Introduction and objectives. To assess the effect of different forms of atherosclerotic disease on prognosis in diabetic patients.

Methods. This multicenter prospective cohort study involved 1423 consecutive patients with diabetes mellitus who were recruited by 31 primary care physicians. The patients’ characteristics were recorded and they were followed up for 45 (10) months.

Results. The mean age of the patients (50% male) was 66 years, 64% had hypertension, 70% had dyslipidemia, and 26% had had a previous cardiovascular event. By the end of follow-up, 81 (6.2%) had died, 40 (3%) of whom due to cardiovascular causes, and 393 (30%) had been hospitalized, 179 (14%) of whom for cardiovascular disease. Multivariate analysis identified the following factors as independent predictors of mortality: age (hazard ratio [HR]=1.08; 95% confidence interval [CI], 1.05-1.11), previous cardiovascular disease (HR=2.15; 95% CI, 1.12-4.14) and diuretic treatment (HR=3.40; 95% CI, 1.76-6.56), while the prescription of an angiotensin-converting enzyme inhibitor or an angiotensin-receptor antagonist had a protective effect (HR=0.48; 95% CI, 0.25-0.93). Compared with diabetics without a previous cardiovascular event, the risk of a cardiovascular event during follow-up was greater in those with a history of either ischemic heart disease (HR=2.48; 95% CI, 1.51-4.07), cerebrovascular disease (HR=2.51; 95% CI, 1.28-4.92), or peripheral vascular disease (HR=1.46; 95% CI, 0.81-2.60).

Conclusions. The increase in the risk of a cardiovascular event was similar in diabetics with ischemic heart disease and those with cerebrovascular disease. In both cases, the risk was more than double that in patients without a history of cardiovascular disease.

Key words: Diabetes mellitus. Atherothrombosis. Prognosis. Primary care.
La diabetes mellitus (DM) es una de las enfermedades de mayor impacto en salud pública en España. Su alta prevalencia y asociación con complicaciones cardiovasculares1,2 hace que sea un serio desafío para el sistema de salud. En efecto, el manejo del DM consume alrededor del 14% del gasto sanitario anual en España.3

Durante los últimos 20 años, se ha observado un aumento en la cifra de personas que tienen sobrepeso y padecen DM en el extranjero; este aumento ha sido principalmente debido a cambios en el estilo de vida. Actualmente se cree que alrededor del 10%-19% de la población española tiene algún grado de DM, siendo más prevalente en personas de mayor edad.4

Los complicaciones cardiovasculares son más prevalentes en pacientes con DM avanzado; en los pacientes con DM tipo 2 (DM2), las complicaciones cardiovasculares se producen con mayor frecuencia que en aquellos con DM tipo 1 (DM1).5

Conclusiones. El incremento del riesgo de complicaciones cardiovasculares se ve mayor en los diabéticos que en el resto de la población. Además, el DM tipo 2 es más prevalente en pacientes que tienen antecedentes de enfermedad cardiovascular isquémica (HR = 2,48; IC del 95%, 1,51-4,07), enfermedad cerebrovascular (HR = 2,51; IC del 95%, 1,28-4,92) y enfermedad vascular periférica (HR = 1,46; IC del 95%, 0,81-2,60).


**ABBREVIATIONS**

ACEi: angiotensin converting enzyme inhibitors  
ARA-II: angiotensin II receptor antagonists  
CVD: cerebrovascular disease  
DM: diabetes mellitus  
IC: ischemic cardiomyopathy  
PVD: peripheral vascular disease

**INTRODUCTION**

La diabetes mellitus (DM) es una de las enfermedades de mayor impacto en salud pública en España. Su alta prevalencia y asociación con complicaciones cardiovasculares1,2 hace que sea un serio desafío para el sistema de salud. En efecto, el manejo del DM consume alrededor del 14% del gasto sanitario anual en España.3

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**METHODS**

**Study Protocol**

Este estudio prospectivo, multi-centro de cohortes (algunos de los cuales han sido descritos en un trabajo previo)28 involucró a 31 médicos de primer nivel que trabajaban en 10 centros de salud en el suroeste de la provincia de A Coruña, en el noroeste de España. El estudio inicial se diseñó para incluir a 1423 pacientes consecutivos durante un periodo de 4 años. Los criterios de inclusión fueron: edad mayor de 18 años, diagnóstico previo de DM, y la presencia de al menos una complicación cardiovascular.25

En el seguimiento, se administró un anticoagulante de forma sistémica en el caso de la miocardiopatía isquémica (IC),13-17 enfermedad cerebrovascular (CVD),18-21 y muerte a causa de estas condiciones. Aunque la enfermedad cardiovascular periférica (PVD) es menos común durante los primeros años de padecer DM, es 4-5 veces más prevalente en pacientes con DM avanzado que en la población no-diabética.22

En España, la PVD se asocia a menudo con antecedentes de enfermedad cardiovascular (IC),23-25 enfermedad cardiovascular periférica (PVD) es común en pacientes con DM avanzado, y los diabéticos con DM avanzado tienen una mayor probabilidad de complicaciones cardiovasculares.24

El análisis de los datos se realizó utilizando la prueba de chi-cuadrado para comparar las diferencias entre grupos. Se consideró estadísticamente significativo un p < 0.05.
Variables Analyzed

All patients were subjected to anamnesis, a physical examination, and biochemical and electrocardiographic (ECG) tests. Patient demographic, anthropometric, and clinical characteristics were also recorded, as was the treatment each patient was prescribed.

Patients with a body mass index (BMI) of ≥30 were considered to be obese. Blood pressure was measured on the day of inclusion using a calibrated sphygmomanometer. After a 5 min rest period a first reading was taken, followed by a second reading 5 min later. The mean result was then calculated; a value of <130/80 mm Hg was taken to reflect good control of blood pressure. A baseline fasting blood sugar level of <126 mg/dL and a glycohemoglobin level of <7% were considered to represent good control of these variables, as were values of <50 mg/dL for triglycerides, <180 mg/dL for total cholesterol, and <100 mg/dL for low density lipoprotein cholesterol (LDL-C). In women, high density lipoprotein cholesterol (HDL-C) was considered under control when values of >50 mg/dL were recorded; in men, >40 mg/dL was considered satisfactory. The normality value for albuminuria was taken as >30 mg/dL/24 h.

After the 4 years of follow-up, the mortality data collected were analyzed, taking into account the cause of death. Morbidity data were also analyzed, taking into account admissions to hospital and the reason for such admission. The cause of death was obtained from the corresponding death certificate, and the reason for hospitalization from hospital release records; these documents were available in the medical histories of the patients stored at the health centers.

The patients were grouped depending on whether or not they suffered cardiovascular disease (divided into IC, CVD or PVD, or atherothrombotic events in more than 1 area) prior to their inclusion in the study. The IC group included patients with a prior diagnosis of angina or myocardial infarction or who had undergone a coronary revascularization procedure (percutaneous or/surgical). The CVD group included patients with a prior diagnosis of ictus or transitory ischemic attack. The PVD group included patients with a diagnosis of intermittent claudication or aneurysm of the abdominal aorta, or who had undergone a revascularization procedure in the lower limbs (percutaneous or/surgical) or abdominal aorta surgery.

Statistical Analysis

Qualitative variables were expressed as absolute frequencies and percentages. Quantitative variables were expressed as means (standard deviation). A descriptive analysis of the categorical variables was performed using frequency tables. The Pearson $\chi^2$ test was used to determine the significance of differences between qualitative variables. Means were compared using the Student $t$ test for independent samples.

The probability of survival during follow-up was determined using the Kaplan-Meier test, employing the logrank test to compare the curves of different subgroups of patients. Variables found to be significant in univariate analysis were included in Cox multivariate analysis (forward stepwise conditional method). The variables that maintained significance (age, sex, blood pressure, prior cardiovascular disease, and treatment with diuretics, beta-blockers, angiotensin converting enzyme inhibitors [ACEi], nitrates, and angiotensin II receptor antagonists [ARA II]) were those that were finally used to adjust the model. The results are expressed as hazard ratios (HR) and 95% confidence intervals (95% CI). All calculations were performed using SPSS v.14.0. software for Windows. Significance for was set at $P<.05$ for differences with a probable type I error.

RESULTS

Characteristics of the Patients Studied

Of the 1423 patients initially included, 8% had DM type 1 (DM1). Half of the patients were male; the mean age of the patients was 66 (11) years (age range, 18-97 years). The mean age of the male patients was significantly higher than that of the female patients. Some 47% of the patients studied were obese, 70% showed dyslipidemia, and more than half had some cardiovascular disease or a lesion in another organ. All the risk factors studied, except for smoking, were more common among the female patients, while the males showed a greater actual presence of cardiovascular disease or lesions in other organs (58% compared to 45%; $P<.001$). Table 1 shows the characteristics of the patients and their treatment depending on whether they had cardiovascular disease or not. Those with cardiovascular disease were older and more frequently showed evidence of kidney damage (albuminuria). The prevalence of high blood pressure was high in all cardiovascular disease subgroups. Some 72.6% of the patients received monotherapy for their diabetes; only 4% took 3 or more medications. Some 19.5% received insulin; 25% of the patients with cardiovascular disease were administered insulin. A strong relationship was seen between high blood pressure and treatment with diuretics; 29.1% of patients who were hypertensive received these drugs compared to only 4.8% of those who were not ($P<.001$).

Table 2 shows that blood pressure was well controlled in only 14% of hypertensive patients, and baseline glycemia was adequate in only 22%. The patients with IC showed better control of their blood pressure and plasma lipids than did those of the other subgroups. No significant differences were seen with respect to carbohydrate metabolism variables.
After a mean follow-up time of 44.6 (10.2) months (median, 48.1 months), total mortality had reached 6.2%. Some 49% of deaths had a cardiovascular cause. The hospitalization rate reached 30%. Table 3 shows the mortality and hospitalization rates plus their associated causes for the subjects as a whole and depending upon whether or not they suffered cardiovascular disease. Mortality was higher in patients with cardiovascular disease, among whom death due to cardiovascular cause
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TABLE 3. Mortality and Hospitalization Rates. Distribution With Respect to Prior Cardiovascular Disease

<table>
<thead>
<tr>
<th>Prior Cardiovascular Disease, No. (%)</th>
<th>Total</th>
<th>NCV</th>
<th>IC</th>
<th>CVD</th>
<th>PVD</th>
<th>MD</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>1314</td>
<td>974</td>
<td>57</td>
<td>109</td>
<td>62</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raw mortality</td>
<td>81</td>
<td>50</td>
<td>5</td>
<td>9</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cause of death</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-cardiovascular</td>
<td>41</td>
<td>30</td>
<td>4</td>
<td>2</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>40</td>
<td>20</td>
<td>1</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sudden death</td>
<td>9</td>
<td>5</td>
<td>1</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart failure</td>
<td>12</td>
<td>5</td>
<td>3</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>8</td>
<td>5</td>
<td>3</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ictus</td>
<td>4</td>
<td>2</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>7</td>
<td>3</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospitalizations</td>
<td>393</td>
<td>246</td>
<td>27</td>
<td>37</td>
<td>32</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular reasons</td>
<td>179</td>
<td>92</td>
<td>12</td>
<td>20</td>
<td>21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death and/or hospitalization</td>
<td>411</td>
<td>257</td>
<td>30</td>
<td>38</td>
<td>32</td>
<td></td>
<td></td>
</tr>
<tr>
<td>for cardiovascular reasons</td>
<td>234</td>
<td>130</td>
<td>16</td>
<td>24</td>
<td>23</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CVD indicates cerebrovascular disease; IC, ischemic cardiomyopathy; MD, multiple cardiovascular disease; NCV, no cardiovascular disease; PVD, peripheral cardiovascular disease.

*1 indicates NCV compared to IC; 2, NCV compared to CVD; 3, NCV compared to PVD; 4, NCV compared to MD; 10, PVD compared to MD; a, P<.001; b, P<.01; c, P<.05.

was more common. The combination of death + hospitalization for cardiovascular reasons was significantly more common in the subgroups of patients with cardiovascular disease than in the group with no cardiovascular disease. In this latter group, the most common reasons for hospitalization were non-cardiovascular (unlike in the cardiovascular disease subgroups).

The actuarial probability of survival at 4 years was 93.8%. The Kaplan-Meier curves of Figure 1 show that the probability of survival was significantly lower for those patients with a prior diagnosis of IC than for patients with no cardiovascular disease.

Multivariate analysis showed age, the suffering of cardiovascular disease, and treatment with diuretics to be independent predictors of mortality; treatment with ACEi and/or ARA-II was found to be protective (Figure 2).

Table 4 and Figure 3 show that patients with a cardiovascular complication were at greater risk of suffering new events or death of cardiovascular cause than those who had no background of cardiovascular disease. The patients with IC were at greater risk of suffering a new cardiovascular event in the same area; similar results were found for patients with CVD.

DISCUSSION

The risk of suffering a cardiovascular event (death and/or hospitalization for a cardiovascular cause) was found to be similar in the patients with a prior diagnosis of IC, CVD, or PVD, and more than double that for patients with no evident clinical cardiovascular disease. In the members of the IC subgroup, the most common place for the recurrence of clinical complications (death and/or a new event) was the coronary vascular area; in contrast, for those in the CVD subgroup, recurrences were more likely in the cerebrovascular area. The increased risk of ictus among the IC subgroup patients should also be noted.

To our knowledge, the Barbanza Diabetes study is the first to describe the mid-term (4 years) prognoses of the members of a homogeneous cohort of diabetics with and without clinical cardiovascular disease in Spain. The characteristics of this large group are those expected of a coastal population from Galicia (the region where the study was performed)—high blood pressure, a high salt intake, and a higher incidence of ictus than in Spain’s other regions. In addition, the present study takes into account the different forms of atherothrombotic disease with which these patients presented.

A number of studies have analyzed the cardiovascular risk of diabetics with and without clinically important IC. Recently, the mid term prognosis (follow-up=3 years) of a group of 776 Dutch diabetics with and without evident cardiovascular disease (n=458 and 318 respectively) was investigated, and it was concluded that, compared to diabetic patients with no such disease, the risk of a new cardiovascular complication (cardiovascular death or non-fatal ischemic stroke or acute myocardial infarction [AMI]) was greater among those with IC, CVD or PVD (4.3, 3.8, and 4.6 times respectively). The risk of suffering cardiovascular complications during follow-up was greater among the patients of the present study, both for those with and without prior cardiovascular disease. However,
it should be remembered that the Dutch cohort study only included mortality and non-fatal stroke or AMI while the present work included hospitalizations for all cardiovascular causes. It should also be noted that the risk observed for the Dutch cohort was only slightly greater than for the present IC and CVD subgroups, but more than double that recorded for the PVD subgroup. Differences in patient characteristics might account for these differences since the present study involved consecutive diabetic patients receiving assistance from primary care physicians, while the Dutch patients were diabetics referred for consultation to a university hospital. The differences in the recording of hospitalizations may also have led to these differences.

A study that investigated the 10 year prognosis of a group diabetic patients with cardiovascular disease (IC, CVD, or PVD) showed their risk of complications to be 6 times that of persons without diabetes or cardiovascular disease.¹²
### TABLE 4. Risk of Cardiovascular Events and Cardiovascular Death. Distribution With Respect to Prior Cardiovascular Disease

<table>
<thead>
<tr>
<th>Prior Cardiovascular Disease</th>
<th>NCV</th>
<th>IC</th>
<th>CVD</th>
<th>PVD</th>
<th>MD</th>
<th>P *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n=1314)</td>
<td>974 (74.1)</td>
<td>112 (8.5)</td>
<td>57 (4.3)</td>
<td>109 (8.3)</td>
<td>62 (4.7)</td>
<td></td>
</tr>
<tr>
<td>Death/hospitalization for cardiovascular reasons (n=194 [14.8%])</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1</td>
<td>3.34 (2.15-5.19)</td>
<td>2.66 (1.41-5)</td>
<td>1.98 (1.15-3.39)</td>
<td>3.35 (1.94-5.7)</td>
<td></td>
</tr>
<tr>
<td>Death/hospitalization for IC (n=66 [5%])</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1</td>
<td>8.81 (4.70-16.5)</td>
<td>1.81 (0.42-7.73)</td>
<td>0.93 (0.22-3.97)</td>
<td>4.68 (1.88-11.65)</td>
<td></td>
</tr>
<tr>
<td>Death/hospitalization for CVD (n=43 [3.3%])</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1</td>
<td>4.29 (1.63-11.3)</td>
<td>8.39 (3.19-22.07)</td>
<td>2.85 (0.93-8.75)</td>
<td>3.59 (1.02-12.6)</td>
<td></td>
</tr>
</tbody>
</table>

ACEi indicates angiotensin converting enzyme inhibitors; ARA-II, angiotensin II receptor antagonists; CVD, cerebrovascular disease; HBP, high blood pressure; HR, hazard ratio; IC, ischemic cardiomyopathy; MD, multiple disease; NCV, no cardiovascular disease; PVD, peripheral vascular disease.

*1 indicates NCV compared to IC; 2, NCV compared to CVD; 3, NCV compared to PVD; 4, NCV compared to MD; 5, IC NCV compared to CVD; 6, IC NCV compared to PVD; a, P<.001; b, P<.01; c, P<.05.

*Adjusted for age, sex, HBP, prior cardiovascular disease, and treatment with diuretics, beta-blockers, nitrates, ACEi, and ARA-II.
The present study describes the characteristics of recurrences in diabetic patients with different forms of clinical, atherothrombotic disease. While those with IC or CVD were at a greater risk of a recurrence of a clinical complication in the same area, it should be noted that the IC patients had a greater risk of suffering ictus than did the CVD patients of suffering a myocardial ischemic event. Although the small number of patients in each subgroup requires caution be used in the interpretation of these results, no other study has described the pattern of recurrence of cardiovascular disease in diabetics with a prior diagnosis of atherothrombotic disease. In agreement with the recommendations made in clinical guidelines, this indicates the need to look for asymptomatic vascular disease in other areas, especially CVD in patients with IC.\textsuperscript{33,34}

The present results agree, to some extent, with those recorded in a large international registry (the REACH Registry). The latter includes the data of 68,236 patients with clinical IC, CVD, or PVD and of 12,422 patients at high cardiovascular risk (at least 3 risk factors for atherothrombosis) but with no clinical manifestation of disease. After a follow-up period of 1 year, recurrence in CVD and IC subgroup patients was found to be more common in the same vascular area. Some 5.3\% of the patients with multiple cardiovascular risk factors, 15.2\% of the IC patients, 14.5\% of the CVD patients, and 21.1\% of the PVD patients died of cardiovascular causes, suffered a non-fatal stroke or AMI, or required hospitalization for an atherothrombotic event.\textsuperscript{35}

In the present study, age, prior cardiovascular disease and treatment with diuretics were independent predictors of mortality. The first 2 of these variables have also been identified as such in nearly all cardiovascular disease registries. The fact that treatment with diuretics should be a predictor probably reflects the influence of heart failure and the need to use more drugs to control more advanced high blood pressure.

It should be noted that treatment with ACEi and/or ARA-II had a protective effect. The same has been seen in a number of clinical trials (MicroHOPE,\textsuperscript{36} BENEDICT,\textsuperscript{37} IDNT,\textsuperscript{38} IRMA-II,\textsuperscript{39} RENAAL,\textsuperscript{40}) involving diabetics. The present data reinforce the recommendations to be found in current practice guidelines, which indicate the blocking of the renin-angiotensin system to be one of the pillars of the therapeutic strategy to be followed.

**Limitations of the Study**

The present study has the advantage that it involves a registry in which the physicians directly responsible for the patients make and record the diagnosis of DM, record the risk factors for any concomitant cardiovascular disease, record the characteristics of the treatment to be followed, and note the cardiovascular complications that arise during follow-up. However, more than 7\% of the subjects were lost to follow-up. This may have had some influence on the results, although it is similar to that described in other population registries for cardiovascular diseases.

For the majority of patients, possible changes in the therapeutic strategy were never recorded. Along with the initial treatment provided, such changes could have influenced the prognosis. However, this is a limitation of nearly all registries on cardiovascular risk and disease.

It is possible that some patients may have suffered cardiovascular complications that did not require hospitalization, leading to the eventual undervaluation of cardiovascular risk.

Concluding a protective action for ACEi and ARA-II suffers from the methodological limitations associated with making clinical observations from registries, although a number of the clinical trials mentioned above vouch for their effect.

Finally, mortality may have been undervalued since patients lost to follow-up may have died.

**CONCLUSIONS**

This study, which investigates the mid-term prognosis of diabetic patients (from a single geographical area) with clinical cardiovascular disease (IC, CVD, or PVD), shows that cardiovascular mortality and morbidity are similar irrespective of the vascular area affected. The results reveal the recurrence of atherothrombotic disease in each subgroup to be more common in the same vascular area. Treatment with drugs designed to block the renin-angiotensin system (ACEi and ARA-II) was found to be an independent predictor of improved prognosis; this should be interpreted with caution, however, since it is a finding associated with a patient registry rather than a clinical trial.

The present results highlight the importance of better implementation of the recommendations made in clinical guidelines, both in terms of diagnostic assessment and therapeutic practice.

**Researchers of the Barbanza Group**


**REFERENCES**

González-Juanatey JR et al. Influence of Atherothrombosis on Prognosis of Diabetes


