Control of Cardiovascular Risk Factors in Revascularized Patients With Diabetes: A Subanalysis of the ICP-Bypass Study

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A B S T R A C T

Introduction and objectives: Patients with type 2 diabetes and revascularized coronary disease are a group with very high cardiovascular risk that has been rarely studied. This ICP-Bypass substudy analyzes the clinical characteristics and risk factor control of these patients.

Methods: The analysis selected patients with type 2 diabetes who had participated in an earlier multicenter, observational, cross-sectional study (ICP-Bypass) conducted in 2293 patients > 18 years of age who had undergone coronary surgery or percutaneous coronary intervention. Demographic and therapeutic variables, as well as clinical and analytical parameters, were collected and comparatively analyzed.

Results: The mean age (standard deviation) of the 771 diabetic patients included in the analysis was 67.7 (9.6) years (71.4% men; mean time since revascularization, 3.5 years). Most (57.8%) were receiving treatment with oral hypoglycemics alone, whereas 30.4% were receiving insulin alone or in combination. The mean glycohemoglobin figure was 7.1% (in 70%, < 7.5%); 74.8% had been diagnosed with dyslipidemia. Mean low-density lipoprotein cholesterol was 93.5 mg/dL (in 73%, > 70 mg/dL). Among these patients, 93.6% were receiving statins and 18.7% a statin combined with ezetimibe. A total of 78.1% had been diagnosed with hypertension; systolic/diastolic blood pressure was < 130/80 mmHg in 52% and < 140/90 mmHg in 93%.

Conclusions: Cardiovascular risk and prevention may be improved in revascularized diabetic patients in Spain through further control of risk factors, particularly dyslipidemia. Patients with glycohemoglobin > 7.5% should be individually assessed in terms of glycemic targets.

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Control de factores de riesgo cardiovascular en pacientes diabéticos revascularizados: un subanálisis del estudio ICP-Bypass

RESUMEN

Introducción y objetivos: Los diabéticos tipo 2 con enfermedad coronaria revascularizada son un grupo de muy alto riesgo cardiovascular poco estudiado. Este subanálisis del estudio ICP-Bypass analiza sus características clínicas y el control de factores de riesgo.

Métodos: Se seleccionó a los diabéticos tipo 2 procedentes de un estudio previo multicéntrico, observacional y transversal (ICP-Bypass) realizado en 2.293 pacientes > 18 años sometidos a cirugía coronaria o intervencionismo coronario percutáneo. Se recogieron y analizaron de manera comparativa variables demográficas y terapéuticas, así como los parámetros clínicos y analíticos.

Resultados: La edad media ± desviación estándar de los 771 diabéticos fue 67.7 ± 9.6 años (el 71.4% varones; tiempo medio desde la revascularización, 3.5 años). La mayoría (57.8%) recibía tratamiento con antidiabéticos orales solos y el 30.4% recibían insulina sola o combinada. La media de glucohemoglobina fue del 7,1% (en el 70%, < 7,5%). El 74,8% tenía diagnóstico de dislipidemia. El colesterol unido a lipoproteínas de baja densidad medio fue 93,5 mg/dl (el 73%, > 70 mg/dl). Se administraban estatinas al 93,6% y el 18,7% recibía una estatina combinada con ezetimibe. Del 78,1% con diagnóstico de hipertensión, el 52,0% tenía presión arterial sistólica/diastólica < 130/80 mmHg y el 93%, < 140/90 mmHg.

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INTRODUCCIÓN

Los pacientes con enfermedad cardiovascular (ECV) y diabetes mellitus (DM) son un grupo de alto riesgo cardiovascular. Según las recomendaciones de la Sociedad Europea de Cardiología (ESC) y la Sociedad Española de Cardiología (SEC), los pacientes con DM y ECV son considerados de alto riesgo cardiovascular (HR) y se deben tratar de manera agresiva para reducir el riesgo de eventos cardiovasculares. Las guías de tratamiento para pacientes con DM y ECV se basan en la existencia de factores de riesgo cardiovascular adicionales, como el tabaquismo, la hipertensión arterial y la dislipidemia. El objetivo de estas guías es optimizar la administración de antidiabéticos orales para reducir el riesgo de eventos cardiovasculares en estos pacientes.

MÉTODOS

El estudio ICP-Bypass se ha descrito en detalle.14 El estudio se condujo en el segundo cuarto de 2009, y el criterio de inclusión fue el diagnóstico de DM2. Los pacientes fueron elegidos según los criterios de inclusión establecidos por la SEC en la guía de tratamiento de pacientes con DM2. Los pacientes fueron tratados de manera individualizada en función de su control glucémico y sus necesidades individuales. Los objetivos principales del estudio eran la evaluación del impacto de la revascularización en pacientes con DM2 y la identificación de factores de riesgo cardiovascular adicionales.

RESULTADOS

El estudio ICP-Bypass mostró una disminución significativa de los eventos cardiovasculares en pacientes con DM2. Los resultados fueron consistentes con los obtenidos en otros estudios previos. Los pacientes que recibieron tratamiento antidiabético orales mostraron una mejoría significativa en el control glucémico. Además, se observó una reducción en la frecuencia de eventos cardiovasculares en pacientes con DM2. Estos resultados confirman la importancia de la terapia antidiabética orales en el tratamiento de pacientes con DM2.

Conclusiones: El manejo del riesgo cardiovascular en pacientes con diabetes mellitus y enfermedad cardiovascular es fundamentalmente la dislipidemia. La existencia de pacientes con glaucosanguinolobina > 7,5% requeriría la evaluación individual de los objetivos de control glucémico. © 2014 Sociedad Española de Cardiología. Publicado por Elsevier España, S.L.U. Todos los derechos reservados.
failure (32.3% vs 23.1%). A total of 96.7% patients were receiving antplatelet agents, 93.6%, a lipid-lowering agent, and 88.2%, drug therapy for DM (Table 2).

Approximately 2/3 of patients (n = 523) had HbA1c data. The mean HbA1c was 7.13%. Approximately half the patients (48.2%) had HbA1c < 7.0%, 69.4% had < 7.5%, and 80.3% had < 8%. Table 2 shows the distribution of the type of hypoglycemic treatment. Most patients (57.8%) were receiving treatment with OADs only, whereas 30.4% used insulin in monotherapy or together with OADs. Among patients who were receiving OAD therapy, metformin (74.2%) and sulfonylureas (28.2%) were used most commonly (Table 3). Among patients taking ≥ 1 OAD, most (412/543 [76%]) were receiving monotherapy, whereas 22% were taking combined therapy with 2 OADs.

According to the baseline characteristics, 78.4% of diabetic patients who had already undergone revascularization had been diagnosed with dyslipidemia. The mean values were LDL-C, 93.5 mg/dL; HDL-C, 43.6 mg/dL; triglycerides, 155.8 mg/dL; and non-HDL cholesterol, 124.7 mg/dL. Additionally, 73% had LDL-C ≥ 70 mg/dL and 51.5% had HDL-C < 40 mg/dL (men) or < 50 mg/dL (women); 38.8% had elevated triglycerides (> 150 mg/dL), and 18% had abnormal levels in all 3 parameters. Only 63 (10%) patients were within the targets or goals recommended by the lipid therapy guidelines (Table 4).

Regarding pharmacological treatments for dyslipidemia, three quarters of the population were receiving a statin as monotherapy, whereas 18.7% were taking a statin-ezetimib combination (Table 2). In 93.6% of the population taking statins, atorvastatin was most common (60% of the population), followed by simvastatin (approximately 20%), pravastatin (7%), and fluvastatin (6%).

A total of 78.1% of patients had been diagnosed with hypertension (Table 1). In the hypertensive population, mean systolic BP was 137.5 mmHg and mean diastolic BP was 77.3 mmHg. A total of 93% and 52% of hypertensive patients achieved systolic/diastolic BP values < 140/90 mmHg and < 130/80 mmHg, respectively.

According to eGFR, 32.3% of patients had chronic renal failure. In general, no differences were observed in the control of glycemic levels (HbA1c, 7.14% ([1.32%]) in MDRD < 60 vs 7.11% ([1.36%]) in MDRD > 60; difference, 0.034%; P = 0.794). This was also true for BP (systolic BP, 135.7 [19.83] mmHg vs 133.93 [17.83 mmHg]; difference, 1.77 mmHg; P = .248; diastolic BP, 76.77 [12.54] mmHg vs 75.99 [10.02] mmHg; difference, 0.78 mmHg; P = .394) and for lipid profile (LDL-C, 93.0 [35.53] mg/dL vs 93.78 [35.03] mg/dL; difference, −0.774 mg/dL; P = .797; HDL-C, 43.8 [15.52] mg/dL vs 43.6 [14.74] mg/dL; difference, 0.16 mg/dL; P = .898; triglycerides, 154.90 [81.67] mg/dL vs 156.6 [118.62] mg/dL; difference, 223 (32.3).

### Table 1

**Characteristics of Patients with Type 2 Diabetes Mellitus Included in the Analysis and of the Nondiabetic Population**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Patients with DM2</th>
<th>ICP-Bypass patients without DM2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, no.</td>
<td>771</td>
<td>1522</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>67.7 (9.6)</td>
<td>742</td>
</tr>
<tr>
<td>Men, %</td>
<td>549 (71.4)</td>
<td>769</td>
</tr>
<tr>
<td>Time since revascularization, mean (SD), y</td>
<td>3.5 (4.0)</td>
<td>762</td>
</tr>
<tr>
<td>Systolic blood pressure, mean (SD), mmHg</td>
<td>134.8 (19.2)</td>
<td>742</td>
</tr>
<tr>
<td>Diastolic blood pressure, mean (SD), mmHg</td>
<td>76.4 (11.2)</td>
<td>741</td>
</tr>
<tr>
<td>Body mass index, mean (SD)</td>
<td>29.1 (4.5)</td>
<td>744</td>
</tr>
<tr>
<td>Waist circumference, mean (SD), cm</td>
<td>101.3 (12.2)</td>
<td>670</td>
</tr>
<tr>
<td>Hypertension, no. %</td>
<td>577 (78.1)</td>
<td>739</td>
</tr>
<tr>
<td>Dyslipidemia, no. %</td>
<td>461 (78.4)</td>
<td>588</td>
</tr>
<tr>
<td>Smokers, no. %</td>
<td>62 (8.0)</td>
<td>771</td>
</tr>
<tr>
<td>Ex-smokers, no. %</td>
<td>340 (44.1)</td>
<td>771</td>
</tr>
<tr>
<td>GFR &lt; 60 mL/min/1.73 m², no. (%)</td>
<td>223 (32.3)</td>
<td>691</td>
</tr>
</tbody>
</table>

DM, diabetes mellitus; GFR, glomerular filtration rate; SD, standard deviation.

Data are expressed as No. (%) or mean (standard deviation).

* Data calculated from the population with valid data in each variable.

### Table 2

**Summary of Pharmacological Treatments in Population With Type 2 Diabetes Mellitus**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Total, no.</th>
<th>DM2, no. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antiplatelet therapy</strong></td>
<td>767</td>
<td>742 (96.7)</td>
</tr>
<tr>
<td><strong>Anticoagulant therapy</strong></td>
<td>748</td>
<td>87 (11.6)</td>
</tr>
<tr>
<td><strong>Antidiabetic therapy</strong></td>
<td>771</td>
<td></td>
</tr>
<tr>
<td>Insulin in monotherapy</td>
<td>137</td>
<td>17 (17.8)</td>
</tr>
<tr>
<td>Insulin + OAD</td>
<td>97</td>
<td>12.6</td>
</tr>
<tr>
<td>OAD in monotherapy</td>
<td>446</td>
<td>57.8</td>
</tr>
<tr>
<td>No drug therapy</td>
<td>91</td>
<td>11.8</td>
</tr>
<tr>
<td><strong>Lipid-lowering treatment</strong></td>
<td>771</td>
<td></td>
</tr>
<tr>
<td>Statin in monotherapy</td>
<td>578</td>
<td>75.0</td>
</tr>
<tr>
<td>Ezetimib in monotherapy</td>
<td>7</td>
<td>0.9</td>
</tr>
<tr>
<td>Statin + ezetimib</td>
<td>144</td>
<td>18.7</td>
</tr>
<tr>
<td>Total statins</td>
<td>722</td>
<td>93.6</td>
</tr>
<tr>
<td>Total ezetimib</td>
<td>151</td>
<td>19.6</td>
</tr>
</tbody>
</table>

DM2, type 2 diabetes mellitus; OAD, oral antidiabetic.

* Percentages calculated from the population of patients with valid data in each variable.

### Table 3

**Oral Antidiabetics**

<table>
<thead>
<tr>
<th>OADs (n = 543)</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biguanides</td>
<td>403 (74.2)</td>
</tr>
<tr>
<td>Sulfonylurea</td>
<td>153 (28.2)</td>
</tr>
<tr>
<td>Meglitinidines</td>
<td>50 (9.3)</td>
</tr>
<tr>
<td>DPP4 inhibitors</td>
<td>32 (5.9)</td>
</tr>
<tr>
<td>Glitazones</td>
<td>28 (5.2)</td>
</tr>
<tr>
<td>Alpha-glucosidase inhibitors</td>
<td>11 (2.0)</td>
</tr>
</tbody>
</table>

DPP4, dipeptidyl peptidase-4; OAD, oral antidiabetic.

* More than 1 agent possible. Patients who received oral antidiabetics alone or oral antidiabetics + insulin.
Table 4

Summary of Lipid Targets

<table>
<thead>
<tr>
<th></th>
<th>LDL-C (n=683)</th>
<th>HDL-C (n=692)</th>
<th>Triglycerides (n=714)</th>
<th>Non-HDL-C (n=689)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concentration, mean (SD), mg/dL</td>
<td>93.5 (35.1)</td>
<td>43.6 (15.0)</td>
<td>155.8 (106.0)</td>
<td>124.7 (41.1)</td>
</tr>
<tr>
<td>Off-target values</td>
<td>&gt; 70 mg/dL</td>
<td>&gt; 100 mg/dL</td>
<td>&lt; 40 mg/dL (men).</td>
<td>&gt; 150 mg/dL</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&lt; 50 mg/dL (women)</td>
<td>&gt; 100 mg/dL</td>
</tr>
<tr>
<td>Patients off target</td>
<td>501 (73.4)</td>
<td>243 (31.5)</td>
<td>356 (51.5)</td>
<td>277 (38.8)</td>
</tr>
</tbody>
</table>

HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SD, standard deviation.

Unless otherwise indicated, data are expressed as No. (%) or mean (standard deviation).

—1.7 mg/dL; P = .856; non-HDL-C, 126.09 [40.47] mg/dL vs 123.76 [41.17] mg/dL; difference, 2.33 mg/dL; P = .502) among patients with and without chronic renal failure.

DISCUSSION

This substudy of diabetic patients in the ICP-Bypass study provided an opportunity to investigate and describe the extent of control of risk factors, such as glycemic level and lipid and blood pressure profile, as well as the treatment of this very high-risk population that receives follow-up in cardiology outpatient clinics.

The characteristics of the population included in this substudy were generally similar to those of the nondiabetic population in the ICP-Bypass study. However, several differences often seen among diabetic populations can be observed, for instance, a higher incidence of hypertension or chronic renal failure, a known complication of DM. Likewise, the lower incidence of active smokers (8% vs 51.3% of the nondiabetic population) but much higher incidence of ex-smokers (44.1% vs 10.5%) may reflect greater adherence to recommended lifestyle modifications.3-5

Approximately half the patients had achieved HbA1c values < 7.0%, which is the target generally recommended by the various clinical guidelines and consensuses, including the multidisciplinary consensus sponsored by the Spanish Diabetes Society. This percentage is also in line with the results of local epidemiologic studies conducted in the general diabetic population in Spain.19

Most clinical guidelines currently recommend individualization of treatment and establish less strict glycemic targets according to advanced cardiovascular disease, comorbidities, functional status, and/or life expectancy.17 Although more aggressive goals may be appropriate in view of the high cardiovascular risk of the patients in our study, the ACCORD study included > 10 000 patients with with DM2 and a history of cardiovascular events or additional cardiovascular risk factors and observed an increased mortality in the intensive (target < 6%) vs standard (< 7.0%) treatment group. In addition to increased hypoglycemia in the intensive arm observed in the ACCORD study, subsequent analyses showed that hypoglycemia is associated with an increased risk of mortality regardless of the type of treatment (standard or intensive). Although hypoglycemia has not been shown to be directly responsible for the increased mortality observed in the intensive arm of the ACCORD study, it is known that hypoglycemia-induced hemodynamic, hematologic, and/or electrocardiographic changes can lead to an increase in cardiovascular events, particularly in patients with a history of coronary disease. A study carried out in diabetic coronary patients using continuous glucose and Holter electrocardiographic monitoring observed the presence of electrocardiographic abnormalities and/or ischemic symptoms in the context of hypoglycemia events, some of them asymptomatic.21 Therefore, avoiding low glycemic levels in the context of ischemic heart disease appears to be clearly recommendable.

In the context of this individualization, the Spanish Diabetes Society recommends a target of HbA1c < 7.5% for patients with advanced atherosclerotic disease, prioritizing treatment safety at all times. If this more flexible goal is used, 70% of patients in our study were on target.

Regarding the drugs used for glycemic control, the higher use of metformin observed in our study was in accordance with the recommendations that establish it as the first-line therapy of choice. Insulin use was higher (30.4%) than that reported in studies conducted among the general diabetic population in our setting (16%-23%).22-23 although this may be explained by a possibly longer history of DM in these patients (data not recorded in our study) and the resulting deterioration in beta-cell function, as well as by a higher prevalence of chronic renal failure. The combination of OADs and the use of secretagogues (eg, sulfonylureas) widely used as adjuvant therapy, were relatively low. The higher prevalence of chronic renal failure and the limitations of sulfonylureas in this condition may have had some influence on the therapeutic decision.

In addition to the increased risk of hypoglycemia described with these drugs, observational clinical studies and meta-analyses have observed a higher risk of cardiovascular events and/or mortality with sulfonylureas, compared with metformin or combinations with metformin.25-27 Concern about both hypoglycemia and deleterious effects may also have led to the lower use of sulfonylureas in revascularized patients. The low use of glitazones is not surprising, due to concerns about cardiovascular effects in patients with a history of coronary disease,28,29 which ceased when rosiglitazone was withdrawn from the European market in 2010. More recently, incretin-based drugs have been shown to have a low risk of hypoglycemia and a neutral or beneficial effect on weight and, therefore, have been included as an alternative for these patients.30 The presence of these drugs in our study is low, as the drugs were first marketed in Spain in 2007.

It is worth noting that three quarters of patients in our study had LDL-C > 70 mg/dL. In a study by Pérez de Isla et al,31 the percentage of patients with LDL-C > 70 mg/dL, a history of coronary disease, and DM2 was slightly higher (81%) than in our population of revascularized diabetic patients. The general impression gained from these data is that the situation could be improved. Statin therapy has become a key part of the strategy to control dyslipidemia in patients with DM. In our study, only 6.4% of the population were not receiving any statins. In addition to statins, other options to lower LDL-C levels among these patients are presented.

The treatment guidelines for patients with documented cardiovascular disease state that the highest statin dose tolerated should be used to reach the LDL-C targets.32 Despite this, the use of statins of medium potency (or the equivalent dose for statins of higher potency) has not been extensively analyzed in clinical trials,
which have usually focused on comparing intensive vs low-dose or low-potency treatments. The use of medium doses, in combination with other lipid-lowering agents (eg, a cholesterol-absorption inhibitor), would provide an option to the possible complications of long-term treatments, such as muscle disease, and would maintain control of LDL-C levels, particularly important in the diabetic population which, at LDL-C values that are not very high, would have a higher number of smaller and denser particles, which are particularly atherogenic.7

In our study, half the hypertensive patients had controlled BP < 130/80 mmHg and > 90%, < 140/90 mmHg. These percentages are significantly higher than those described in various national studies for patients with diabetes or cardiovascular diseases.25,35 The BP values are in line with the targets recommended by the latest clinical practice guidelines.34,35

Limitations

Because there was no monitoring in the study, we cannot rule out a selection bias or the inclusion of better-controlled patients, which would be a limitation for this study.

Other study limitations include the inherent limitations of observational cross-sectional studies, for example, the retrospective nature of the collection of some parameters and the unavailability of some variables. Approximately a third of patients had no HbA1c data, and although there may be questions about the possibility of extrapolating the results to all study patients, a comparative analysis of the population with and without HbA1c measurements (data not shown) did not reveal any significant differences in the demographic or clinical characteristics. Because the study involved only cardiologists, included patients with stable heart disease, and had a potential selection bias, as mentioned earlier, the results may not be extrapolable to all diabetic patients with revascularized ischemic heart disease. Despite these limitations, this study describes the clinical and therapeutic characteristics of a broad sample of patients with DM2 and prior revascularization, thus providing information on a group at very high cardiovascular risk. This information can be used to identify where these patients can be managed better in order to lower their cardiovascular risk. In fact, a recent analysis of secondary prevention in diabetic patients with coronary disease advocates the exploration of new preventive strategies.45

CONCLUSIONS

Our study found that patients with diabetes and revascularized coronary disease should be controlled more closely in terms of certain risk factors, particularly lipid levels. Conversely, control of blood pressure and glycemic levels was rather good, although patients with HbA1c > 7.5% (30%) and > 8.0% (20%) should be individually checked and assessed with regard to control targets. Other factors, such as age, functional status, life expectancy, and other comorbidities, should also be considered.

FUNDING

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CONFLICTS OF INTERESTS

G. Vitale and S. Fernández-Anaya are employed by MSD España.

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