

Effect of Diabetes on the Clinical Characteristics and Prognosis of Patients With Chronic Ischemic Heart Disease. The CIBAR Study

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The aim of this study was to evaluate the effect of diabetes mellitus on the prognosis of patients with chronic ischemic heart disease. The multicenter prospective cohort study involved 1108 outpatients with ischemic heart disease whose clinical characteristics were recorded by 69 primary care physicians. Morbidity and mortality were recorded during a mean follow-up period of 6.9 months. Overall, 29% of patients were diabetic; they were older than non-diabetics, presented with more risk factors, had poorer blood pressure control, and had more comorbid conditions. In addition, diabetics were more likely to be prescribed renin-angiotensin system blockers, calcium channel blockers, diuretics and lipid-lowering drugs. Cardiovascular mortality and hospitalization rates were higher in diabetics. On multivariate analysis, diabetes was found to be an independent predictor of a cardiovascular event (hazard ratio=1.81; 95% confidence interval, 1.17-2.82). Prognosis in chronic ischemic heart disease is relatively good, although it is worse in diabetics, which means that treatment and disease controls targets must be more rigorously applied in these patients.

Key words: Coronary heart disease. Diabetes mellitus. Primary care.

Influencia de la diabetes en las características clínicas y el pronóstico de pacientes con cardiopatía isquémica crónica. Estudio CIBAR

Evaluamos el impacto de la diabetes mellitus (DM) en el pronóstico de pacientes con cardiopatía isquémica crónica (CIC). Estudio multicéntrico de cohortes prospectivas, en el que 69 médicos de atención primaria registraron características de 1.108 pacientes ambulatorios con CIC y analizaron la mortalidad y la morbilidad tras un seguimiento medio de 6,9 meses. Los diabéticos (29%) eran mayores que los no diabéticos, tenían más factores de riesgo, peor control de presión y más comorbilidades y recibían más bloqueadores del sistema renina-angiotensina, antagonistas del calcio, diuréticos e hipolipemiantes. La mortalidad y los ingresos por causa cardiovascular fueron mayores en los diabéticos. En el análisis multivariable, la DM fue un determinante independiente de eventos cardiovasculares (*hazard ratio* = 1,81; intervalo de confianza del 95%, 1,17-2,82). La CIC tiene un pronóstico relativamente benigno, aunque empeora en los diabéticos, por lo que en ellos el tratamiento y los objetivos de control han de ser más estrictos.

Palabras clave: Cardiopatía isquémica crónica. Diabetes mellitus. Atención primaria.

*The Barbanza Group and CIBAR Study investigators are listed in the appendix.

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INTRODUCTION

Recent therapeutic advances have reduced mortality due to ischemic heart disease over the last 25 years¹; this fact, in addition to an aging population, has increased the prevalence of chronic ischemic heart disease (CIHD).²

However, there is little available information on the clinical characteristics and prognosis of patients with CIHD in our area. This is especially true for identifying the prevalent clinical elements (such as diabetes mellitus [DM]) which are associated with a greater risk of complications during follow-up. These could help us come up with strategies to improve patient management.

The aim of the CIBAR Study is to describe demographic, clinical and therapeutic characteristics, and their impact on prognosis in a homogeneous cohort of outpatients with CIHD. We present said objectives in this subanalysis and assess the impact of DM.

METHOD

With the participation of 69 primary care physicians, during the month of February 2007 all patients that complied with the inclusion criteria were recruited into this prospective, multicenter cohort study. The exclusion criteria were: over 18 years of age, previous diagnosis of ischemic heart disease, with a minimum duration of 1 year according to the hospital discharge report, and patient consent.

In all cases anamneses, physical exams, electrocardiograms and biochemical tests were available. Demographic, anthropometric and clinical characteristics were recorded, along with additional diagnostic tests (echocardiograms, stress tests and coronary angiographies) that were noted in the patients' clinical histories, prescribed treatment, complications from moment of diagnosis to inclusion in the study and hospitalizations during the previous 12 months.

After 6 months of follow-up, mortality and morbidity data (hospital re-admittances) were analyzed according to causation. For the analysis, patients were separated into 2 groups: diagnosed or not with DM at the time of inclusion. To guarantee data quality, an internal audit was performed.

The results of qualitative variables are expressed in absolute values and percentages, and the results of quantitative variables, as mean (standard deviation). To compare the groups, the Student *t* test was used for parametric variables and the Mann-Whitney *U* test for non-parametric variables. To determine the significance of the association between qualitative variables, Pearson's χ^2 test was used.

Survival estimates were calculated using Kaplan-Meier curves, and a log-rank test was used for inter-group comparison.

A univariate analysis was performed to establish the factors that predicted cardiovascular events (death and/or admittance), and the statistically significant variables were included in a Cox multivariate analysis using the "forward conditional" method. The Cox model was adjusted using the variables that maintained their significance, as well as age and sex, and the results were expressed as a hazard ratio (HR) with a 95% confidence interval (CI).

SPSS software for Windows, version 15.0, was used for the statistical data analysis. Differences with a probability of type I error below 5% ($P < .05$) were considered statistically significant.

RESULTS

A total of 1848 patients with ischemic heart disease were screened for the study, 448 patients were excluded because they did not have a hospital discharge report, 279 because informed consent or essential data were missing, and 13 because fewer than 12 months had passed since diagnosis. This meant that 1108 outpatients were recruited with a hospital diagnosis of ischemic heart disease (55% with infarction, 32% with unstable angina and 31% with stable angina).

Diabetes was present in 28.7% and the mean time from diagnosis to inclusion in the study was 7.6 (6) years. There were no significant differences between diabetics and non-diabetics. Sample characteristics, risk factors and comorbidities, additional tests, and patient treatment at the time of diagnosis are presented in Table 1, whereas, Table 2 shows the degree of control of the different risk factors. During the 12 months prior to inclusion, 203 patients (18%) had been admitted for cardiovascular causes, with no differences between diabetics and non-diabetics.

After a mean follow-up of 6.9 (0.9) months, during which 3 patients were lost to follow-up, 15 patients died (1.4%). In Figure 1 it is possible to see mortality and hospitalization rates, as well as their causes. Mortality was significantly higher in the diabetic patient subgroup. This was also the case in the combination of death and hospitalization due to cardiovascular causes. Under multivariate analysis (Figure 2), DM was found to be an independent predictor of cardiovascular events (mortality and/or admittance).

DISCUSSION

Our study population, which is representative of patients with ischemic heart disease, with

TABLE 1. Patient Clinical Characteristics, Risk Factors, Comorbidities, Diagnostic Tests and Treatment Included in the CIBAR Study. Distribution According to Presence of Diabetes Mellitus

	Total	DM	No DM	P
Patients	1108 (100)	318 (28.7)	790 (71.3)	
Age, mean (SD), y	69.2 (11.1)	71.1 (9.8)	68.5 (11.5)	<.001
Sex (males)	798 (72)	212 (66.7)	586 (74.2)	.015
Obesity ^a	436 (39.4)	154 (48.4)	282 (35.7)	<.001
Central obesity ^b	604 (54.5)	198 (62.3)	406 (51.4)	.001
Metabolic syndrome ^c	490 (44.2)	247 (77.7)	243 (30.8)	<.001
Dyslipemia	779 (70.3)	257 (80.8)	522 (66.1)	<.001
Arterial hypertension	726 (65.5)	240 (75.5)	486 (61.5)	<.001
Current smokers	110 (9.9)	25 (7.9)	85 (10.8)	.151
Total smokers ^d	549 (49.5)	139 (43.7)	410 (51.9)	.014
Heart failure	120 (10.8)	45 (14.2)	75 (9.5)	.032
Auricular fibrillation	159 (14.4)	56 (17.6)	103 (13)	.058
Stroke	97 (8.8)	31 (9.7)	66 (8.4)	.481
Peripheral vasculopathy	153 (13.8)	73 (23)	80 (10.1)	<.001
Valvulopathy	175 (15.8)	54 (17)	121 (15.3)	.524
Abdominal aneurysm	24 (2.2)	6 (1.9)	18 (2.3)	.821
Syncope	96 (8.7)	27 (8.5)	69 (8.7)	1
Kidney failure ^e	102 (9.2)	44 (13.8)	58 (7.3)	.001
Anemia ^f	143 (12.9)	51 (16)	92 (11.6)	.038
Echocardiogram	854 (77.1)	246 (77.4)	608 (77)	.937
Preserved systolic function ^g	719 (64.2)	203 (62.7)	516 (64.9)	.462
Coronary angiography	827 (74.6)	236 (74.2)	591 (74.8)	.879
Multivessel lesions	405 (36.5)	135 (41.9)	270 (34.1)	.009
Antiaggregants	914 (82.5)	263 (82.7)	651 (82.4)	.931
Anticoagulants	184 (16.6)	58 (18.2)	126 (15.9)	.372
Nitrates	571 (51.5)	181 (56.9)	390 (49.4)	.024
Beta-blockers	665 (60)	184 (57.9)	481 (60.9)	.378
ACEI and/or ARA-II	674 (60.8)	229 (72)	445 (56.3)	<.001
Antialdosterones	57 (5.1)	25 (7.9)	32 (4.1)	.015
Digitalis	57 (5.1)	28 (8.8)	29 (3.7)	.001
Calcium antagonists	422 (38.1)	140 (44)	282 (35.7)	.011
Diuretics	367 (33.1)	128 (40.3)	239 (30.3)	.002
Statins	967 (87.3)	289 (90.9)	678 (85.8)	.022
Lipid lowering drugs ^h	977 (88.2)	292 (91.8)	685 (86.7)	.018

Abbreviations: ARA-II, angiotensin II receptor antagonists; DM, diabetes mellitus; ACEI, angiotensin-converting enzyme inhibitors.

^aBMI (body mass index) >30.

^bAbdominal perimeter ≥102 cm in men or ≥88 cm in women.

^cATP-III of 2001.

^dPrevious (former smoker) or current smoker.

^eHistory of renal failure.

^fHemoglobin <13 g/dL in men and <12g/dL in women.

^gPreserved systolic function (left ventricular ejection fraction ≥50%).

^hStatins and/or ezetimibe. Data expressed as n (%) or as a mean (standard deviation).

TABLE 2. Control of Risk Factors in Patients Included in the CIBAR Study. Distribution According to Presence of Diabetes Mellitus

	Total	DM	No DM	P
Patients	1108 (100)	318 (28.7)	790 (71.3)	
Blood pressure <130/80 mmHg	413 (37.3)	99 (31.1)	314 (39.8)	.007
Glycemia ^a	705 (63.6)	56 (17.6)	649 (82.1)	<.001
Total cholesterol >175 mg/dL	577 (52.1)	190 (59.9)	387 (49)	.001
HDL-C ^b	704 (63.5)	177 (55.6)	527 (66.7)	.001
LDL-C <100 mg/dL	454 (41)	153 (48.1)	301 (38.1)	.004
Triglycerides <150 mg/dL	865 (78.1)	218 (68.5)	647 (81.9)	<.001

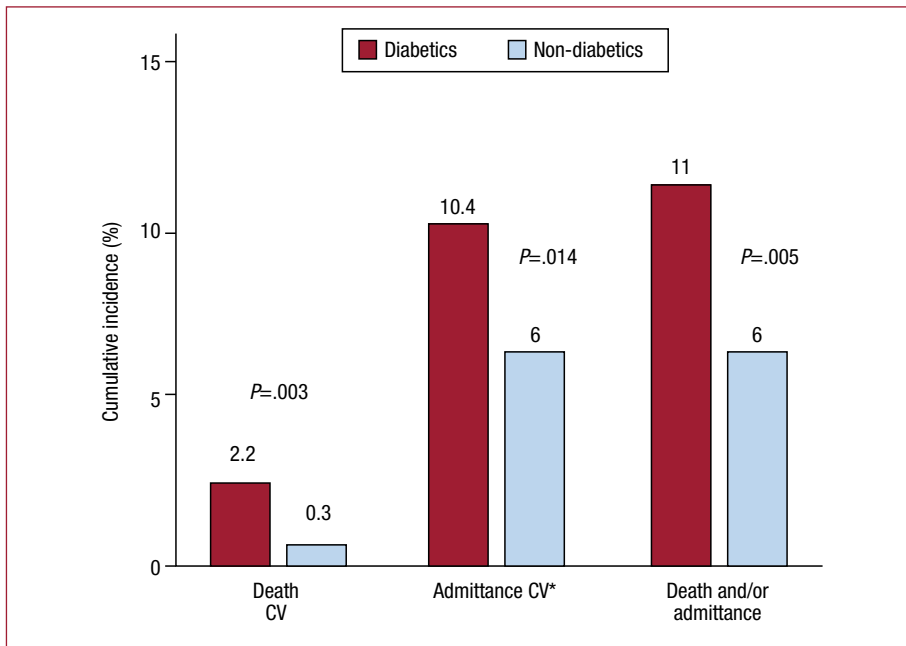


Figure 1. Cumulative incidence of mortality and morbidity in patients included in the CIBAR study. Distribution according to presence of diabetes mellitus. CV: cardiovascular. *Patients that have been hospitalized for cardiovascular causes during follow-up.

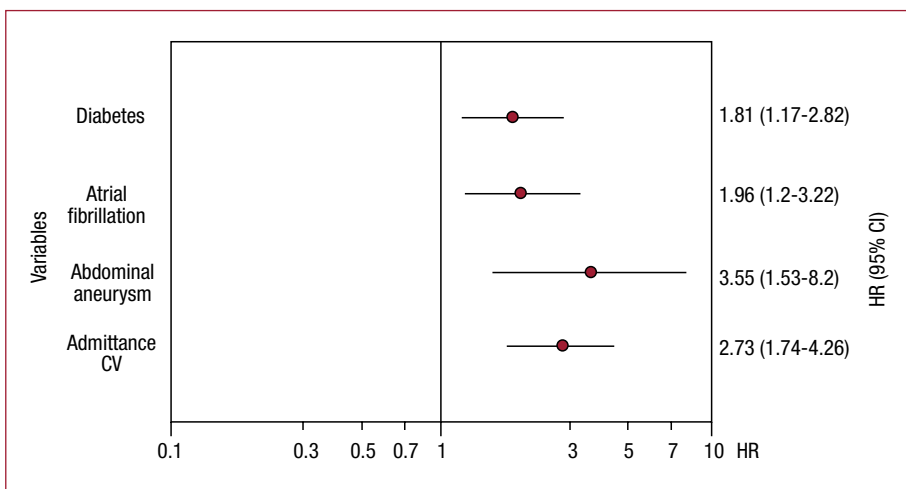


Figure 2. Cox regression. Factors determining cardiovascular events (deaths and/or hospitalizations). Adjusted according to age, sex, time since diagnosis, arterial hypertension, diabetes mellitus, heart failure, atrial fibrillation, syncope, abdominal aneurysm, anaemia, coronary surgery, aspirin, oral anticoagulants, angiotensin converting enzyme inhibitors, angiotensin II receptor antagonists, diuretics, nitrates, digitalis, complications and prior hospitalization for cardiovascular causes. CI: confidence interval; CV: cardiovascular; HR: hazard ratio.

approximately one third diagnosed with DM, had a relatively benign prognosis. The unfavorable impact of DM on prognosis was confirmed, even on short-term prognosis. Total mortality rate of this group was greater than that of most clinical trials carried out with patients suffering from ischemic heart disease, which is about 1.5% per annum, but these included a much lower percentage of diabetics (12%-17%), and no specific analysis of this subgroup.³

As far as we know, the CIBAR Study describes for the first time in Spain the clinical and epidemiological characteristics and short-term prognosis of a homogeneous cohort of patients with CIC. In addition to being of clinical interest, this study could have certain implications when implementing

integrated follow-up strategies between cardiologists and primary care physicians.

Acceptable compliance with clinical practice guides' therapeutic recommendations stands out in the study, with significant differences in treatments with statins and renin-angiotensin-aldosterone system blockers between diabetics and non-diabetics. In spite of this correct compliance, the targets for controlling cardiovascular risk factors were not achieved in a large percentage of patients. In the case of diabetics, only total cholesterol and low density lipoproteins cholesterol (LDL-C) concentrations were controlled better than in the non-DM group. However, there was still a significant residual risk related to dyslipemia (patients with non-controlled

LDL-C, high-density lipoproteins cholesterol [HDL-C] and triglycerides). There was little control of blood pressure in these patients and the percentage of diabetics with good glycemia control was low.

The unfavorable influence of DM on prognosis after an acute coronary syndrome⁴ and also in the case of patients with heart failure⁵ is known, but there is little data on patients with CIC. In fact the studies carried out in Spain have selected patients after admittance for an acute ischemic event.⁶⁻⁸ In the Euro Heart Survey on Diabetes and the Heart,⁹ the negative influence of a previous or recent diagnosis of DM was seen after one year's evolution, with a mortality of 7.7% in known diabetics and of 5.5% in recently diagnosed diabetics, in comparison with 2.2% of patients with normal glycaemia, although only 38% had diagnosed CIC.

In the Euro Heart Survey of Stable Angina,¹⁰ total annual mortality was 1.5%, and DM was an independent variable for risk of mortality and/or acute myocardial infarction (HR=2.03). Therapeutic compliance, according to the guides' recommendations, significantly improved prognosis.

All the patients included in our study were diagnosed with CIC with more than 1 year's evolution, which was one of the differences from other studies. In spite of the low mortality and morbidity and the fact that most patients were treated according to established indications, a negative impact of DM was seen, which tripled the risk of death over a short follow-up period (7 months), since most deaths in diabetics were due to cardiovascular causes. The difference in hospital admittance due to this cause was also significant, and especially for those due to stroke (2.2% in comparison with 0.5%).

Limitations

Although there was no bias in patient selection and only 3 patients were lost during follow-up, the study population can be considered to be selected since it was chosen by physicians who worked voluntarily. Moreover, the classification into diabetics and non-diabetics was done *a posteriori*. Furthermore, some data on antidiabetic treatment has not been analyzed and we do not know the dosage of the drugs used, or the degree of therapeutic compliance. These factors could influence the control of different risk factors as well as patient prognosis.

In conclusion, CIC is a condition with a relatively benign prognosis, although some subgroups of patients, such as diabetics, have a worse prognosis, and must be identified to apply stricter treatment controls and risk control targets.

In spite of an acceptable level of knowledge and the application of the recommendations in the guidelines, ideal objectives are attained in a very small percentage of patients.

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APPENDIX. Researchers of the Barbanza Group and the CIBAR Study

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