditional risk factors or the presence of proteinuria. On follow-up, these patients experience an excess of cardiac deaths, to which coronary atherosclerosis and proteinuria make independent, quantitative contributions. [Diabetologia (2000) 43: 632–641]

Keywords Coronary atherosclerosis, coronary artery disease, macrovascular complications, cardiac mortality, atherosclerosis, cardiovascular risk factors.

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Abbreviations: ATS, Atherosclerosis score; OR, odds ratio; CHD, coronary heart disease; PMI, previous myocardial infarction; MI, myocardial infarction; LAD, left descending artery; CX, circumflex artery; RCA, right coronary artery; CSO, clinically significant obstruction; LV, left ventricular; BP, blood pressure; CABG, coronary artery by-pass surgery; PTCA, percutaneous coronary angioplasty; LVH, left ventricular hypertrophy.

The age-adjusted prevalence of coronary heart disease (CHD) in patients with Type II (non-insulin-dependent) diabetes mellitus is approximately 40 % [1] and over half of all diabetic subjects eventually die from an acute or chronic complication of CHD [2]. Ever since the Framingham study [3], prospective studies have consistently found that in diabetic patients the susceptibility to, and mortality from, CHD is at least twice as high as in non-diabetic subjects [1]. A recent population-based study has shown that in diabetic patients without CHD the risk of death from a coronary event is similar to that of non-diabetic patients who have suffered a prior myocardial infarction (MI) [4]. This implies that coronary atherosclerosis in diabetic patients without CHD symptoms is already advanced.

The basis for this excess CHD morbidity and mortality is not completely understood. Although most of the classic risk factors (e. g. hypertension, dyslipidaemia, left ventricular hypertrophy, overweight) are over represented in diabetes, they explain only a small fraction of its excess CHD [5]. Recent evidence has indicated that severe hyperglycaemia and a long duration of the disease both enhance the risk of fatal and non-fatal ischaemic events but the effect is quantitatively small compared with the overall CHD excess [6]. Also, the pathologic basis of CHD in diabetes is controversial. Although several autopsy [7–9] and angiographic studies [10, 11] have reported more severe and diffuse atherosclerotic involvement of the coronary vasculature in diabetic subjects, negative reports are well represented in the literature [12–15]. Thus, alternative mechanisms have been proposed to explain CHD in diabetes: functional abnormalities of small vessels [16, 17], reduced metabolic resistance of the myocardium to ischaemia [18], linkage dysequilibrium between the genes responsible for diabetes and cardiovascular disease [19] and "new" cardiovascular risk factors [20]. Among the latter, abnormal urinary protein excretion has emerged as one of the most consistent CHD risk predictors, especially among diabetic patients [21]. What links proteinuria with CHD is equally controversial. Proteinuria has been interpreted as an index of more diffuse vascular atherosclerosis [22] or as a marker for an unfavourable cardiovascular risk factor profile [23].

At least in part, these uncertainties could be due to the paucity of collated information, as population-based studies lack anatomical data and post-mortem or angiographic investigations either include small numbers of patients or lack clinical and follow-up information. In this study, we analysed the clinical, angiographic, and follow-up data of a large cohort of consecutive patients referred to our coronary division over a decade with the aim of evaluating the effect of diabetes and proteinuria on both coronary atherosclerosis (as assessed by angiography) and prognosis.

Subjects and methods

Patient selection. Over the decade 1983–1992, 2253 of the 4754 patients admitted to our coronary division underwent coronary angiography as part of the clinical work-up of symptoms or signs of heart disease. The indications for angiography were: ischaemic heart disease ($n = 1949$), cardiomyopathy ($n = 124$), valvular disease ($n = 111$), arrhythmia ($n = 33$) and other ($n = 36$).

Database. Since 1983, the relevant clinical data of each patient have been transferred immediately after discharge to a database created for this purpose. Each patient record consisted of the following blocks of information:

1. *Demographics*: (sex, age, height, weight, years of school education).
2. *Clinical data*: history of resting or effort angina, myocardial infarction, acute cerebro-vascular events, coronary by-pass surgery and coronary angioplasty. The baseline 12-lead electrocardiogram (ECG) was categorised as normal or with one of the following abnormalities: ST-T changes (including ST depression, ST elevation, T wave inversion), acute or previous myocardial infarction (PMI), left or right bundle branch block, atrial or ventricular arrhythmias. The presence of left ventricular hypertrophy (LVH) was detected by means of mono-dimensional or bi-dimensional echocardiography in 2058 patients.
3. *Angiographic data*: Any stenosis in a main coronary artery [main stem (MS), left descending artery (LAD), circumflex artery (CX) and right coronary artery (RCA)] was graded in one of four levels (50, 75, 90, and 100 %); stenoses smaller than 50 % were defined as irregularities. A coronary vessel was considered to have a clinically significant obstruction (CSO) if it was narrowed by at least 50 % with respect to the pre-stenotic segment; when multiple stenoses were present on the same main vessel, the grade of the narrowest one was considered. Stenoses of secondary branches were described but not considered to be CSO unless the branch represented the largest terminal segment of a main coronary vessel. These descriptions constituted the basis for the diagnosis of one-vessel, two-vessel or three-vessel disease. Each haemodynamist had trained his/her visual grading against the quantitative approach. To validate the visual grading system, in a subset of 181 stenoses selected at random from the present data the visual grading and the reading obtained by the quantitative method [computer-assisted edge evaluation (Kontron M14, Kontron Image Analysis Division, Munich, Germany)] were compared in a blind fashion. When the per cent reduction of the stenotic segment relative to the pre-stenotic segment was calculated as the ratio of the two areas, the values coded as irregularities, 50 %, 75 % and 90 % by visual grading corresponded to 53 ± 5, 74 ± 3, 80 ± 1, 83 ± 1 % narrowing, respectively, on quantitative angiography.

Clinical chart review. Additional information was obtained from a detailed review of the clinical charts. The following variables were thus added:

1. Family history of ischaemic heart disease, hypertension, diabetes mellitus, or stroke, expressed as present or absent according to whether one or more first-degree relatives were affected. For the first variable a score was also derived as the sum of all affected relatives (scored as 1 for a parent, $1/n$ for each affected of n siblings, 0.5 for each second-degree relative; values were multiplied by five if the subject was affected before 60 years of age).

2. Patients were classified as cigarette smokers, past smokers or non-smokers. Cigarette consumption (in pack-years) was estimated by multiplying the number of packets a day by the years of smoking (when not specified, age 17 was assumed as the beginning).
3. Patients with either a previous diagnosis of hypertension or with blood pressure (BP) ≥ 140/90 mmHg on repeated in-hospital measurements were labelled as hypertensive; whenever possible, disease duration was also estimated. Systolic and diastolic BP and heart rate were recorded as the average of five morning values during the first 5 days after admission to hospital.
4. Patients were classified as having known diabetes if they reported a previous diagnosis or were receiving antidiabetic treatment. The latter was categorised into three groups: diet, oral agents and insulin. Diabetes duration was estimated from the patient's previous laboratory reports as well as from interviewing the patient or his/her family members. Patients with a previous diagnosis of Type I (insulin-dependent) diabetes mellitus and those who had started insulin therapy before the age of 40 years were classified as having Type I diabetes and excluded from the analysis ($n = 10$). Patients with two or more consecutive fasting plasma glucose concentrations above 7.00 mmol/l and no history of diabetes were classified as having newly diagnosed diabetes.
5. From the routine chemistry done on admission, the following data were taken: plasma glucose, total cholesterol, triglycerides, uric acid and creatinine concentrations. Protein concentration on morning spot urine was measured by the tetrabromophenol blue method (Arkray Factory, Shiga, Japan); clinical grade proteinuria was defined as a concentration greater than 300 mg/l.
6. In addition to grading coronary disease in terms of CSO (i.e. the most severe obstruction on a major branch), the overall atherosclerotic involvement of the coronary vasculature was quantified by a modification of a method proposed previously [24]. From the original descriptions of the angiograms, an index (ATS score) was calculated by summing the per cent narrowing of all stenoses, including multiple stenoses along the same main vessel or those on secondary branches (irregularities were taken as 40 % stenosis). This ATS score was calculated for each of the main coronary vessels as well as for the entire visible coronary tree.
7. From the haemodynamic report, the following variables were collected: intra-aortic systolic and diastolic BP, left ventricular (LV) end-diastolic pressure, LV ejection fraction (available only for a subgroup of patients). Global LV dysfunction was graded as 0 = normal, 1 = mildly impaired, 2 = moderately impaired, and 3 = severely impaired, as judged by the cardiologist on the ventriculogram.

Follow-up data. Information concerning death, new acute myocardial infarction and surgical or transluminal coronary revascularisation was collected yearly up to 10 years after discharge from the following sources: outpatient visits, telephone interviews (with the patients, close relatives or the referring physician), questionnaires sent to all patients, and death certificates. Of the 2253 patients only 85 had a follow-up time shorter than 12 months, the majority ($n = 78$) because death occurred within 1 year, the rest (mean follow-up period 3.6 months) because further information was not obtained. All the subjects were included in the analysis. The information concerning the events was interpreted by a cardiologist (S. Severi) who classified the events as follows: no event, non-fatal myocardial infarction, cardiac death (which included sudden death, acute left ventricular dysfunction, fatal myocardial infarction and death during or immediately after coronary bypass surgery), non-cardiac death (which included cancer, accident, stroke, acute pulmonary disease, etc.). Before permanent storage, each record was checked by a computer expert (P. Landi) and a senior cardiologist (S. Severi) for logical or clinical inconsistencies as well as uniformity of entry criteria. Regular quality control of the data was done by a computer expert dedicated to the maintenance of the database.

Methods. Cardiac catheterisation was done according to the Judkins' technique; LV end-diastolic and aortic pressures were measured routinely during catheterisation. Selective left and right coronary angiography and left ventriculography were carried out (in that order), with multiple views (two for the ventriculography and six for the coronaries). The images were recorded on 35-mm film and reviewed by the two haemodynamists who had done the invasive study. Echocardiography was done as described previously [25].

Statistical analysis. Values are given as means ± SD. Between-group mean differences were tested by the unpaired t test (or ANOVA) or the chi-squared test, for continuous variables and proportions, respectively. Serum triglycerides concentrations and smoke load were logarithmically transformed for statistical analysis. The ATS score was not normally distributed, essentially due to a large group of patients with normal coronaries ($n = 557$) and a few ($n = 54$) with a very high (> 700) ATS score. Therefore, all analyses including ATS were also run with the logarithmically transformed variable, with or without the patients with normal coronaries included; between-group differences were also tested with the use of non-parametric tests on the raw data. As the pattern of results was superimposable regardless of the approach, we only report the results obtained with the untransformed variable. Multiple regression and logistic analysis were carried out by standard methods. We also calculated 95 % confidence intervals (CI). Survival was analysed by generating Kaplan-Meier curves for two groups, which were then compared by the Wilcoxon test. Analysis of mortality was done with the use of Cox regression models. We considered differences significant at p less than 0.05.

Results

Clinical and biochemical characteristics. Of the 2253 subjects, 269 (12 %) had diabetes, the majority (86 %) with a previous diagnosis. Among the diabetic patients, 46 % were treated with diet alone, 40 % with oral agents and 14 % with insulin. Age (60 ± 7, 61 ± 8, 59 ± 8 years) and BMI (28 ± 4, 27 ± 3, 27 ± 3 kg · m^{-2}) were similar in these three treatment groups but both disease duration (7 ± 8, 13 ± 7, 20 ± 12 years, $p < 0.001$ by ANOVA) and fasting plasma glucose levels (7.2 ± 2.3, 7.7 ± 3.6, 10.3 ± 5.5 mmol/l, $p < 0.001$) increased across treatment groups. Compared with the non-diabetic subjects (Table 1), diabetic patients were more often female, were older and heavier, had more diabetes but less CHD in the family, and were less frequently smokers; prevalence of hypertension, and systolic BP and heart rate values were significantly higher. Diabetic subjects showed a slightly lower prevalence of resting or effort angina alone (18 vs 22 % and 20 vs 24 %, respectively, $p = 0.08$ for both),

Table 1. Clinical characteristics

	Non-diabetic subjects mean ± SD	Diabetic patients mean ± SD	*p*
n	1984	269	
Female (%)	19	27	< 0.0003
Age (years)	55 ± 10	60 ± 8.1	< 0.0001
BMI ($kg \cdot m^{-2}$)	26.2 ± 3.2	27.3 ± 3.4	< 0.0001
FHD (%)	14	36	< 0.0001
FHH (%)	21	18	NS
FHS (%)	20	22	NS
FHCHD (score)	1.10 ± 2.10	0.79 ± 1.60	< 0.03
Hypertension prevalence (%)	38	56	< 0.0001
Diabetes duration (years)	–	11 ± 9	
School education (years)	8.7 ± 4.6	8.1 ± 4.6	NS
Ethanol consumption ($g \cdot week^{-1}$)	177 ± 186	113 ± 152	< 0.0001
Smoking (n/ex/y) (%)	25/52/23	37/50/13	< 0.0001
Cigarette consumption (pack-years)	35 (20–53)	40 (17–61)	< 0.01
Systolic BP (mmHg)	128 ± 14	133 ± 16	< 0.0001
Diastolic BP (mmHg)	80 ± 8	80 ± 8	NS
Mean BP (mmHg)	96 ± 9	98 ± 10	< 0.02
Heart rate (bpm)	65 ± 8	68 ± 9	< 0.0001

FHD = Family history of Type II diabetes; FHH = family history of hypertension; FHS = family history of stroke; FHCHD = family history of ischaemic heart disease; smoking (n/ex/y) = non-smokers, past smokers, current smokers; cigarette consumption, of smokers and past smokers only, is expressed as geometric mean and [25th and 75th centile]; BP = arterial blood pressure

but a higher prevalence of combined resting and effort angina (39 vs 28%, $p < 0.01$). In addition to more frequent PMI, (44 vs 38%, $p = 0.05$), the prevalence rates of previous coronary artery by-pass surgery (CABG) (3.0 vs 1.1%, $p < 0.02$), percutaneous coronary angioplasty (PTCA) (1.9 vs 0.4%, $p < 0.05$), cerebro-vascular events (4.1 vs 1.9, $p < 0.03$) and peripheral vascular disease (7.8 vs 4.7%, $p < 0.05$) were all significantly higher among diabetic patients.

Fasting plasma glucose (7.67 ± 3.55 vs 4.90 ± 0.86 mmol/l, $p < 0.0001$) and triglyceride concentrations (2.03 ± 1.24 vs 1.78 ± 1.02 mmol/l, $p < 0.005$) were higher in diabetic patients; serum total cholesterol (5.60 ± 1.7 vs 5.47 ± 1.26 mmol/l), creatinine (96 ± 50 vs 92 ± 34 μmol/l), and uric acid concentrations (323 ± 95 vs 317 ± 89 μmol/l) also tended to be higher ($0.05 < p < 0.10$ for all). Clinical grade proteinuria was found in 12.3% of diabetic patients ($p < 0.02$ vs 7.6% of non-diabetic subjects). Regardless of diabetes status, proteinuria was associated with higher plasma glucose (5.8 ± 2.7 vs 5.2 ± 1.6 mmol/l, $p < 0.001$), higher serum creatinine (102 ± 63 vs 92 ± 35 μmol/l, $p = 0.02$), slightly higher diastolic and systolic BP (82 ± 8/130 ± 16 vs 80 ± 81/27 ± 14 mmHg, $p < 0.05$ for both) and larger use of diuretics (35 vs 23%, $p < 0.001$), whereas no differences were observed in serum lipids or PMI prevalence. When present in diabetic patients, proteinuria was associated with higher plasma glucose (9.2 ± 4.8 vs 7.4 ± 3.3 mmol/l, $p < 0.0001$), higher plasma creatinine (104 ± 41 vs 95 ± 53 μmol/l, $p < 0.02$) and larger use of diuretics (61 vs 34%, $p < 0.001$, all *p* values refer to the interaction between diabetes and proteinuria).

Although none of the individual ECG alterations was more prevalent among diabetic than non-diabetic patients, the former were less likely to have a normal ECG. Diabetic patients also had a higher intra-arterial systolic BP, a poorer LV function and a higher prevalence of LVH (Table 2).

Angiographic data. Although most patients in the cohort had clinically significant obstructions (CSO) in the coronary bed, there were significantly fewer diabetic than non-diabetic patients with normal coronary arteries (Table 3). The odds ratio (OR) for diabetic patients having at least one CSO was 2.66 (adjusted by sex, age, and presence of effort angina; CI: [1.79–4.03]). In particular, the difference between the two groups was accounted for by a higher prevalence of three-vessel disease (Adjusted for sex, age and symptoms OR = 2.21 [CI: 1.61–3.01]). When CSO was compared in each coronary vessel (Fig. 1), the diabetic group showed a trend towards higher prevalences of any degree of obstruction; the difference was particularly evident for the more severe degrees of stenosis ($\geq 90\%$, $p < 0.02$) and did not show a preferential anatomic localisation.

When the ATS score was considered, 9.7% of diabetic compared with 26.8% of non-diabetic patients had a completely normal coronary tree ($p < 0.001$); the OR for abnormal coronaries adjusted for age, sex and symptoms was 3.52 (CI: 2.22–5.79). In addition, the total ATS score was significantly higher in diabetic patients across age groups (Fig. 2), the difference levelling off after age 65 years. The mean ATS score values in each coronary artery were higher in diabetic than non-diabetic patients (LAD: 144 ± 117

Table 2. Cardiac functional indices

	Non-diabetic subjects mean ± SD	Diabetic patients mean ± SD	*p*
Normal ECG (%)	28	22	< 0.02
Atrial fibrillation (%)	2.8	3.7	NS
Left bundle branch block (%)	3.9	3.0	NS
Right bundle branch block (%)	3.9	4.9	NS
Left anterior fascicular block (%)	3.2	3.7	NS
Resting ST-T changes (%)	43	43	NS
Echo LVH (%)	12	24	< 0.0001
Intra-arterial systolic BP (mmHg)	134 ± 22	143 ± 26	< 0.0001
Intra-arterial diastolic BP (mmHg)	72 ± 11	72 ± 12	NS
LV end-diastolic BP (mmHg)	10 ± 7	12 ± 11	< 0.0005
LV ejection fraction (%)	55 ± 14	50 ± 17	< 0.0005
Vtg LV dysfunction score (0–3)	1.5 ± 1.3	1.8 ± 1.1	< 0.0005
Current use of diuretics (%)	22	37	< 0.0001
Current use of digitalis (%)	11	16	< 0.03

Vtg = ventriculography, Echo = echocardiography

Table 3. Angiografic findings

	Non-diabetic subjects (%)	Diabetic patients (%)	*p*
No CSO (> 50 %)	32.7	15.2	< 0.00001
1-vessel disease	29.3	23.8	NS
LAD	57.1	60.9	NS
CX	12.8	18.8	NS
RCA	30.1	20.3	NS
2-vessel disease	21.3	26.0	NS
LAD + RCA	51.4	50.4	NS
LAD + CX	28.5	25.2	NS
CX + RCA	20.1	24.4	NS
3-vessel disease	15.1	30.5	< 0.00001
3-vessels + MS	1.6	4.5	< 0.005

MS = main stem

Table 4. Follow-up data

	Non-diabetic subjects	Diabetic patients	*p*
n	1984	269	
Mean follow-up (months)	91	76	< 0.0001
CABG surgery	419 (21.1 %)	76 (28.3 %)	< 0.0001
PTCA	371 (18.7 %)	65 (24.2 %)	< 0.05
All-cause death	303 (15.3 %)	65 (24.2 %)	< 0.0001
Cardiac death	193 (9.7 %)	50 (18.6 %)	< 0.0001
Non-cardiac death	97 (4.9 %)	13 (4.8 %)	NS
Unknown cause death	13 (0.7 %)	2 (0.7 %)	NS

Cardiac death = fatal acute myocardial infarction, sudden death, left ventricular failure, death during or immediately after CABG surgery

vs 91 ± 100, CX: 98 ± 91 vs 52 ± 72, RCA: 99 ± 85 vs 63 ± 75 ATS units, $p < 0.0001$ for all); percentagewise, the difference was more pronounced for the CX (+ 88 %) than for the LAD or RCA artery (+ 58 and + 57 %, respectively). When patients with normal coronaries were excluded, the differences between the diabetic and non-diabetic group were smaller (LAD: 175 ± 106 vs 143 ± 91, CX: 128 ± 83 vs 104 ± 69, RCA: 128 ± 74 vs 111 ± 68 ATS units) but still statistically significant ($p < 0.001$ or less for all) and similar among the three main coronary vessels.

By multivariate analysis, sex, age, diabetes, serum cholesterol concentration, family history of CHD, cigarette consumption and school education all were independent correlates of ATS, together explaining 23 % of total ATS variability. In the multivariate model, a significant ($p < 0.03$) interaction between sex and diabetes on ATS was found, such that diabetes was associated with an excess of 114 ATS units in men and 187 ATS units in women. Prevalence of PMI was associated with worse coronary atherosclerosis in both diabetic (420 ± 210 vs 299 ± 236 ATS units, $p < 0.0001$) and non-diabetic patients (304 ± 192 vs 154 ± 184 ATS units, $p < 0.0001$). Thus, diabetic patients without PMI had similar ATS as non-diabetic subjects without PMI. In contrast, proteinuria was not associated with a higher ATS score either in the diabetic (366 ± 243 vs 354 ± 233 units) or non-diabetic group (231 ± 201 vs 207 ± 197 units). Within the diabetic group, the only variable that was independently (of sex and age) associated with ATS was serum cholesterol, whereas plasma glucose, disease duration and type of treatment were not correlated with the severity of coronary atherosclerosis.

Follow-up data. Over a mean follow-up period of 89 months, significantly more diabetic patients underwent coronary revascularisation, either by PTCA or CABG. All-cause death occurred in a larger proportion of diabetic than non-diabetic subjects, the excess mortality being entirely explained by an about twofold higher incidence of cardiac death (Table 4), the age and sex-adjusted odds ratio being OR = 1.34 (1.14–1.57). Furthermore, cardiac survival was significantly higher in women than in men among non-dia-

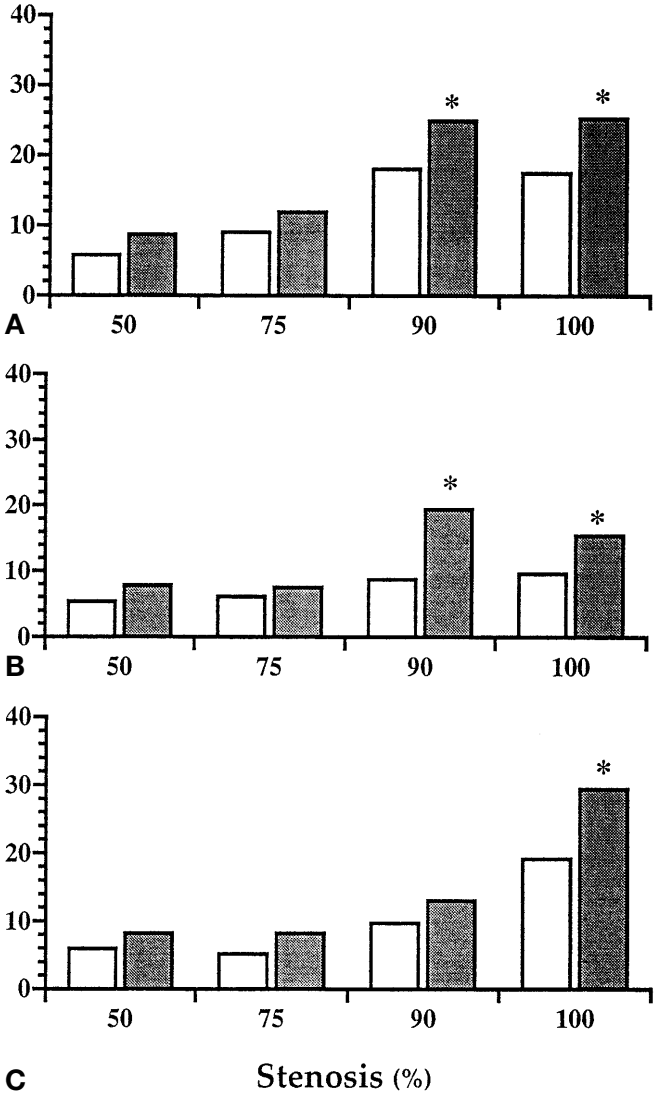

Fig. 1 A–C. Prevalence rate of individual degrees of clinically significant (> 50 %) obstruction (CSO) detected by angiography in the main coronary arteries; **A** left anterior descending artery, **B** circumflex artery, **C** right coronary artery of 1984 non-diabetic and 269 diabetic patients. *indicates a statistically significant chi-squared test. □, Non-diabetic subjects; ▒, diabetic patients

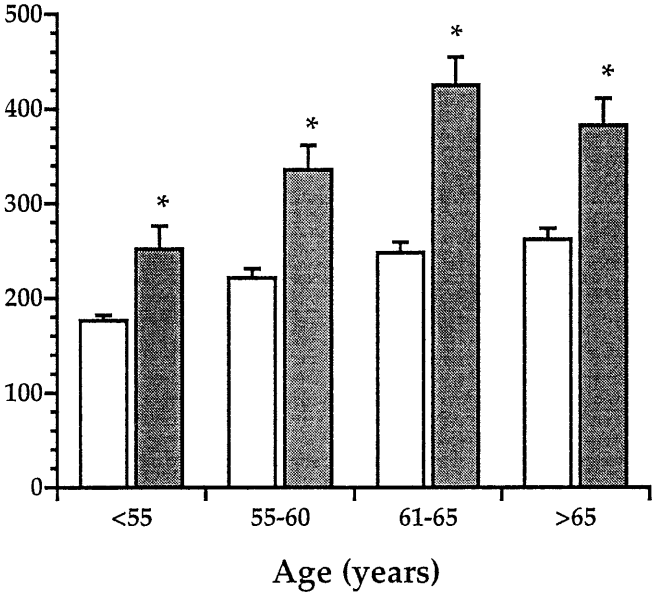

Fig. 2. Sum of all atherosclerotic narrowings detected by angiography in any segment of the coronary tree (ATS score) in 1984 non-diabetic and 269 diabetic patients stratified by age. □, Non-diabetic subjects; ▒, diabetic patients

betic subjects (age-adjusted OR = 0.71 [0.57–0.87]) but this sex protection was lost among diabetic patients (age-adjusted OR = 0.91 [0.67–1.23]). In a Cox model adjusting for age, sex, family history of CHD, cigarette and alcohol consumption, school education and serum cholesterol (i.e. the independent correlates of ATS), diabetes was still associated with a significant excess risk of dying of a cardiac cause (OR = 1.37 [CI: 1.14–1.60]). Among diabetic patients, neither disease duration nor type of treatment was a statistically significant risk factor for fatal cardiac events. When the entire cohort was stratified by quartiles of ATS, cardiac mortality was progressively higher with worse coronary atherosclerosis ($p <$ 0.0001, Fig. 3). When ATS (as a continuous variable) was introduced in a multivariate model together with age, sex and diabetes it still was a significant predictor of cardiac death (OR for each 100 units increment = 1.24 [CI: 1.18–1.31]) but diabetes lost most of its predictive value (OR = 1.15 [0.97–1.35], $p = 0.07$).

Prevalence of PMI was associated with significantly worse cardiac survival in both diabetic and non-diabetic subjects ($p < 0.0001$ for both); diabetic patients without evidence of PMI had similar cardiac mortality curves to non-diabetic subjects with PMI (Fig. 4). Likewise, the presence of proteinuria predicted more fatal cardiac events in the entire cohort (OR = 1.67 [1.37–2.02]) after adjusting by age, sex, plasma creatinine, diabetes and ATS score); this association was, however, largely due to the much higher cardiac mortality of the diabetic patients with proteinuria (Fig. 5). Among diabetic patients, after adjusting for age and sex the ATS score (OR = 1.23 [1.09–1.37]) and proteinuria (OR = 1.46 [1.03–1.99]) were still additive and independent predictors of cardiac death.

Discussion

The current results show that, among patients undergoing coronary angiography: (1) diabetes is associated with more severe atherosclerosis of the coronary vessels independently of other cardiovascular risk factors; (2) the effect of diabetes on coronary atherosclerosis is greater in women than in men; (3) coronary atherosclerosis explains the higher cardiac mor-

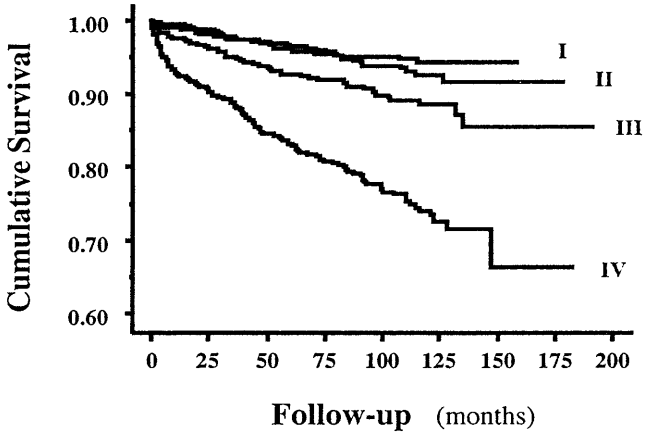

Fig. 3. Kaplan-Meier survival curves for cardiac death in 2253 patients after discharge from a coronary division by quartile of ATS score

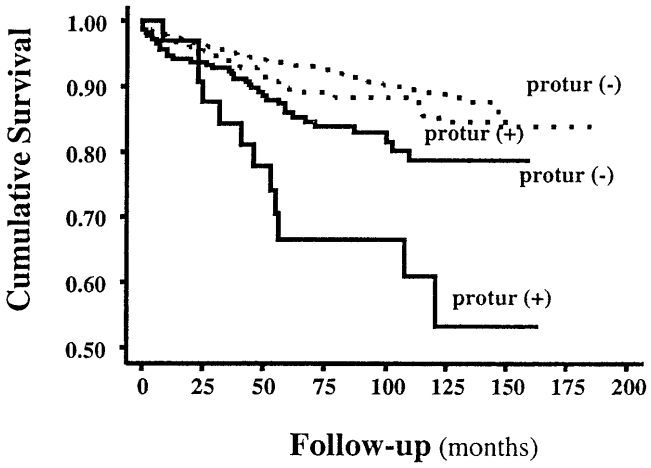

Fig. 5. Kaplan-Meier survival curves for cardiac death in 2253 patients according to the presence of clinical grade proteinuria (*protur*) and diabetes. - - - Non-diabetic subjects, — diabetic patients

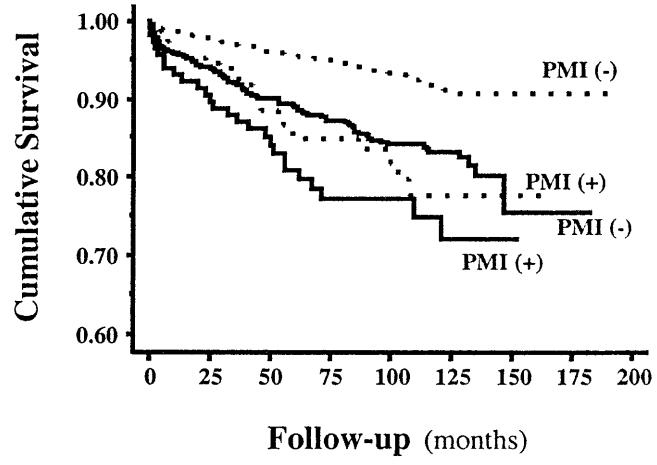

Fig. 4. Kaplan-Meier survival curves for cardiac death in 2253 patients according to the presence of previous myocardial infarction (PMI) and diabetes. - - - Non-diabetic subjects, — diabetic patients

tality of diabetic patients; (4) diabetic patients without PMI have a similar degree of coronary atherosclerosis and mortality rates as non-diabetic patients with a PMI and (5) proteinuria is not by itself a marker of coronary atherosclerosis but does identify, especially in diabetic people, a subgroup of patients at high risk of cardiac death.

Strictly speaking, these conclusions apply to a selected group, such as are patients who are referred to a coronary division for the evaluation of a chest pain syndrome. That the diabetic group represented 12% of the entire cohort in a region where the prevalence of diabetes is estimated at 3–4% [26] indicates that the referral bias enriched the cohort with patients at high risk for CHD. Nevertheless, our diabetic group showed most of the clinical features of Type II diabetes as are observed in clinic or population-based cohorts. Thus, age, glycaemic control and disease duration across treatment groups and prevalence of associated conditions (obesity [as a BMI > 25 kg · m^{-2}] = 52 vs 43% of non-diabetic subjects, hypertension = 56 vs 38% and hypertriglyceridaemia [as serum triglycerides > 2 mmol/l] = 30 vs 21%, peripheral vascular disease = 7.8 vs 4.7%, $p < 0.002$) all reproduced the characteristics of a non-selected or less selected patient series [27]. In addition, the pattern of associations between coronary atherosclerosis (as the ATS score) and cardiovascular risk factors was strikingly similar to that which has been reported for CHD events in the general population. Thus, male sex, advancing age, serum total cholesterol concentration, familial CHD and smoking, i.e. 5 of the 7 classic CHD predictors of the Framingham model, were independent correlates of the severity of anatomical changes in our cohort. Finally, the larger excess of coronary atherosclerosis in diabetic women compared with diabetic men parallels the excess of clinical CHD in diabetic women reported repeatedly in population-based surveys [28]. The lower prevalence of familial CHD in diabetic subjects, on the other hand, could result from selection; given their specific risk, diabetic patients manifest the disease even in the presence of a weak genetic pressure compared with the non-diabetic population.

A methodological issue is whether within our cohort the comparison between diabetic and non-diabetic subjects was affected by unmeasured biases. Thus, if silent ischaemia is more frequent in diabetic patients [29] referral to our coronary division for angiography might be delayed, resulting in a relative abundance of diabetic patients with more severe coronary stenosis. Although this possibility cannot be ruled out, it is noteworthy that in the present diabetic cohort the prevalence rate of PMI on history was sim-

ilar to that shown by the ECG (43.9 vs 43.7%, p = NS). In addition, a physician's awareness that diabetic patients are at high CHD risk and could potentially benefit from aggressive treatment (e.g. CABG [30]) could have preferentially channelled patients with diabetes to our coronary division. Finally (and more importantly), the higher incidence of cardiac death in diabetic patients could have selectively removed patients with more extensive coronary disease, whereby the negative effect of diabetes on coronary atherosclerosis and life expectancy would be underestimated. This survival bias is suggested by the finding that the effect of diabetes on ATS seems to decline after age 65 years. On balance, it seems possible to conclude that, in the kind of group that we studied selection did not skew the results too far away from the natural course of coronary atherosclerosis in diabetes.

The concept that diabetes is associated with more severe atherosclerosis of the coronary vasculature has been challenged recently by a study [15], in which a similar degree of atherosclerotic involvement in 55 Type II diabetic patients compared with 55 well-matched non-diabetic subjects was reported. In that study only seven patients were, however, women (= 13%, compared with 27% of our diabetic group). Because the effect of diabetes on clinical CHD [31] and coronary atherosclerosis is stronger in women than in men, it is expected that the difference in coronary atherosclerosis between men with or without diabetes should be comparatively small. In addition, in that study [15] patients and control subjects were matched for most major cardiovascular risk factors and were selected to have haemodynamically significant narrowing (> 50%) in at least one vessel. As shown by the present results, part of the effect of diabetes on coronary vessels is an increased likelihood of having at least some atherosclerotic lesion. If only affected vessels are compared between diabetic and non-diabetic subjects in our cohort, the ATS excess in diabetic patients was reduced from 60 to 18%. Therefore, the discrepancy between the current findings and those of the other study is only apparent.

In a previous large angiographic study comparing 466 diabetic with 5620 non-diabetic subjects [11], the excess coronary atherosclerosis was 60% in women and 24% in men and was only partially explained by common risk factors. Although in general agreement with our results, that study did not distinguish between Type I and Type II diabetes and provided no information on treatment, disease duration or glycaemic control. In another angiographic study [32], a relation between severity of the hyperglycaemia and the probability of having a haemodynamically significant stenosis was found in a mixed group of Type I and Type II diabetic patients; severity of the disease was, however, only judged from the type of antidiabetic treatment and the extent of coronary disease was not quantified. In contrast, in a large post-mortem study [8] comparing coronary atherosclerosis between diabetic and non-diabetic subjects, neither the duration nor the severity of diabetes correlated with the atherosclerotic involvement of the coronary arteries. Although our findings are apparently in agreement with the latter study, the interpretation cannot ignore that our patients (as well as those in that study [8]) were cardiological referrals with a mean age of 60 years, in whom the coronary disease was presumably more advanced than in the diabetic population at large. Thus, the effect of metabolic control and diabetes duration on coronary disease is likely to be more evident at earlier stages in the course of diabetic macroangiopathy [33]. Notably, when analysing the diabetic group alone, serum cholesterol, in addition to age and sex, still was a statistically significant correlate of ATS. This finding implies that, although cholesterol in itself does not explain the excess atherosclerosis of diabetes, it continues to exert an independent atherogenic influence in patients with diffuse coronary disease. This result is in full agreement with the subgroup analysis of the 4S study [34], showing that cholesterol lowering was at least as effective in diabetic patients as in the whole cohort in reducing CHD incidence.

On follow-up, cardiac mortality was quantitatively related to the severity of coronary atherosclerosis, whether this was expressed as number of vessels involved (one, two, or three-vessel disease) or as overall coronary narrowing. Consistent with the worse status of their coronaries, the diabetic patients in our cohort experienced statistically significantly more cardiac mortality than the non-diabetic subjects, as is the case in the general population [35]. The finding that the ATS score statistically replaced diabetes in the full prediction model supports the conclusion that the amount of atherosclerosis largely accounts for the unfavourable outcome of the diabetic person. It is well established that factors other than coronary atherosclerosis are responsible for a fraction of cardiac deaths among diabetic patients. Thus, LV dysfunction, arrhythmias and a specific diabetic cardiomyopathy have been advocated as independent risk factors in patients with diabetes [36]. In our patients when the available indices of ventricular dysfunction (e.g. the ejection fraction, left ventricular diastolic pressure and the dysfunction score) were adjusted statistically by the ATS score, they were, however, no longer significantly different between diabetic and non-diabetic subjects. Our results therefore are compatible with the conclusion that underlying coronary atherosclerosis is still the major cause of heart dysfunction in diabetic patients after discharge from a coronary division.

The current results on the effect of PMI on cardiac mortality are virtually superimposable on, and extend, those recently reported in a population-based

cohort [4]. That report confirmed that diabetes imposes a cardiac death risk that is roughly equivalent to that carried by a PMI. Angiography documented that coronary atherosclerosis is indeed the pathologic basis for the observed difference between diabetic and non-diabetic subjects. The higher cardiac mortality we found among proteinuric patients, particularly if diabetic, also reproduces previous findings in population-based cohorts [21]. Worse coronary atherosclerosis was, however, not the pathologic basis for the prognostic value of proteinuria, either in non-diabetic or in diabetic subjects. Of note is that very few patients with proteinuria had serum creatinine concentrations exceeding 177 μmol/l (3.8% vs 0.9% of non-proteinuric subjects), thereby ruling out renal failure as the cause for the increased cardiac mortality. The only clinical features characterising the proteinuric patients were a worse glycaemic control and a more frequent use of diuretics. This suggests that the enhanced mortality associated with the presence of proteinuria is linked with cardiac failure, which in turn could be favoured by chronic hyperglycaemia. In support of this interpretation, several reports have documented that cardiac failure is a prevalent cause of death in diabetic patients after an acute myocardial infarction [37] and that more severe hyperglycaemia during the hospital phase is associated with a worse prognosis after myocardial infarction [38, 39]. In addition, the DIGAMI study has established that early and continued control of hyperglycaemia by insulin treatment is quite effective in reducing cardiac mortality in diabetic patients after myocardial infarction [40]. Despite these clues, the interrelations between low-grade proteinuria, hyperglycaemia and cardiac events might be explained by other mechanisms (e.g. microvascular dysfunction, proness to plaque rupture and thrombosis) which could not be evaluated in this study.

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