INCIDENCE OF COMPLICATIONS AND MORTALITY IN A TYPE 2 DIABETES PATIENT COHORT STUDY FOLLOWED FROM DIAGNOSIS IN A PRIMARY HEALTHCARE CENTER

Manel Mata-Cases, Cristina de Prado-Lacueva, Virginia Salido-Valencia, Ester Fernández-Bertolín, José Casermeiro-Cortés, Manuel García-Durán, Susana Jabalera-López, Maria Isabel Fernández-Sanmartín

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) is associated with microvascular and macrovascular complications [1,2]. Moreover, T2DM is an independent risk factor for cardiovascular disease [3] and is frequently associated with other cardiovascular risk factors (CVRF) such as hypertension, dyslipidemia and obesity. The levels of glucose and Glycosylated Hemoglobin (HbA1c) are directly related to the increased risk of microvascular and macrovascular complications [3,4]. There are cohort follow up studies based on cross-sectional studies [6-10] or population-based computer records [11-13] with the aim of establishing the incidence or prevalence of complications or mortality [14-18]. On the other hand, studies on the incidence of complications in patient cohorts followed from the moment of T2DM diagnosis [19-29] are more interesting, although the majority only explore macrovascular disease [19,21,22] or mortality [19-21,24-28]. However, the main limitation of those studies is that it is difficult to determine the start of the illness, which may be several years before clinical diagnosis [29], when blood glucose levels prior to diagnosis are not available. The most well-known source of information is the United Kingdom Prospective Diabetes Study (UKPDS), a clinical trial carried out in the United Kingdom between 1978 and 1998. The observational epidemiological analysis of the entire patient cohort, independently of the type of treatment to which they were assigned, constitutes a source of data so as to calculate the T2DM complications incidence rates relative to the mean HbA1c values during the follow up [30] as well as the coronary and cerebrovascular risk prediction equation [31].

Several follow up studies of those recently diagnosed have been done in order to validate different coronary risk tables [24] or to learn the causes of mortality in our

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country [25]. Then again, none relative to the incidence of microvascular complications have been published.

The aim of the present study is to determine the microvascular and macrovascular complications incidence and death rates in a recently-diagnosed T2DM patient cohort. They were diagnosed between 1991 and 2000 and followed until the end of 2006 in a primary healthcare center. As secondary objectives, the aims were to identify the factors associated with the incidence of complications and mortality and the time-period between T2DM diagnosis and the appearance of complications.

MATERIALS AND METHODS

A retrospective longitudinal observational study was designed that included T2DM cases diagnosed between 1991 and 2000 in a primary healthcare center. The center is the main healthcare resource in the area. It is a poor area in the mainly Caucasian neighborhood of La Mina de Sant Adrià de Besòs (Barcelona, Spain) in which the Romani ethnic group makes up some 20% of the total population.

A detailed description of the methodology as well as the characteristics of the patients and the presence of cardiovascular disease at the time of diagnosis has been previously published [32,33].

Of the total diabetes cases, 598 patients, 118 were excluded for not having blood glucose measurements below the threshold for diabetes diagnosis in the 3 years prior to diagnosis. Another four patients were excluded for having been followed for a period of less than a year and another 7 became diabetes-free during the follow up period. In the end, 469 were included.

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The standing criteria for the diagnosis of T2DM were applied at each instance: those of the World Health Organization (WHO) up until July of 1997 [15]; from July 1997, the fasting glycaemia ≥126 mg/dl following the criteria of the American Diabetes Association [16] that was also accepted by WHO [17].

The clinical records of all the patients were reviewed in order to register variables related to the follow up on T2DM and to detect the complications that arose up to December of 2006.

Study variables.

The clinical characteristics registered upon diabetes diagnosis were: age, gender, diagnostic glucose values, HbA1c, blood pressure, total cholesterol, High-density lipoprotein (HDL) and Low-density lipoprotein (LDL) cholesterol, weight and height. The following CVRF were also registered: hypertension (blood pressure ≥140/90 mm Hg), hypercholesterolemia (total cholesterol ≥250mg/dl), hypertriglyceridemia (triglycerides ≥150mg/dl), obesity (body mass index ≥30 kg/m^2) and current or ex-smoker. The measurement of HbA1c was instituted in mid-1992. The mean HbA1c was calculated during the follow up period based on the annual average of the values annotated in the clinical history.

The macrovascular variables were: coronary heart disease (acute myocardial infarction –AMI-, angina pectoris –in the absence of AMI- and silent AMI based on electrocardiographic criteria), cerebrovascular disease (stroke or transitory ischemic accident), peripheral arteriopathy and a combined variable of all of them. As far as microvascular complications go: nephropathy (macroalbuminuria: Albuminuria ≥ 300 mg / 24h or albumin/Creatinine ratio ≥ 300 mg/mmol), autonomic or peripheral diabetic neuropathy and diabetic retinopathy (background or proliferative and/or maculopathy) and

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a combined variable of some of them. In those cases in which a funduscopy was not performed over the 3 years prior to the appearance of retinopathy, the midpoint of the period was considered as the start date.

The diabetic foot variable (ulcers or amputations) was not included in the microvascular or macrovascular combined variables.

The follow up period for the microvascular variables was taken from the diagnosis up to the date of the last screening. In the case in which any data was not available, the value was considered missing. For macrovascular variables and mortality, the follow up period was until the appearance of the event or the date of the last visit.

In the case of deceased patients, the cause of death was investigated in the clinical records and the center's death registry. The data was requested from the National Institute of Statistics in those cases in which it was not given or there were doubts as to the cause or date.

For the calculation of the annual incidence rate and the analysis of survival, the first event for each complication and the date of appearance were recorded. The events recorded in the paper or computerized clinical records were checked against hospital reports (i.e. admittance for AMI, stroke…), reports from specialists, diagnostic test results (i.e. coronarography, electromyogram, retinal fluorescein angiography, etc.) or clinical anamnesis or examination in the absence of the aforementioned (i.e. intermittent claudication, diabetic foot ulcers or amputations).

Statistical analysis

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The incidence rate per 1000 patients/year for macro and microvascular events and mortality, excluding those patients that already presented the complication at the start of the follow up or during the 3 month after diagnosis, were calculated.

The confidence intervals at 95% (CI 95%) were estimated assuming a Poisson distribution.

The survival curves were calculated separately for males and females with the Kaplan-Meier method for the microvascular and macrovascular variables and mortality. The comparison between the survival curves according to independent variables was done with the Log-Rank test.

In order to evaluate the relationship between variables and the appearance of events, adjusting for the follow up time, the Cox proportional models were estimated separately for males and females. Those variables that turned out to be marginally significant with a $p<0.20$, those considered clinically relevant (like the basal HbA1c and the mean during the follow up) and all the major interactions were included for each model (macrovascular, microvascular and mortality). Previously, linearity and proportionality criteria for each co-variable were assessed. The model was adjusted by excluding: first, the non-significant interactions; second, those variables that were not significant and whose exclusion did not change the beta coefficients of the other variables by more than 20%. Each final model is presented with the estimate of the hazard ratio (HR) and the 95% CI. The validation of the model was carried out by the Hosmer and Lemeshow calibration test [37], and the area under the curve (AUC). For its calculation, the Somer's D correlation ranges index was used for the analysis of the data [38].

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RESULTS

Of the 469 cases included, 253 were women (53.9%). The mean age at diagnosis was 60.4 (SD 10.7) years [in women 61.7 (SD 10.9) years and in men 58.9 (SD 10.2) years; p=0,006]. Of those studied, 96.4% of the patients presented some of the CVRF studied. The most prevalent in the diagnosis were (Table 1): hypertension (72.3%), obesity (60.6%), hypercholesterolemia (50.5%) and current or former smoking (40.8%; 23.7% smokers and 17.1% ex-smokers) with statistically significant differences depending on gender and age groups. There were significantly more smokers and ex-smokers among males (42.1% and 32.9%, respectively in males and 7.9% and 3.6% in females; p<0.001). ~~Women presented obesity (p<0.001) and hypertension (p=0.002) more frequently. Patients younger than 65 years of age had greater mean diastolic blood pressure (DBP) values (p=0.006), first HbA1c and follow up HbA1c means (p<0.001 and p=0.031, respectively) and lower HDL cholesterol values (p=0.015); a higher tobacco habit prevalence (p=0.001) and less hypertension prevalence (p=0.033).~~ Cardiovascular disease was present more frequently at diagnosis in ex-smokers (28.7%) than in smokers (18%) or non-smokers (11.2%) (p<0.001).

During the follow up period (8.81 yrs., SD 3.21), forty-seven patients (10%) moved to another center and there were 80 deaths (17%); 44 males and 36 females. The cause of death was tumoral in 31 cases (38.75%), macrovascular in 24 cases (30%), other causes in 22 cases (27.5%) and unknown in 3 cases (3.75).There were no significant differences between genders except for mortality due to tumors which was more frequent in men (52.3%) than women (22.2%) (p=0.008).

The frequency of complications prior to diagnosis and the annual incidence rate for macrovascular complications (24.10), microvascular complications (29.11), and mortality

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(19.23) during the follow up are shown in Table 2. Males had more macrovascular complications (29.28 versus 20.48 in females) except for cerebrovascular disease (10.36 versus 11.55). The annual rate of microvascular complications (34.51 versus 24.30) and mortality (23.52 versus 15.72) were also greater in men. However, none of them reached statistically significant levels. Those over 65 years of age had a higher incidence of macrovascular complications (p=0.049) and, specifically, cerebrovascular disease (p<0.001). The time of survival up to the appearance of macrovascular complications was not related to the HbA1c values. The survival time period for microvascular complications was less when the first HbA1c was greater than 7% (p<0,001) and when the mean follow up HbA1c was greater than 7% (p=0,001) in both sexes (Figure 1). The variables related to the greater probability of having a macrovascular complication in the follow up were different between men and women (Table 3). In women, the risk is increased with greater first HbA1c values (HR 1.31; CI 95%: 1.03-1.66), HbA1c in the follow up (HR 5.26; CI 95%: 1.61-17.19) and with age (HR 1.30; CI 95%: 1.10-1.53). The relationship between the HbA1c and the appearance of macrovascular complications behaves differently depending on the age of the woman. The strength of the association diminishes when the age increases. In males, the variables associated with a greater risk of complications are age (HR 1.05; CI 95%: 1.01-1.09) and the total cholesterol level even though the magnitude of the association is weak (HR 1.01; CI 95%: 1.00-1.02).

Microvascular complications in women are related to the initial HbA1c value (HR 1.40; CI 95%: 1.20-1.63) and the HDL cholesterol (HR 0.95; CI 95%: 0.91-0.99). In males, the variables associated with microvascular complications are HDL cholesterol (HR 0.97; CI 95%: 0.94-1.00) and, above all, hypertension (HR 2.92; CI 95%: 1.28-6.69). On the

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other hand, the HbA1c does not reach a statistically significant level (HR 1.2; CI 95%: 0.94-1.54).

In terms of mortality in women, the probability of dying is greater the lower the HDL (HR 0.92; CI 95%: 0.88-0.96) and the DBP (HR 0.71; ICI 95%: 0.54-0.94) are and whether a smoker or non-smoker (HR 3.67; CI 95%: 1.16-11.56). Age interacts slightly in the relationship between DPB and mortality. The most relevant factor in males in relation to mortality is age (HR 1.07; CI 95%: 1.04-1.11) and smoking. Then again, this association is not statistically significant (HR 1.91; CI 95%: 0.85-4.32).

The differences between the expected and the observed mortality rates were statistically significant according to the Hosmer and Lemeshow calibration test. It showed a low adjustment of this model. The other models (micro and macrovascular complications) had an acceptable adjustment and a high predictive capacity (AUC >65).

DISCUSSION

This study gives the complications and mortality incidence rates in patients recently diagnosed with T2DM identified during a 10 year period in a primary care center and followed an average of almost 9 years. The annual rates for death and complications in this Mediterranean population were lower than those published in anglo-saxon countries [19-23, 26-27,30] except for the mortality rates observed in the UKPDS epidemiological study in which patients were younger (53 yrs.) than those in our study (60 yrs.) [30].

Studies of recently diagnosed patients are rare in the international literature [19-28]. In our country only two follow up studies of recently diagnosed patients with the aim of validating different coronary risk tables relative to their comparison with the accumulated incidence observed [24] or to find out the rates and causes of mortality [25] have been

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published.

In terms of the observed annual incidence rates, it is worthy to note that they are greater in males for all complications except for cerebrovascular disease as well as for mortality. However, the differences are not significant due to the low number of cases.

With regards to the causes of mortality, the main cause in our study was not cardiovascular but tumoral. This is different from the majority of cohort follow up epidemiological studies based on cross sectional studies [1,2,14-18], as well as in those of the recently diagnosed [19-21,26,27,30]. On the other hand, the causes of mortality were quite similar to ours in the only study in our country carried out in Asturias [25].

The survival curves show how the initial and the mean HbA1c in the follow up greater than 7% are significantly related to the microvascular complications but not to the macrovascular complications. Then again, an inverse relationship in the survival curves was observed in our study with mortality greater in those that had a mean HbA1c <7% during the follow up. This significance disappeared upon separating by gender as much in terms of the survival curves as in the Cox regression after adjusting for other variables.

The Cox regression analysis reveals that the variables related to a greater probability of having a cardiovascular event in the follow up were different for men and women. These relationships probably have something to do with the difference of the prevalence of risk factors between the sexes. One might emphasize that in spite of the great difference in smoking habits in men as opposed to women (75% vs 11.5%) the rate of coronary heart disease was not substantially different (15.10 vs 11.39). This fact is perhaps related to the greater prevalence of obesity and Hypertension in women. It is surprising that

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recognized risk factors like smoking, hypertension and LDL-cholesterol are not significant predictors of cardiovascular disease. It is probably due to the low incidence of complications related to the bias of survival as those patients that already had cardiovascular disease have been excluded. In these excluded patients, the association was significant (previously published data), but it was only for smoking [33]. A more extended follow up with a greater number of events would have conferred significance to the differences. On the other hand, it is true that smoking is positively related to mortality, although it is only significant in women.

With respect to the relationship between the HbA1c and the complications, the results are dissimilar in the analysis by sexes. Thus, the macrovascular complications are associated with the initial and the follow up HbA1c in a significant way in females but not in males. In terms of microvascular complications, the HbA1c again behaves differently by gender: it is the initial HbA1c in women while it is the mean in the follow up in men although it was not confirmed in the Cox regression. With respect to mortality, no relationship to the HbA1c was observed in either men or women. With respect to the relationship of DBP to death in women, it agrees with that observed in other studies in which a relationship was seen between lower blood pressure values and a greater probability of death in people of advanced age [39].

The main limitations of our study are due to its retrospective observational design. The variables and the complications were obtained from the clinical records and some of them might have been missed. For some variables like smoking, the length of the follow-up permitted the retrieval of this data retrospectively in those cases without information annotated at the moment of diagnosis. In the case of retinopathy and/or nephropathy, a

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significant number of patients did not have annual screening. The exclusion of the patients that did not have a screening or with a short follow up (up to the last screening), might explain why the microvascular rates were greater than the macrovascular rates. We excluded 118 patients without any glycaemia measurement before diagnosis so as to be sure that they were at the onset of the disease. Excluded patients were less obese, hypertensive and hypercholesterolemic (previously published data) [33]. In fact, in our cohort, the main reason for diabetes diagnosis was the monitoring of blood samples in the follow up of hypertension and hypercholesterolemia [32]. However, there was the same sex distribution, mean age and HbA1c and smoking prevalence at diagnosis for excluded and included patients [33].

As a routine clinical practice study, diagnosis was usually made with fasting plasma glucose values but 87 patients (18%) where diagnosed based on an OGTT. These patients were mainly diagnosed before 1997. After that year, in which the ADA proposed abandoning the use of OGTT for clinical purposes, it was rarely performed in our center. Finally, the low socioeconomic level and the ethnic composition of our community can impede the generalization of the results to other populations.

CONCLUSIONS

Our study provides the annual death and complications rates in a patient cohort followed from diagnosis with the findings being that they are greater for microvascular complications than for macrovascular complications. The annual rates for death and complications in this Mediterranean population were lower than those published in anglo-saxon countries. In terms of mortality, unlike in other studies, only a third of the deaths were for cardiovascular causes. Except for cerebrovascular disease, males had

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greater death and complication rates. Multi-center studies carried out in primary care centers that include a greater number of participants and events are needed. They would make it possible to confirm these results and allow for greater accuracy in the analysis of the observed differences by age and gender.

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Variable and number of patients (N) *	Total N=469	Men N=216	Women N=253	< 65 years N=296	≥65 years N=173
Age (years). mean (SD)	60.4(10.7)	58.9 (10.2)†	61.7(10.9)†	54.01 (7.1)†	71.41 (5.6)†
Mean follow-up period in years (SD)	8.81 (3.2)	8.61 (3.1)	8.98 (3.3)	9.37 (3.2)†	7.84 (2.9)†
Prevalence of Cardiovascular risk at diagnosis of T2DM					
Hypertension	72.3%	65.3%†	78.3%†	68.9%†	78%†
SBP in mmHg. Mean (SD). N=444	143.74 (15.2)	139.4 (14.4)†	147.4 (14.9)†	142.67 (15.8)	145.52 (13.9)
DBP In mmHg. mean (SD). N=444	84.8 (9.3)	84.1(9.5)	85.4 (9.1)	85.73 (9.3)†	83.23 (9.1)†
Hypertriglyceridemia	34.1%	34.7%	33.6%	37.2%	28.9%
Hypercholesterolemia	50.5%	48.1%	52.6%	51%	49.7%
Total cholesterol in mg/dl. mean (SD). N=447	227.6 (44.4)	223.7 (44.3)	231.03 (44.4)	227.37 (46.2)	228.13 (41.4)
HDL-cholesterol in mg/dl. mean (SD). N=420	47.6 (11.6)	45.34 (11.4)†	49.53 (11.6)†	46.51 (11.5)†	49.36 (11.7)†
Obesity (BMI≥30 kg/m^2)	60.6%	44.4%†	74.3%†	62.5%	57.2%
Smoking (current or former)	40.8%	75%†	11.5%†	46.3%†	31.2%†
Glycemic control					
First HbA1c %. mean (SD). N=466	7 (1.6)	6.97 (1.5)	7.05 (1.7)	7.14 (1.6)†	6.81(1.6)†
Mean follow-up HbA1c % (SD). N=466	7.17 (1.2)	7.15 (1.3)	7.18 (1.2)	7.35 (1.3)†	6.86 (1.1)†

Table 1. Basal characteristics of the patients. by sex and age groups.

SD: standard deviation; SBP: sistolic blood pressure; DBP: diastolic blood pressure; BMI: body-mass index; CVRF: cardiovascular risk factors; HbA1c: glycosilated haemoglobin; HDL-cholesterol: high density lipoprotein-cholesterol .

* Number of patients are shown only when available data are less than the total population (N=469)

† p<0.05

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	Previous to T2DM diagnosis n=469	Patients with event	Global incident rates IRx1000 (CI 95%)	Incident rates in Men IRx1000 (CI 95%)	Incident rates in Women IRx1000 (CI 95%)	Incident rates in <65 years old IRx1000 (CI 95%)	Incident rates in >65 years old IRx1000 (CI 95%)
Microvascular n=324	13	77	29.11(22.97-36.38)	34.51(24.98-46.49)	24.30(16.83-33.96)	28.11(20.80-37.17)	31.04(20.63-44.86)
Retinopathy N=324	1	28	9.91(6.58-14.32)	10.46(5.72-17.56)	9.41(5.14-15.79)	11.89(7.45-17.99)	6.15(2.26-13.39)
Nephropathy* n=432	9	29	7.57(5.07-10.87)	9.41(5.38-15.28)	6.10(3.25-10.44)	6.18(3.53-10.04)	10.48(5.58-17.91)
Neuropathy N=466	3	29	7.27(4.87-10.45)	10.09(5.98-15.95)	4.99(2.49-8.93)	7.46(4.56-11.52)	6.89(3.15-13.08)
Diabetic foot N=469	0	7	1.70 (0.68-3.51)	2.17(0.59-5.55)	1.32(0.27-3.87)	1.45(0.39-3.70)	2.23(0.46-6.51)
Macrovascular n= 395	74	78	24.10 (19.05-30.08)	29.28(20.82-40.03)	20.48(14.57-28.00)	20.35(14.90-27.15)	32.79(22.43-46.29)
CHD n=428	41	47	13.02 (9.57-17.32)	15.10(9.68-22.47)	11.39(7.22-17.08)	11.84(7.93-17.01)	15.52(9.20-24.52)
AMI n=455	14	14	3.51(1.92-5.89)	6.24(3.11-11.16)	1.35(0.28-3.94)	3.35(1.53-6.35)	3.84(1.25-8.97)
CVD n=442	27	42	11.04(7.96-14.92)	10.36(6.03-16.59)	11.55(7.48-17.05)	6.91(4.10-10.92)	19.98(12.80-29.73)
PA n=449	20	33	8.51(5.86-11.95)	13.78(8.74-20.68)	4.52(2.17-8.32)	7.90(4.89-12.08)	9.82(5.07-17.15)
Mortality n=469		80	19.23(15.25-23.93)	23.52(17.09-31.57)	15.72(11.01-21.76)	11.49(7.86-16.23)	34.86(25.70-46.22)

Table 2. Incidence rates per 1000 patients/year and 95% confidence intervals for micro and macrovascular complications and mortality

IRx1000: incidence rate per 1000 patients/year ; CHD: coronary heart disease; AMI: acute myocardial infarction; CVD: cerebrovascular disease; PA: peripheral arteriopathy.

* macroalbuminuria(>300mg/dL)

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MACROVASCULAR EVENTS

Women	Adj_HR	95%CI	Adj_HR	p	Crude_HR	95%CI	Crude_HR	p
Age at diagnosis	1.3	1.1	1.53	0.002	1.03	1.00	1.07	0.067
First HbA1c	1.31	1.03	1.66	0.026	1.15	0.99	1.34	0.064
Mean follow-up HbA1c	5.26	1.61	17.19	0.006	1.06	0.84	1.34	0.63
Age† mean follow-up HbA1c	0.97	0.95	0.99	0.004				
	AUC: 0.71 (95%CI: 0.64- 0.79)					H-L test: p=0.301		

Men	Adj_HR	95%CI	Adj_HR	p	Crude_HR	95%CI	Crude_HR	p
Age at diagnosis	1.05	1.01	1.09	0.012	1.04	1.00	1.07	0.025
Total cholesterol	1.01	1	1.02	0.053	1.01	1.00	1.02	0.034
Mean follow-up HbA1c	1.13	0.84	1.52	0.408	1.01	0.78	1.31	0.923
	AUC: 0.67 (95%CI: 0.57- 0.76)					H-L test: p=0.536		

MICROVASCULAR EVENTS

Women	Adj_HR	95%CI	Adj_HR	p	Crude_HR	95%CI	Crude_HR	p
Age at diagnosis	1.01	0.97	1.05	0.541	1.03	1.00	1.07	0.067
HDL-cholesterol	0.95	0.91	0.99	0.01	0.99	0.96	1.02	0.543
First HbA1c	1.4	1.2	1.63	<0.001	1.15	0.99	1.34	0.064
	AUC: 0.71 (95%CI: 0.62- 0.80)					H-L test: p=0.61		

Men	Adj_HR	95%CI	Adj_HR	p	Crude_HR	95%CI	Crude_HR	p
Age at diagnosis	1.01	0.97	1.04	0.607	1.00	0.97	1.03	0.952
HDL-cholesterol	0.97	0.94	1	0.057	0.96	0.93	1.00	0.025
Mean follow-up HbA1c	1.2	0.94	1.54	0.136	1.34	1.06	1.69	0.015
Hypertension	2.92	1.28	6.69	0.011	2.84	1.32	6.14	0.008
	AUC: 0.68 (95%CI: 0.60- 0.76)					H-L test: p=0.59		

MORTALITY

Women	Adj_HR	95%CI	Adj_HR	p	Crude_HR	95%CI	Crude_HR	p
Age at diagnosis	0.8	0.58	1.1	0.165	1.10	1.06	1.13	<0.001
HDL-cholesterol	0.92	0.88	0.96	<0.001	0.95	0.91	0.99	0.027
Smoking	3.67	1.16	11.56	0.027	1.05	0.37	2.97	0.928
Diastolic Blood Pressure	0.71	0.54	0.94	0.017	0.96	0.92	1.00	0.027
Age† Diastolic Blood Pressure	1	1	1.01	0.035				

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	AUC: 0.85 (95%CI: 0.79- 0.91)				H-L test: p<0.001			
Men	Adj_HR	95%CI Adj_HR		p	Crude_HR	95%CI Crude_HR		p
Age at diagnosis	1.07	1.04	1.11	<0.001	1.07	1.04	1.11	<0.001
Smoking	1.91	0.85	4.32	0.119	1.67	0.74	3.78	0.216
	AUC: 0.71 (95%CI: 0.64- 0.78)				H-L test: p=0.052			

Table 3. Factors associated with the appearence of events. Cox proportional regression models

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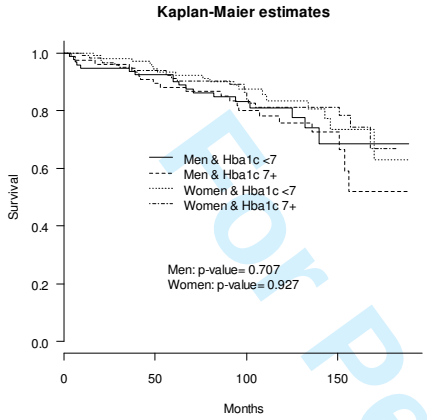
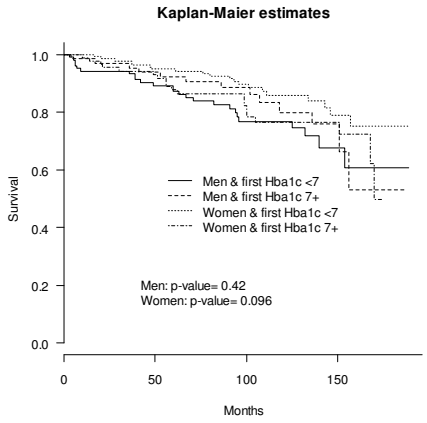
Figure 1. Survival curves for macrovascular and microvascular complications and mortality by first HbA1c and mean follow up HbA1c. Comparisons between patients with HbA1c ≥7% or HbA1c <7%.

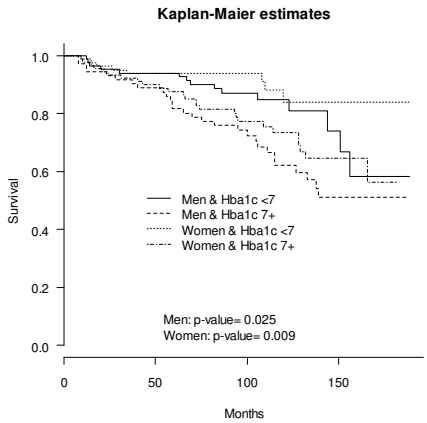
A. FIRST MACROVASCULAR COMPLICATION
Mean follow-up HbA1c



B. FIRST MACROVASCULAR COMPLICATION
First HbA1c



C. FIRST MICROVASCULAR COMPLICATION.
Mean follow up HbA1c



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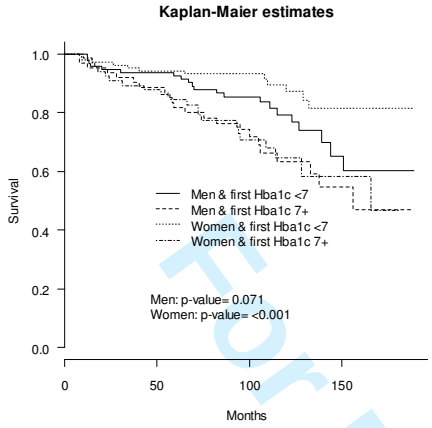
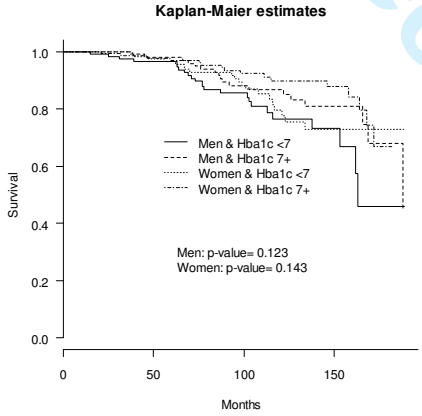
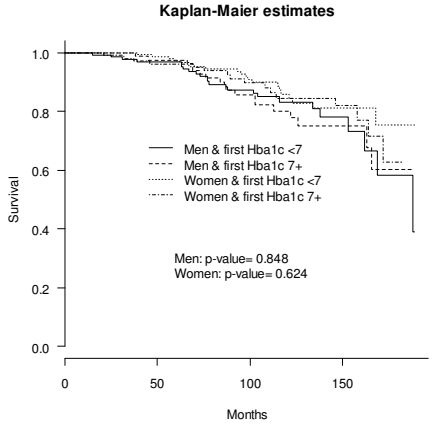
D. FIRST MICROVASCULAR COMPLICATION.
First HbA1c



E. MORTALITY.
Mean follow up HbA1c



F. MORTALITY.
First HbA1c



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