

Original article

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



Pilar Mazón-Ramos,^{a,*} Alberto Cordero,^b José Ramón González-Juanatey,^a Vicente Bertomeu Martínez,^b Elías Delgado,^c Gustavo Vitale,^d and Silvia Fernández-Anaya^d

^aServicio de Cardiología, Complejo Hospitalario Universitario de Santiago, Santiago de Compostela, A Coruña, Spain

^bServicio de Cardiología, Hospital Universitario de San Juan, San Juan de Alicante, Alicante, Spain

^cServicio de Endocrinología, Hospital Central de Asturias, Oviedo, Asturias, Spain

^dDepartamento Médico, Merck Sharp & Dohme (MSD), Spain

Article history:

Received 13 November 2013

Accepted 12 March 2014

Available online 12 September 2014

Keywords:

Diabetes mellitus

Atherosclerosis

Revascularization

Coronary disease

ABSTRACT

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 ezetimib. 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.

© 2014 Sociedad Española de Cardiología. Published by Elsevier España, S.L.U. All rights reserved.

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 $\pm$ desviación estándar de los 771 diabéticos fue 67,7 $\pm$ 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 dislipemia. 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 ezetimiba. Del 78,1% con diagnóstico de hipertensión, el 52,0% tenía presión arterial sistólica/diastólica < 130/80 mmHg y el 93%, < 140/90 mmHg.

Palabras clave:

Diabetes mellitus

Aterosclerosis

Revascularización

Enfermedad coronaria

* Corresponding author: Servicio de Cardiología, Complejo Hospitalario Universitario de Santiago, Travesía A Choupana s/n, 15706 Santiago de Compostela, A Coruña, Spain.
E-mail address: pilarmazon@yahoo.es (P. Mazón-Ramos).

Conclusiones: En el manejo del riesgo y la prevención cardiovascular de los pacientes diabéticos revascularizados en España se observa margen de mejora en el control de factores de riesgo, fundamentalmente la dislipemia. La existencia de pacientes con glucohemoglobina > 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.

Abbreviations

BP: blood pressure
HbA_{1c}: glycohemoglobin
HDL-C: high-density lipoprotein cholesterol
LDL-C: low-density lipoprotein cholesterol
OAD: oral antidiabetic

INTRODUCTION

Patients with ischemic heart disease who have diabetes mellitus (DM) are a group at increased cardiovascular risk.^{1,2} According to the latest guidelines on cardiovascular prevention and DM, prediabetes, and cardiovascular disease published by the European Society of Cardiology, patients with type 2 DM (DM2) are considered to be at high to very high cardiovascular risk—similar to patients with acute coronary syndrome or disease—if they also have a history of cardiovascular disease or other associated risk factors.^{3–5} Therefore, patients with DM and ischemic heart disease are at very high risk and have a high prevalence of dyslipidemia and hypertension.⁶ Additionally, DM is associated with a more atherogenic lipid profile, due to the smaller, denser low-density lipoproteins than those found in nondiabetic patients and lower high-density lipoprotein cholesterol (HDL-C) concentrations, which may contribute to increased cardiovascular risk in these patients.⁷

The various clinical guidelines and consensus recommend a multifactorial approach toward the diabetic patient that considers both glycemia and all other related risk factors, in order to minimize macrovascular and microvascular mortality and morbidity, as observed in the Steno-2 study.^{8,9} However, the target for each risk factor should be individualized in some cases. Intensive pharmacological interventions aimed at lipid management and control have been shown to help lower cardiovascular risk in high-risk patients, regardless of the degree of control achieved.¹⁰ In particular, a sharp drop in low-density lipoprotein cholesterol (LDL-C) has been shown to lower the rate of cardiovascular events in diabetic patients by 21%.¹¹ Unlike lipid intervention studies, however, the concept of “the lower, the better” is ruled out in hypertension control due to the presence of the J-curve. In the case of glycemic control, the strictness of the target depends on patient age, functional status, and comorbidities.^{12,13}

The ICP-Bypass study investigated the characteristics and residual risk in a population of patients with ischemic heart disease (for the purposes of the study, patients with a history of coronary revascularization).¹⁴ Because these DM patients are at very high risk according to the European Society of Cardiology Guidelines^{3,4,15} and there are few data on risk factors in the diabetic population with a history of coronary disease who have undergone surgery revascularization or percutaneous coronary intervention, the aim of this study was to investigate and describe the characteristics of patients with DM2 in the ICP-Bypass study, including the impact of chronic renal failure and the presence and degree of control of other associated risk factors.

METHODS

The ICP-Bypass study has already been described in detail.¹⁴ The study was conducted in the second quarter of 2009, and each of the 199 participating investigators included the first 14 patients who underwent revascularization (bypass or percutaneous coronary intervention > 3 months earlier) and came for follow-up at cardiology outpatient clinics in hospitals or health care centers in Spain. At the inclusion visit, patients signed their informed consent, completed a study-specific questionnaire to collect age, weight, height, waist circumference, and blood pressure (BP) at the time of the visit, as well as the presence of cardiovascular risk factors and laboratory parameters: HDL-C, LDL-C, triglycerides, glycohemoglobin (HbA_{1c}), and creatinine in the previous 3 months. Current medical treatments related to risk factor management and control were also collected.

For the present analysis, the variables were retrieved from the main study database and patients were selected if they had been diagnosed with DM2 according to the medical history, were receiving at ≥ 1 oral antidiabetic (OAD) agent, or had HbA_{1c} > 6.5%. Patients were considered to have hypertension or dyslipidemia if the diagnosis had been previously recorded in the medical history. For LDL-C, these post-hoc analyses assumed a therapeutic goal < 70 mg/dL, in accordance with the latest guidelines published after the initial analysis.^{3,15} Controlled BP was established as < 140/90 mmHg. The MDRD-4 (Modification of Diet in Renal Disease-4) formula¹⁶ was used to calculate the eGFR (estimated glomerular filtration rate) from the recorded variables and to define the presence or absence of chronic renal failure as a possible risk-modifying factor. Chronic renal failure was considered to exist if eGFR < 60 mL/min/1.73 m², which corresponds to chronic kidney disease stages 3 to 5.

Statistical Analysis

The qualitative variables were evaluated by the χ^2 test and the quantitative variables by Student *t* test and analysis of variance; only valid data were included, and missing data were not allocated. *P* values < .05 were considered statistically significant. No adjustments were made for multiplicity, and no interim analyses were performed. No inferential analyses were performed with variables that had qualitative or binary answers. The analysis was performed using SPSS version 18.

RESULTS

The ICP-Bypass study population that met the inclusion criteria consisted of 2292 patients, of whom 771 (34%) had DM2. Among these 771 already revascularized diabetic patients (mean time since revascularization, 3.5 years; median, 1.90 [3.96]; Q = 0.55; Q3 = 5.08 years), a total of 32.3% had renal failure (eGFR < 60 mL/min/1.73 m²), and the mean eGFR was 71.5 mL/min/1.73 m². The patient characteristics are summarized in Table 1. The main differences compared with the total population for the main study were a lower percentage of active smokers (8.0% vs 51.3% of the total population) and a higher prevalence of hypertension (78.1% vs 55.9%) and renal

Table 1

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

	Patients with DM2	No. [*]	ICP-Bypass patients without DM2	No. [*]
Patients, no.		771		1522
Age, mean (SD), y	67.7 (9.6)	742	64.4 (11.6)	1474
Men, no. %	549 (71.4)	769	1,236 (81.6)	1514
Time since revascularization, mean (SD), y	3.5 (4.0)	762	3.4 (4.1)	1505
Systolic blood pressure, mean (SD), mmHg	134.8 (19.2)	742	131.0 (18.1)	1460
Diastolic blood pressure, mean (SD), mmHg	76.4 (11.2)	741	75.6 (10.8)	1434
Body mass index, mean (SD)	29.1 (4.5)	744	28.1 (3.8)	1454
Waist circumference, mean (SD), cm	101.3 (12.2)	670	97.6 (13.2)	1255
Hypertension, no. %	577 (78.1)	739	816 (55.9)	1460
Dyslipidemia, no. %	461 (78.4)	588	720 (67.9)	1061
Smokers, no. %	62 (8.0)	771	177 (11.8)	1504
Ex-smokers, no. %	340 (44.1)	771	771 (51.3)	1504
GFR < 60 mL/min/1.72 m ² , no. (%)	223 (32.3)	691	307 (23.1)	1327

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.

failure (32.3% vs 23.1%). A total of 96.7% patients were receiving antiplatelet agents, 93.6%, a lipid-lowering agent, and 88.2%, drug therapy for DM (Table 2).

Approximately 2/3 of patients (n = 523) had HbA_{1c} data. The mean HbA_{1c} was 7.13%. Approximately half the patients (48.2%) had HbA_{1c} < 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 (HbA_{1c}, 7.14% ([1.32%]) in MDRD < 60 vs 7.11% ([1.36%]) in MDRD > 60; difference, 0.034%; P = .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,

Table 2

Summary of Pharmacological Treatments in Population With Type 2 Diabetes Mellitus

	Total, no.	DM2, no. (%) [*]
Antiplatelet therapy	767	742 (96.7)
Anticoagulant therapy	748	87 (11.6)
Antidiabetic therapy	771	
Insulin in monotherapy		137 (17.8)
Insulin + OAD		97 (12.6)
OAD in monotherapy		446 (57.8)
No drug therapy		91 (11.8)
Lipid-lowering treatment	771	
Statin in monotherapy		578 (75.0)
Ezetimib in monotherapy		7 (0.9)
Statin + ezetimib		144 (18.7)
Total statins		722 (93.6)
Total ezetimib		151 (19.6)

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

OADs (n = 543) [*]	No. (%)
Biguanides	403 (74.2)
Sulfonylurea	153 (28.2)
Meglitinides	50 (9.3)
DPP4 inhibitors	32 (5.9)
Glitazones	28 (5.2)
Alpha-glucosidase inhibitors	11 (2.0)

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

	LDL-C (n = 683)		HDL-C (n = 692)	Triglycerides (n = 714)	Non-HDL-C (n = 689)
Concentration, mean (SD), mg/dL	93.5 (35.1)		43.6 (15.0)	155.8 (106.0)	124.7 (41.1)
Off-target values	> 70 mg/dL	> 100 mg/dL	< 40 mg/dL (men), < 50 mg/dL (women)	> 150 mg/dL	> 100 mg/dL
Patients off target	501 (73.4)	243 (31.5)	356 (51.5)	277 (38.8)	481 (69.7)

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; $P = .850$; 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.¹⁴ 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.¹⁶ Likewise, the lower incidence of active smokers (8% vs 51.3% of the nondiabetic study 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 HbA_{1c} values < 7.0%, which is the target generally recommended by the various clinical guidelines and consensuses,¹⁷ including the multidisciplinary consensus sponsored by the Spanish Diabetes Society.¹⁸ 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 study²⁰ 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 study²⁰, 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 HbA_{1c} < 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,²⁴ 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.^{3,15} 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.¹⁰ 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,³² particularly important in the diabetic population which, at LDL-C values that are not very high, 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.^{23,33} 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 HbA_{1c} 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 HbA_{1c} 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.³⁶

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 HbA_{1c} > 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

The ICP-Bypass study was funded by MSD (Merck Sharp & Dohme) Spain.

CONFLICTS OF INTERESTS

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

REFERENCES

- García MJ, McNamara PM, Gordon T, Kannel WB. Morbidity and mortality in diabetics in the Framingham population. Sixteen year follow-up study. *Diabetes*. 1974;23:105–11.
- Panzram G. Mortality and survival in type 2 (non-insulin-dependent) diabetes mellitus. *Diabetologia*. 1987;30:123–31.
- Perk J, De Backer G, Gohlke H, Graham I, Reiner Z, Verschuren M, et al. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). *Eur Heart J*. 2012;33:1635–701.
- Rydén L, Grant PJ, Anker SD, Berne C, Cosentino F, Danchin N, et al. ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD: The Task Force on diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and developed in collaboration with the European Association for the Study of Diabetes (EASD). *Eur Heart J*. 2013;34:3035–87.
- Grupo de Trabajo de la SEC para la guía de la ESC sobre diabetes, prediabetes y enfermedad cardiovascular, revisores expertos para la guía de la ESC sobre diabetes, prediabetes y enfermedad cardiovascular, Comité de Guías de la SEC. Comentarios a la guía de práctica clínica de la ESC sobre diabetes, prediabetes y enfermedad cardiovascular. *Rev Esp Cardiol*. 2014;67:87–93.
- Stamler J, Vaccaro O, Neaton JD, Wentworth D. Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. *Diabetes Care*. 1993;16:434–44.
- Mooradian AD. Dyslipidemia in type 2 diabetes mellitus. *Nat Clin Pract Endocrinol Metab*. 2009;5:150–9.
- Gaede P, Vedel P, Parving HH, Pedersen O. Intensified multifactorial intervention in patients with type 2 diabetes mellitus and microalbuminuria: the Steno type 2 randomised study. *Lancet*. 1999;353:617–22.
- Gaede P, Vedel P, Larsen N, Jensen GV, Parving HH, Pedersen O. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *N Engl J Med*. 2003;348:383–93.
- Cannon CP, Braunwald E, McCabe CH, Rader DJ, Rouleau JL, Belder R, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med*. 2004;350:1495–504.
- Cholesterol Treatment Trialists' Collaborators, Kearney PM, Blackwell L, Collins R, Keech A, Simes J, Peto R, et al. Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a meta-analysis. *Lancet*. 2008;371:117–25.
- Redon J, Mancia G, Sleight P, Schumacher H, Gao P, Pogue J, et al. Safety and efficacy of low blood pressures among patients with diabetes: subgroup analyses from the ONTARGET (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial). *J Am Coll Cardiol*. 2012;59:74–83.
- Skyler JS, Bergenstal R, Bonow RO, Buse J, Deedwania P, Gale EA, et al. Intensive glycemic control and the prevention of cardiovascular events: implications of the ACCORD, ADVANCE, and VA Diabetes Trials: a position statement of the American Diabetes Association and a Scientific Statement of the American College of Cardiology Foundation and the American Heart Association. *J Am Coll Cardiol*. 2009;53:298–304.
- González-Juanatey JR, Cordero A, Vitale GC, González-Timón B, Mazón P, Bertomeu V. Magnitud y características del riesgo residual lipídico en pacientes con antecedentes de revascularización coronaria: estudio ICP-Bypass. *Rev Esp Cardiol*. 2011;64:862–8.
- Reiner Z, Catapano AL, De Backer G, Graham I, Taskinen MR, Wiklund O, et al. European Association for Cardiovascular Prevention & Rehabilitation. ESC/EAS Guidelines for the management of dyslipidaemias: the Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). *Eur Heart J*. 2011;32:1769–818.
- Levey AS, Bosch JP, Lewis JB, Greene T, Rogers R, Roth D; Modification of Diet in Renal Disease Study Group. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. *Ann Intern Med*. 1999;130:461–70.
- Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, et al. Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care*. 2012;35:1364–79.
- Menéndez Torre E, Lafita Tejedor FJ, Artola Menéndez S, Millán Núñez-Cortés J, Alonso García A, Puig Domingo M, et al.; Grupo de Trabajo de Consensos y Guías Clínicas de la Sociedad Española de Diabetes. Recomendaciones para el tratamiento farmacológico de la hiperglucemia en la diabetes tipo 2. *Aten Primaria*. 2011;43:202. e1–9.
- Pérez A, Franch J, Cases A, González Juanatey JR, Conthe P, Gimeno E, et al. Relación del grado de control glucémico con las características de la diabetes y el tratamiento de la hiperglucemia en la diabetes tipo 2. Estudio DIABES. *Med Clin (Barc)*. 2012;138:505–11.
- Bonds DE, Miller ME, Bergenstal RM, Buse JB, Byington RP, Cutler JA, et al. The association between symptomatic, severe hypoglycaemia and mortality in type 2 diabetes: retrospective epidemiological analysis of the ACCORD study. *BMJ*. 2010;340:b4909.
- Desouza C, Salazar H, Cheong B, Murgo J, Fonseca V. Association of hypoglycemia and cardiac ischemia: a study based on continuous monitoring. *Diabetes Care*. 2003;26:1485–9.

22. Vidal Pardo JI, Pérez Castro TR, López Álvarez XL, García Soidán FJ, Santiago Pérez F M.I., Muñiz J. Quality of care of patients with type-2 diabetes in Galicia (NW Spain) [OBTEDIGA project]. *Int J Clin Pract.* 2011;65:1067–75.
23. Vinagre I, Mata-Cases M, Hermosilla E, Morros R, Fina F, Rosell M, et al. Control of glycemia and cardiovascular risk factors in patients with type 2 diabetes in primary care in Catalonia (Spain). *Diabetes Care.* 2012;35:774–9.
24. United Kingdom Prospective Diabetes Study Group. United Kingdom Prospective Diabetes Study 24: a 6-year, randomized, controlled trial comparing sulfonylurea, insulin, and metformin therapy in patients with newly diagnosed type 2 diabetes that could not be controlled with diet therapy. *Ann Intern Med.* 1998;128:165–75.
25. Evans JM, Ogston SA, Emslie-Smith A, Morris AD. Risk of mortality and adverse cardiovascular outcomes in type 2 diabetes: a comparison of patients treated with sulfonylureas and metformin. *Diabetologia.* 2006;49:930–6.
26. Hong J, Zhang Y, Lai S, Lv A, Su Q, Dong Y, et al. Effects of metformin versus glipizide on cardiovascular outcomes in patients with type 2 diabetes and coronary artery disease. *Diabetes Care.* 2013;36:1304–11.
27. Schramm TK, Gislason GH, Vaag A, Rasmussen JN, Folke F, Hansen ML, et al. Mortality and cardiovascular risk associated with different insulin secretagogues compared with metformin in type 2 diabetes, with or without a previous myocardial infarction: a nationwide study. *Eur Heart J.* 2011;32:1900–8.
28. Lipscombe LL, Gomes T, Levesque LE, Hux JE, Juurlink DN, Alter DA. Thiazolidinediones and cardiovascular outcomes in older patients with diabetes. *JAMA.* 2007;298:2634–43.
29. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *N Engl J Med.* 2007;356:2457–71.
30. Barnett A. DPP-4 inhibitors and their potential role in the management of type 2 diabetes. *Int J Clin Pract.* 2006;60:1454–70.
31. Pérez de Isla L, Saltijeral Cerezo A, Vitale G, González Timón B, Torres Do Rego A, Álvarez-Sala Walther LA. Prevalencia de colesterol LDL inadecuado en pacientes con enfermedad coronaria y/o diabetes mellitus tipo 2. *Rev Clin Esp.* 2012;212:475–81.
32. Whayne Jr TF. Statin myopathy: significant problem with minimal awareness by clinicians and no emphasis by clinical investigators. *Angiology.* 2011;62:415–21.
33. Cordero A, Bertomeu-Martínez V, Mazón P, Facila L, Bertomeu-González V, Cosin J, et al. Factores asociados a la falta de control de la hipertensión arterial en pacientes con y sin enfermedad cardiovascular. *Rev Esp Cardiol.* 2011;64:587–93.
34. American Diabetes Association. Standards of medical care in diabetes—2013. *Diabetes Care.* 2013;36 Suppl 1:S11–66.
35. Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Bohm M, et al. 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J.* 2013;34:2159–219.
36. Farkouh ME, Boden WE, Bittner V, Muratov V, Hartigan P, Ogdie M, et al. Risk factor control for coronary artery disease secondary prevention in large randomized trials. *J Am Coll Cardiol.* 2013;61:1607–15.