Observation

Cardiovascular complications in Type 2 diabetes mellitus depend on the coronary angiographic state rather than on the diabetic state

To the Editor: Cardiovascular disease is the major complication from Type 2 diabetes mellitus. In a landmark study [1], the risk for myocardial infarction has been reported as high for diabetic patients without prior myocardial infarction compared with non-diabetic patients with prior myocardial infarction. From these data, it has been generalized that Type 2 diabetes bears a risk equal to pre-existing coronary artery disease (CAD) and numerous guidelines have been based on this risk equivalent worldwide. However, other data have challenged the concept, pointing to a lower cardiovascular risk in diabetic patients than in patients already affected by CAD [2, 3]. An important limitation of epidemiologic studies is that the state of the coronary arteries at baseline is not known. Because CAD often is present, albeit silent in diabetic patients, the diabetic state often represents a state of evolving coronary atherosclerosis. We hypothesized that the risk for future cardiovascular events in diabetic patients depends on the state of the coronary arteries at baseline rather than on the diabetic state per se.

We determined the presence of significant coronary atherosclerosis (≥50% stenosis at coronary angiography) and the incidence of cardiovascular events in non-diabetic and diabetic patients with and without CAD. To investigate a high-risk population we studied 750 consecutive patients undergoing coronary angiography at the Federal Academic Hospital of Feldkirch (Landeskrankenhaus Feldkirch), Feldkirch, Austria. Because the symptoms of coronary events can have seasonal variations, special care was taken to recruit this cohort during an entire year, i.e. from October 1999 to October 2000. History of diabetes and fasting plasma glucose concentrations were obtained from all patients. Diabetes mellitus Type 2 was diagnosed according to the WHO criteria. In patients without a history of diabetes but with increased fasting glucose concentrations, an oral glucose tolerance test was used to confirm the diagnosis. All patients not fulfilling any of the WHO criteria were considered "non-diabetic". Angiography and laboratory measurements were carried out as described previously [4]. Individual patients were then allocated to one of four groups: non-diabetic patients without significant coronary atherosclerosis (DM–/CAD–, *n*=244), non-diabetic patients with significant coronary atherosclerosis (DM–/CAD+, *n*=342), and diabetic patients without (DM+/CAD–, *n*=50) or with significant coronary atherosclerosis (DM+/CAD+, *n*=114).

We carried out a prospective study on the 750 patients recruited at baseline from October 1999 to November 2002. An overall follow-up rate of 95.1% could be achieved and the mean follow-up period was 2.2 years. Cardiovascular endpoints were recorded as in [5]. The Ethics Committee of the University of Innsbruck approved the study and all participants gave written informed consent.

The chi-square test was used for the comparison of categorical variables between groups, the Mann-Whitney U test for two-group comparisons, and the Kruskal-Wallis test for four-group comparisons of continuous variables. For the evaluation of endpoints, person years of follow-up were calculated from the baseline to the event or to the follow-up visit. Event-free survival was estimated by an actuarial approach. Pairwise comparisons of event-free survival in the four groups of patients were done with the Wilcoxon-Gehan statistic. We calculated Cox regression models to evaluate the risk for vascular events in the four groups of patients independent of other risk factors of coronary artery disease (age, sex, hypertension, smoking, alcohol consumption, HDL cholesterol, LDL cholesterol). Significance was defined as a two-tailed *p* value of less than 0.05. Results are given as means ± SD if not denoted otherwise.

The incidence of vascular events was strongly affected by the angiographic state but not by the diabetic state: the proportion of patients with vascular events was similar in DM–

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Table 1. Demographic characteristics, biochemical characteristics, medication, and incidence rates of endpoints in the four groups of patients

	DM–/CAD– *n*	DM+/CAD– 244	DM–/CAD+ 50	DM+/CAD+ 342	*p* value 114
Age (years)	61±11	62±10	63±10	65±10	0.090
Male sex (%)	54.1	54.0	78.9	70.2	<0.001
Diabetes duration (years)		5.44±6.70		9.67±9.08	0.011
HbA_{1c} (%)	5.7±0.6	7.2±1.3	5.8±0.5	7.6±1.6	<0.001
Diet only (%)		52.0		38.6	0.110
Metformin treatment (%)		34.0		31.6	0.760
Sulfonylurea treatment (%)		26.0		28.6	0.119
Insulin treatment (%)		12.0		29.8	0.014
Mortality (*n*; [%])	8; [3.3]	3; [6.0]	22; [6.4]	11; [9.6]	0.124
Cardiovascular death (*n*; [%])	4; [1.6]	2; [4.0]	16; [4.7]	7; [6.1]	0.156
Non fatal cardiovascular event (*n*; [%])	6; [2.5]	0; [0.0]	37; [10.8]	23; [20.2]	<0.001
Non fatal MI (*n*; [%])	0; [0.0]	0; [0.0]	7; [2.0]	3; [3.1]	0.073
Other nonfatal vascular events (*n*; [%])	6; [2.5]	0; [0.0]	31; [9.1]	21; [18.4]	0.014
Cumulated vascular end points (*n*; [%])	10; [4.1]	2; [4.0]	53; [15.5]s	30; [26.3]	<0.001

MI, Myocardial infarction
p values are calculated with the Kruskal-Wallis test, the Mann-Whitney U test, and the chi-squared test, respectively

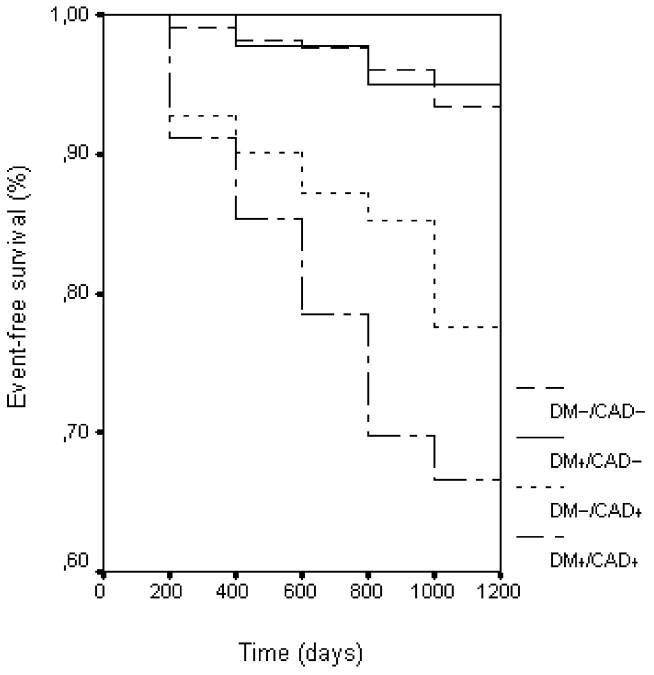

Fig. 1. Event-free survival in the four groups of patients

/CAD– (4.1%) and in DM+/CAD– (4.0%) patients (Table 1, Fig. 1), but higher in DM–/CAD+ (15.5%, $p<0.001$) and DM+/CAD+ patients (26.3%, $p<0.001$) when compared to DM–/CAD–. Also, the incidence of vascular events was higher in DM+/CAD+ than in DM+/CAD– ($p<0.001$) or DM–/CAD+ ($p=0.010$). Most importantly, patients with diabetes only (DM+/CAD–) had a lower event rate than non-diabetic coronary patients (DM–/CAD+, $p=0.033$; Fig. 1).

The diabetic state by itself was not a significant independent predictor for vascular events in Cox regression analysis adjusting for other cardiovascular risk factors (see above; odds ratio =1.522, 95% CI 0.967–2.429; $p=0.069$). However, the presence of significant stenoses was a strong independent predictor for vascular events with an odds ratio of 3.987 (2.146–7.408), $p<0.001$. Also, an interaction term diabetes x CAD was not significant ($p=0.375$) indicating that only the presence of CAD, but not that of diabetes, affects vascular events.

These data confirm our hypothesis that the angiographic state determines the 2-year prognosis of our patients irrespective of the diabetic state. As compared to patients with neither diabetes nor coronary atherosclerosis, people with significant (≥50%) coronary stenoses are at a significantly increased risk for future events. In contrast, the incidence of cardiovascular complications is indistinguishable between diabetic and non-diabetic subjects who do not have significant coronary lesions at baseline. Thus, in the absence of coronary atherosclerosis, the mere presence of diabetes does not affect the prognosis of our patients; however, if coronary atherosclerosis is already present, diabetes adds a further risk to that of CAD.

Our data help to dissolve the discrepancies of the literature. Diabetes can infer a cardiovascular risk as high as CAD if the vast majority of the patients already have significant stenoses; if, however, a substantial proportion of the diabetic population studied is free of coronary lesions, prognosis of diabetic patients will be more favorable than in patients with established CAD. So far, angiography has not been done in epidemiologic studies determining the cardiovascular risk of diabetic patients. Because our DM+/CAD+ patients had a longer duration of diabetes (with a mean of 9.67 years) than our DM+/CAD– patients (mean 5.44 years), we can assume that the patients reported by [1] who had a duration of diabetes of already 8 years at the onset of the study, mostly had coronary atherosclerosis at baseline in contrast to those of [3] who investigated a cohort with newly diagnosed diabetes mellitus. Hence, the cardiovascular risk arising from Type 2 diabetes mellitus strongly depends on the baseline characteristics of the population studied: in the absence of pre-existing coronary lesions, diabetes mellitus is not a risk equivalent to coronary disease in our patients.

It should not be overlooked that our report covers a relatively short period of follow-up (mean 2.2 years). Nevertheless the numbers of endpoints are sufficiently high to distinguish complication rates between the four groups. However, because not all p values are very strong (between 0.033 and 0.001) further evaluations will be necessary to assess the more long-term risk of diabetes per se. Our data alone are good news for both, diabetic patients and professionals in the diabetes field: the simple presence of diabetes mellitus per se, in the absence of pre-existing coronary atherosclerosis, infers a lower cardiovascular risk than previously estimated. This finding could have important psychological implications for diabetic patients.

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