

Incidence of coronary heart disease in type 2 diabetic men and women: impact of microvascular complications, treatment and geographic location.

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Abstract

Objective: Cardiovascular disease (CVD) is the main cause of morbidity/mortality in diabetes. We set forth to determine incidence and identify predictors (including microvascular complications and treatment) of first coronary heart disease (CHD) event in CVD-free type 2 diabetic patients.

Research Design and Methods: A cohort of 6,032 women and 5,612 men, sampled from the nationwide network of hospital-based diabetes clinics, was followed up for 4 years. Baseline assessment included retinopathy, nephropathy, and foot ulcers. First CHD events (myocardial infarction, CABG, PTCA, and ECG-proven angina) were analyzed for 29,069 person-years.

Results: The age-standardized incidence rate (per 1,000 person-years) of first CHD event (n=881) was 28.8[95%CI:25.4-32.2] in men and 23.3[20.2-26.4] in women. Major CHD (myocardial infarction, CABG, PTCA) was less frequent in women (5.8[4.3-7.2]) than in men (13.1[10.9-15.4]), a gender ratio of 0.5[0.4-0.6]. Incidence rates of all outcomes were higher in patients with microvascular complications (for major CHD, age-adjusted rate-ratios were 1.6[1.2-2.21] in men and 1.5[1.0-2.2] in women). By multivariate Cox analysis, age and diabetes duration were risk predictors common to both genders. In men, glycemic control and treated hypertension were additional independent risk factors but residing in the south was associated with a significant, 29% risk reduction; in women, higher triglycerides/lower HDL-cholesterol and microvascular complications were independent risk factors.

Conclusions: In CVD-free patients with type 2 diabetes, risk of first CHD depends on gender, geographic location, and presence of microvascular disease. Hyperglycemia and hypertension, particularly in men, and diabetic dyslipidemia, especially in women, are risk factors amenable to more aggressive treatment.

Introduction

Diabetes is estimated to be responsible for 5.2% of all deaths (1). Ever since the Framingham Study (2), epidemiology has consistently shown that diabetes confers an increased risk for coronary heart disease (CHD) and cardiac mortality (3-6). Salient features of this association are: (a) the relative risk of CHD (7) and fatal CHD (8) is higher in women than in men with diabetes; (b) classical and diabetes-related risk factors both contribute to total CHD risk (6); and (c) insulin treatment may be associated with worse cardiovascular prognosis (9,10). The reasons for the excessive relative CHD risk of diabetic women as compared to diabetic men are incompletely understood. In the Strong Heart study (11), the greater risk for cardiovascular disease (CVD) in women was explained in part by an apparent greater negative impact of diabetes on CVD risk factors. With regard to diabetes-related risk, the WHO multinational Study found that, in type 2 diabetic patients proteinuria and retinopathy were independent predictors of CVD mortality, fatal and non-fatal myocardial infarction (AMI) and stroke (6). Finally, the adverse prognostic value of insulin treatment has traditionally been ascribed to the presence of more advanced disease (12). However, as plasma insulin levels per se have been reported to be significant, if weak, independent CVD predictors (12), the possibility that exogenous hyperinsulinemia may counter the beneficial effects of insulin-induced metabolic control on CVD risk has not been ruled out conclusively.

Estimates of CHD incidence in diabetic patients vary across studies and countries. Source data are remarkably heterogeneous with regard to selection criteria and risk assessment, and few observational studies provide information on the natural course of CHD in patients who periodically refer to hospital-based outpatient clinics. Furthermore, the natural history of CVD in

diabetes is changing. In a recent analysis of the Framingham original and offspring cohorts (13), incident CVD among adults with diabetes was reported to have halved between the examination in 1959-1966 and that in 1977-1995.

In the present study, we set forth to determine the incidence of first CHD events in a large, recent cohort of type 2 diabetic patients who are regularly followed at outpatient clinics, and to identify risk factors that are associated with CHD burden, including presence of microvascular complications and pharmacological treatment.

Methods

The DAI study (Diabetes and Informatics Study Group, Association of Clinical Diabetologist, Istituto Superiore di Sanità [National Institute of Health]) DAI is an observational study of type 2 patients attending hospital-based diabetes clinics of the National Health Service (in Italy, ~80% of known diabetic patients are seen at these clinics at least once a year). A detailed description of the study methodology has been reported (14). In brief, the reference population consisted of all patients with type 2 diabetes (according to WHO criteria) diagnosed after 39 years of age who were seen between September-December 1998 or March-June 1999. At each clinic, patients were chosen (on a 1:4 basis) so as to create a sample representative of the diabetic population seen at that center. A systematic sampling technique was applied by including every 4th patient. A total of 201 clinics throughout the country volunteered for the prevalence study (14), and 157 of them were involved in the incidence study. For this analysis, patients with prevalent CHD (see below for definition), cerebral thromboembolism or peripheral amputations were excluded; the present analysis is thus restricted to the 11,644 patients (6,032 women [4.4% pre-menopausal] and 5,612 men) without evidence of macrovascular

disease at baseline. Follow-up data were collected yearly between 2000-2003. A total of 1,665 patients (788 men and 877 women) were lost to follow up; their baseline clinical characteristics were essentially similar to those of the patients with follow-up data (data not shown).

Data collection and definitions At the baseline and each subsequent visit, a questionnaire was administered. Recorded information included: personal, anthropometric and lifestyle data (including smoking habits and alcohol consumption), clinical history and data relevant to microvascular (retinopathy, blindness, nephropathy, foot ulcers) and macrovascular complications (CHD, cerebral thromboembolism, peripheral amputations), laboratory data, and pharmacological treatment (with oral hypoglycemic agents [OHA], antihypertensive or lipid-lowering agents). Patients were classified as having CHD if they had one of the following: 1) a history of hospital admission for either fatal or non-fatal AMI or an episode of angina; 2) a 12-lead ECG positive for prior AMI or angina by Minnesota coding system (criteria I 1-3, IV 1-3, V 1-2, and VII 1); 3) a history of coronary artery by-pass graft (CABG) or percutaneous transluminal coronary angioplasty (PTCA). All patients had had at least one ECG in the 12 months preceding enrolment to exclude prior AMI. Information, including death, on patients who did not show up at the scheduled visits was obtained from telephone interviews to the patients, their relatives or physicians. All documentation was reviewed by an ad hoc committee to confirm diagnosis.

Measurements Serum HbA_{1c} and lipid profile were determined in the fasting state. Systolic and diastolic blood pressure were measured after the patient had been seated for at least 5 min. A patient was defined hypertensive if he/she had a systolic blood pressure ≥ 140 mmHg and/or a diastolic blood pressure ≥ 90 mmHg or was on antihypertensive treatment. Urinary albumin excretion (UAE) was obtained in a timed overnight collection;

microalbuminuria was defined as UAE between 30-300 mg/l in at least three successive measurements in the absence of other reasons for proteinuria (urinary infection, glomerulonephritis, kidney stones, bladder cancer, etc.). Familial CHD was defined as having a first-degree relative with a CHD episode before 55 years of age. Retinopathy was assessed by an ophthalmologist by comprehensive dilated-eye examination and high-quality stereoscopic photographs.

Statistical analysis Patients were followed up from the baseline visit to the first of the following: a CHD event, death, end of the study, or center drop-out. Population characteristics are given as mean (± 2 SE) or median for continuous variables, and proportions (± 2 SE) for categorical data. Differences between groups were assessed using the t-test or nonparametric tests (Mann-Whitney and Kruskal-Wallis test) for normal and non-normal data, respectively, and the χ^2 test for categorical data. CHD incidence density was standardized on the age distribution of the 1998 Italian population. Univariate and multivariate Cox proportional hazard models were employed to examine risk factors for CHD incidence. Preliminary data exploration was carried out separately in men and women by univariate Cox models of all covariates, adjusted by age at baseline. Interaction between cholesterol level and lipid-lowering therapy, and between blood pressure and antihypertensive therapy were tested. All covariates with a $p < 0.1$ were entered into the final multivariate models. Results were checked by a stepwise technique; the proportional hazards assumption was checked with Schoenfeld residuals. Variables were used without transformation, although the quadratic term for the continuous covariates was first considered and assessed by likelihood-ratio testing. Results are given as hazard ratios and 95% confidence intervals.

The relationship between insulin treatment and CHD risk was explored by propensity score methodology, which is an

alternative technique to control for confounding in observational studies (15). The propensity score is defined as a subject's probability of treatment assignment conditional on measured covariates. It is a one-dimensional variable that summarizes the multi-dimensional pretreatment covariates computed by logistic regression. The propensity score was used as a covariate in additional Cox models. All analyses were performed using the Stata 8.0 statistical package.

Results

During 4 years of follow-up, 881 incident CHD events were observed, yielding an age-standardized incidence rate (per 1,000 person-years) of 28.8 [95%CI: 25.4-32.2] in men and 23.3 [95%CI: 20.2-26.4] in women. AMI, major CHD events (AMI, CABG, and PTCA), and fatal CHD were all significantly more frequent in men than women, whereas rates of CHD other than AMI were similar (Table 1). In the comparison of patients without or with incident CHD (Table 2), age was slightly higher, diabetes duration was longer, prevalence of hypertension and insulin treatment (alone or in combination with OHA) were higher in both men and women with a CHD event. In addition, fewer men with incident CHD resided in the south&islands than in northern/central Italy while in women with incident CHD serum triglycerides were more often above 150 mg/dl (46% vs 41%, $p<0.04$). In both men and women the prevalence of microvascular complications (any or none) at baseline was significantly higher among patients who developed CHD than among those that did not. Correspondingly, incidence rates of all outcomes were higher in patients with than without complications (Table 1).

To explore whether insulin treatment was associated with CHD risk, a propensity score was constructed that included age, diabetes duration, BMI and waist girth, fasting plasma glucose, HbA_{1c}, presence of microvascular complications, and

geographical area, i.e., variables presumed to inform treatment choice. In women but not in men, the relative CHD risk adjusted for the propensity score was higher in insulin-treated than non-insulin-treated patients (RR=1.40 [95%CI: 1.09-1.79]).

In preliminary analyses on the entire cohort, sex interacted with several risk factors; subsequent analyses were therefore performed separately by gender. In univariate models, age, disease duration, serum triglycerides, microangiopathy, antihypertensive therapy and insulin treatment were shared risk factors, whereas waist girth, glycemic control, total cholesterol, blood pressure, and geographic area were additional risk predictors in men, and HDL-cholesterol and lipid-lowering treatment were so in women. The output of a multivariate Cox model of incident CHD – including all risk factors significant at the $p<0.1$ level in univariate analysis – is shown in Fig. 1. Age was a strong predictor in both men and women – a risk increase of 14% and 23% per decade, respectively – as was diabetes duration. HbA_{1c} was an additional risk factor in men (with an estimated 14% risk increase for each 20% increment above the upper limit of normal), whereas a serum triglyceride level ≥ 150 mg/dl was an independent risk predictor, and HDL-cholesterol a protective factor, in women. The presence of microvascular complications enhanced risk by 35% in women and by 20% in men. Men residing in southern regions had a 29% lower CHD risk than men elsewhere in Italy. With regard to pharmacological treatment, hypertension therapy was an independent predictor in men, while insulin treatment (alone or in combination with OHA) predicted a 36% higher risk in women but fell short of statistical significance. These results were almost identical whether or not the propensity score was included in the model.

Discussion

In this nationwide survey of type 2 diabetic patients regularly attending diabetes clinics we found that (a) incident CHD was lower than in several previous surveys, (b) major CHD was twice more frequent in men than women, (c) microvascular complications (renal, ocular or both) carried an independent risk of incident CHD, especially in women, (d) the pattern of CHD risk factors was partly different in men and women, and (e) insulin treatment was not associated with an increased CHD risk. These findings require specification.

Firstly, in observational studies of CHD in diabetes incidence rates have varied widely as a function of ethnic background, inclusion criteria, definition of endpoints, and duration of follow-up. In the PROactive Study, for example, 16% of type 2 patients had a first major coronary event within ~3 years; in that study, however, the majority of patients were at high risk, more than half of them having suffered from a major CVD episode at enrolment (16). Likewise, higher AMI incidence was found in the Helsinki Heart study (1.5%/year in 135 patients) (17) and in another Finnish population-based study (2.9%/year in 1,059 patients) (18). On the other hand, Lee and colleagues (19) reported a CHD (fatal and non-fatal AMI) incidence rate of 10.8 per 1,000 person-years in a larger group of patients with no prior AMI, a figure comparable to ours. Similarly, in the recent FIELD study in type 2 patients – with clinical characteristics and selection criteria similar to our cohort – the 4,900 patients randomized to placebo had a CHD incidence of 11.7 per 1,000 person-years (20). Thus, our relatively low CHD incidence appears to reflect multiple circumstances: first, large population surveys tend to report lower incidence than smaller studies (21); second, countries in southern Europe consistently show lower CHD rates than northern/central European countries (22); and lastly, our diabetic population may be on a declining trend of CVD similar to that recently documented in the Framingham population (13) (although the lack of historical comparison in the

Italian population makes this interpretation only tentative).

Secondly, our findings on gender differences in incident CHD follow the trend emerging from recent meta-analyses of prospective studies, showing that the impact of diabetes on both CHD (7) and fatal CHD (8) is greater in women than men. In fact, in the only population-based, nationwide dataset available for Italy (the CUORE study) (23), the age-standardized incidence of major CHD in the 35-74-year age group was 6.6 (95%CI: 5.8-7.3) per 1,000 person-years in men and 2.0 (95%CI: 1.6-2.3) in women (an age-adjusted women-to-men ratio of 0.3 [95%CI: 0.2-0.3]) (S. Giampaoli, personal communication). The corresponding rates in our cohort in the same age range were approximately twice those of the general population (women/men ratio of 0.5 [95%CI: 0.4-0.6]). Thus, CHD in all its severe manifestations was less frequent – in absolute terms – in our diabetic women than in diabetic men, but with a women/men gradient ~50% higher than that seen in the background population. Less severe CHD (angina and signs of chronic myocardial ischemia) actually showed a similar incidence in men and women with diabetes. In a recent analysis of published data (24), the higher CHD rates of diabetic women have been ascribed to a more adverse profile of classic CHD risk factors. In our cohort, however, no major difference in level of risk factors – except for smoking habits – or pharmacological treatment stood out in the comparison of men and women (Table 2). This gender effect remains, therefore, unexplained.

Thirdly, the excess CVD risk associated with microangiopathy has been repeatedly reported in cross-sectional studies or small incident cohorts (25-29). The WHO multinational study of vascular disease in diabetes (6) found that heavy proteinuria and retinopathy carried a significant relative risk for CVD mortality; the type 2 diabetes cohorts in that study were, however, relatively small, and confounding by HbA_{1c} was not analyzed. No large prospective

study in type 2 patients free of CVD has assessed the risk of a first CHD event associated with microangiopathy in the context of the full set of classical risk factors. The current data offer robust evidence that microvascular complications markedly enhance the risk of a subsequent first coronary event in men as well as women. Interestingly, the excess risk ranged 60-90% for AMI and 20-40% for non-AMI CHD, but rose to 160-130% for fatal CHD (Table 1). Even in the fully adjusted Cox model, microangiopathy retained an independent predictive power, especially in women (Fig. 1). This suggests that mechanisms other than exposure to hyperglycemia underlie the co-development of micro- and macroangiopathy. Advanced glycation end-products (AGE) (29), oxidative stress (30), endothelial dysfunction (31) and subclinical inflammation (32) are candidate mechanisms that can simultaneously impact on the structure and function of both small and large vessels; each has been shown to be operative in type 2 diabetes (33). Established microvascular dysfunction may directly contribute to macroangiopathy by compromising blood supply to large vessels. Alternatively, in our patients hyperglycemia over the years preceding enrolment may have been a common pathogenetic predecessor of both microvascular and macrovascular damage.

Fourthly, in the full Cox model the pattern of CHD risk factors was partly gender-specific, glycemic control and hypertension predominating in men, diabetic dyslipidemia (i.e., high triglycerides and low HDL-cholesterol) and microangiopathy standing out in women. In general, the predictivity for CHD of poor glycemic control, hypertension and dyslipidemia in diabetic patients is well established (34-36), but there is little data on gender-specific risk patterns to compare with our findings. With regard to hypertension, the stronger risk in men could be explained by the fact that our diabetic women were more often on antihypertensive treatment than men (59%

vs 44% of all patients, $p < 0.001$). Conversely, the stronger risk conveyed by higher serum triglyceride levels in women could be due to the fact that their baseline triglyceride levels were higher ($p < 0.001$) (lipid-lowering treatment being equally infrequent in men and women). In addition, in women lower HDL-cholesterol levels were a further independent predictor. Thus, diabetic dyslipidemia appears to be a confirmed risk factor especially in women with diabetes. Interestingly, men, but not women, living in the south enjoyed a substantially lower CHD hazard than patients elsewhere in the country. This protective effect, which resisted all adjustments, may be the first trace of a lifestyle effect to ever have been detected in patients with diabetes. Adherence to a Mediterranean diet (which is higher in southern Italy) has been convincingly associated with a reduction in cardiovascular risk (37,38). Postmenopausal women may be inherently more resistant to diet-related risk reduction, as suggested by a recent study (39). Interactions between risk factors may be distinct in men and women, smoking conjuring up a higher risk in men, menopause doing the same with dyslipidemia in women.

In the UKPDS (40), there emerged no influence of antidiabetic treatment on CVD endpoints in newly diagnosed type 2 patients. In general, the evidence that insulin treatment may itself be a risk factor for CVD in type 2 diabetes is inconclusive (12), but an especially high mortality has been reported in older diabetic women treated with insulin (10). In our cohort, insulin treatment was a risk factor in univariate analysis; a higher proportion of women were on insulin than men (18.9% vs 14.0%, $p < 0.001$, insulin alone or in combination), and in women a higher propensity score was associated with a higher CHD risk. However, in the multivariate Cox model insulin treatment showed a borderline significant association with incident CHD in women whether or not the propensity score was included in the

model (Fig. 1). Though the propensity score may work better when used for matching or stratification than for regression (15), this result would suggest that in diabetic women insulin treatment might be an independent CHD risk factor regardless of treatment assignment. A prudent summary is that insulin treatment is not an independent CHD risk factor either in diabetic men or, most likely, in diabetic women.

In conclusion, this nationwide study outlines the natural history of CHD in type 2 patients managed by current standards of care. The emerging risk profile carries important therapeutic implications. Firstly, glycemic control should be intensified and antihypertensive treatment optimized. Secondly, the proportion of patients eligible for lipid-lowering therapy is certainly higher than the proportion of them actually on lipid-lowering treatment. Lowering LDL-cholesterol, if quite effective, may not be sufficient, especially in diabetic women in whom diabetic dyslipidemia is a significant independent risk factor.

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- Legend to the figure

Figure 1 - Independent predictors of incident CHD in diabetic men and women. Hazard ratios are calculated for the indicated increments in the value of the variable.

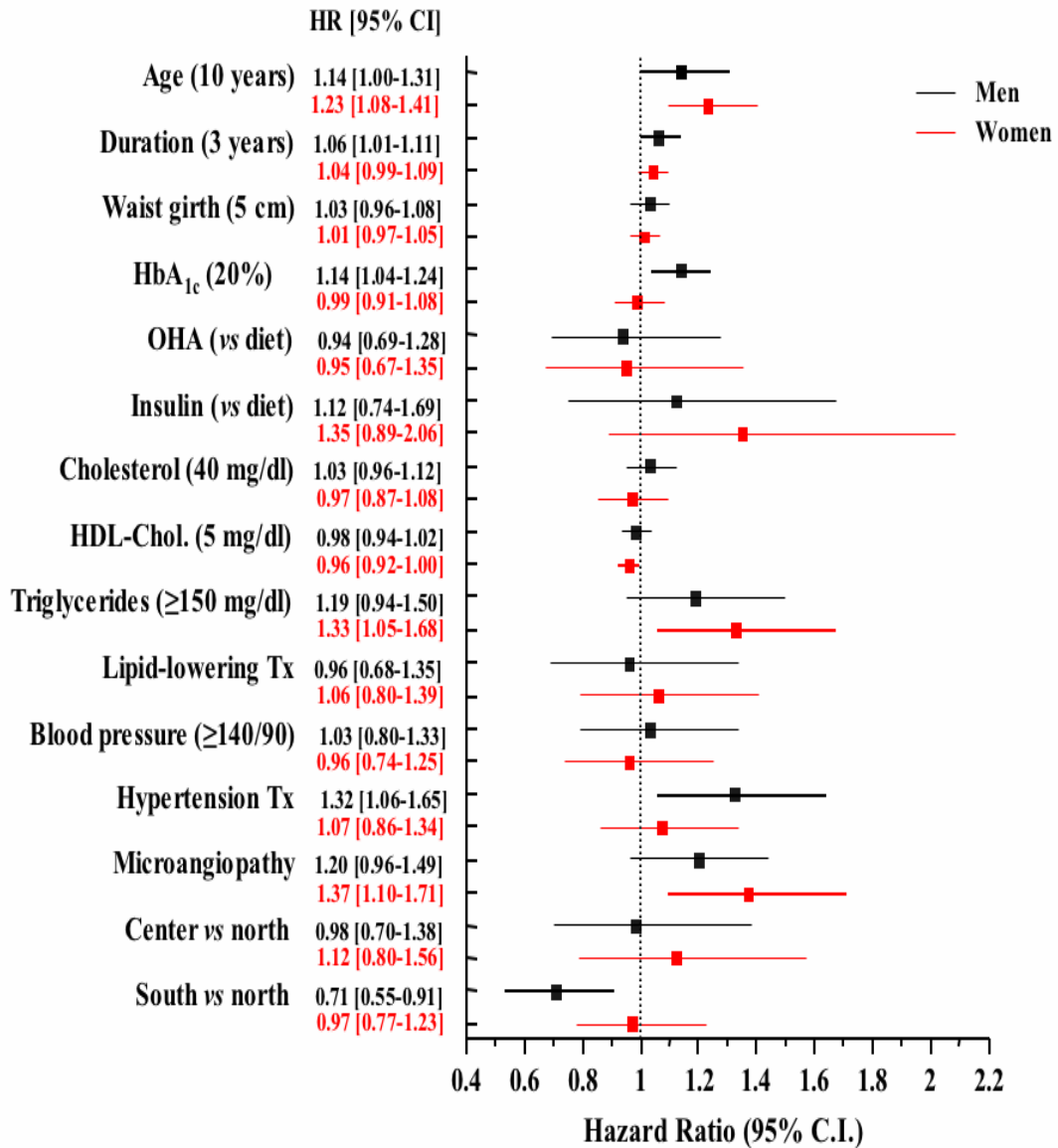


Table 1 – Age-standardized incidence rates (IR, per 1,000 person-years, p-y) of first CHD event in 5,612 diabetic men and 6,032 diabetic women according to the presence of microvascular complications.

	MEN					WOMEN				
	All (13,837 p-y)		Without (9,039 p-y)	With (4,797 p-y)	RR* (95% CI)	All (15,232 p-y)		Without (10,177 p-y)	With (5,055 p-y)	RR* (95% CI)
	n	IR (95% CI)	IR (95% CI)	IR (95% CI)		n	IR (95% CI)	IR (95% CI)	IR (95% CI)	
All CHD	449	28.8 (25.4-32.2)	25.5 (21.6-29.5)	34.9 (28.4-41.5)	1.3 (1.1-1.6)	432	23.3 (20.2-26.4)	19.1 (15.9-22.3)	32.9 (25.5-40.3)	1.5 (1.2-1.7)
AMI	164	10.3 (8.3-12.3)	8.9 (6.6-11.3)	13.4 (9.3-17.4)	1.6 (1.2-2.2)	88	4.7 (3.3-6.1)	3.3 (2.1-4.6)	7.1 (3.9-10.4)	1.9 (1.2-2.8)
Non-AMI CHD	285	18.5 (15.8-21.3)	16.6 (13.5-19.8)	21.6 (16.4-26.8)	1.2 (0.9-1.5)	344	18.6 (15.9-21.4)	15.8 (12.9-18.7)	25.8 (19.1-32.5)	1.4 (1.1-1.7)
Major CHD	208	13.1 (10.9-15.4)	11.4 (8.6-14.2)	16.5 (12.2-20.8)	1.6 (1.2-2.1)	114	5.8 (4.3-7.2)	4.4 (3.1-5.8)	8.2 (4.8-11.5)	1.5 (1.0-2.2)
Fatal CHD	38	2.6 (1.6-3.5)	1.8 (0.8-2.8)	3.7 (2.1-5.4)	2.6 (1.4-5.1)	14	0.6 (0.3-0.9)	0.4 (0.1-0.8)	0.9 (0.3-1.6)	2.3 (0.8-6.5)

* Mantel-Haenszel estimate of the age-adjusted rate ratio for without vs with microvascular complications.

Table 2 – Clinical characteristics of type 2 diabetic patients according to incident coronary events.

	Men		Women		
	Without event (n = 5,163)	With event (n = 449)	Without event (n = 5,600)	With event (n = 432)	
	Mean (\pm 2 SE)				
Age at visit (years)	64 \pm 0.2	66 \pm 0.8	*** 66 \pm 0.2	68 \pm 0.7	***
Body mass index (kg/m ²)	28 \pm 0.1	28 \pm 0.4	29 \pm 0.1	29 \pm 0.5	
Waist girth (cm)	100 \pm 0.3	101 \pm 1.1	96 \pm 0.4	97 \pm 1.2	
Total cholesterol (mg/dl)	207 \pm 1.3	211 \pm 3.8	220 \pm 1.1	221 \pm 4.1	
HDL-cholesterol (mg/dl)	48 \pm 0.4	48 \pm 1.3	52 \pm 0.4	51 \pm 1.4	
LDL-cholesterol (mg/dl)	131 \pm 1.0	134 \pm 3.4	139 \pm 1.0	138 \pm 3.9	
	Median				
Duration of diabetes (years)	7	9	*** 8	10	***
Systolic blood pressure (mmHg)	140	145	150	145	
Diastolic blood pressure (mmHg)	80	80	80	80	
Fasting plasma glucose (mg/dl)	153	159	158	161	
Triglycerides (mg/dl)	127	129	133	143	**
	% (\pm 2 SE)				
Hypertension	78.8 \pm 1.1	87.0 \pm 3.2	*** 86.0 \pm 0.9	90.3 \pm 2.9	*
HbA _{1c} #					
20-50%	28.8 \pm 1.3	31.2 \pm 4.4	31.5 \pm 1.3	32.2 \pm 4.5	
>50%	12.4 \pm 0.9	14.4 \pm 3.3	15.9 \pm 1.0	17.7 \pm 3.7	
Alcohol intake	58.2 \pm 1.4	59.2 \pm 4.6	21.1 \pm 1.1	18.3 \pm 3.7	
Smoking habits					
No	48.0 \pm 1.4	44.1 \pm 4.7	87.3 \pm 0.9	88.4 \pm 3.1	
Current	21.2 \pm 1.1	20.3 \pm 3.8	7.5 \pm 0.7	7.6 \pm 2.6	
Former	30.8 \pm 1.3	35.6 \pm 4.5	5.2 \pm 0.6	3.9 \pm 1.9	
Familiarity for CVD	25.7 \pm 1.2	23.4 \pm 4.0	30.0 \pm 1.2	30.8 \pm 4.4	
Microvascular complications	34.4 \pm 1.3	42.1 \pm 4.7	** 32.8 \pm 1.3	43.3 \pm 4.8	***
Antidiabetic treatment					
Diet	19.0 \pm 1.1	14.3 \pm 3.3	14.2 \pm 0.9	11.3 \pm 3.1	
OHA	67.4 \pm 1.3	67.5 \pm 4.4	** 67.5 \pm 1.3	62.3 \pm 4.7	
OHA + insulin	5.4 \pm 0.6	8.9 \pm 2.7	8.9 \pm 0.8	11.1 \pm 3.0	***
Insulin	8.2 \pm 0.8	9.4 \pm 2.7	9.4 \pm 0.8	15.3 \pm 3.5	
Lipid lowering treatment					
None	90.1 \pm 0.8	89.3 \pm 2.9	83.1 \pm 1.0	78.7 \pm 3.9	
Statins	5.8 \pm 0.6	6.5 \pm 2.3	11.7 \pm 0.9	13.9 \pm 3.3	
Fibrates	3.3 \pm 0.5	4.0 \pm 1.9	4.2 \pm 0.5	5.6 \pm 2.2	
Statins+fibrates	0.2 \pm 0.1	-	0.2 \pm 0.1	0.4 \pm 0.7	
Other	0.7 \pm 0.2	0.2 \pm 0.4	0.8 \pm 0.2	1.4 \pm 1.1	
Geographic area					
North	56.6 \pm 1.4	62.1 \pm 4.6	49.5 \pm 1.3	48.6 \pm 4.8	
Center	10.5 \pm 0.9	11.4 \pm 3.0	* 10.9 \pm 0.8	11.1 \pm 3.0	
South&islands	32.9 \pm 1.3	26.5 \pm 4.2	39.5 \pm 1.3	40.3 \pm 4.7	

proportion of patients with HbA_{1c} values above the unit-based upper limit of normal by the indicated percentage. Such upper limit was between 5.5-6.4% in ~70% of the centers; the mean was 6.1%. The mean HbA_{1c} level was 7.4% in women and 7.1% in men.

OHA = oral hypoglycemic agents

*p<0.05 **p<0.01 ***p<0.001