

ORIGINAL ARTICLE

Therapeutic approach to dyslipidemia and goal achievement in a Spanish population with type 2 diabetes without cardiovascular disease

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Received 7 September 2010; accepted 28 March 2011

KEYWORDS

Type 2 diabetes;
Dyslipidemia;
Cardiovascular risk;
Lipid goals;
Lipid-lowering drugs

Abstract

Objective: To assess the therapeutic approach and lipid goal achievement in a Spanish diabetic population at high cardiovascular risk.

Subjects and methods: A multicenter, descriptive, cross-sectional study consecutively recruited the first 10 patients who attended the primary care unit and had been seen in the 12 months prior to the study visit. Inclusion criteria were type 2 diabetes without cardiovascular disease, LDL cholesterol levels ≤ 160 mg/dL, triglyceride levels ≤ 600 mg/dL, and at least one of the following: retinopathy, albuminuria, current smoking habit, or hypertension.

Results: A total of 2412 patients were evaluated (aged 61.3 ± 8.3 years, 46.8% women, diabetes duration 8.6 ± 7.4 years). As compared to their previous visit (8.1 ± 5 months before), the proportion of patients who achieved LDL-C levels < 100 mg/dL (22.7% vs 28.6%), non-HDL-C levels < 130 mg/dL (27.7% vs 33.8%) and both goals (17.6% vs 22.1%) significantly increased at the time of assessment. Statins were the most widely prescribed lipid-lowering drugs (65.5%) and the lipid-lowering drug was changed from the previous visit in 38.7% of patients, drug dosage was increased in 17.3%, and another drug was added in 5%.

Conclusion: The use of more potent statins and higher statin doses were the most commonly used therapeutic strategies for improving the control of dyslipidemia in patients with type 2 diabetes, but these changes were clearly inadequate to achieve lipid goals in most patients with type 2 diabetes.

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PALABRAS CLAVE

Diabetes tipo 2;
Dislipemia;
Riesgo cardiovascular;
Objetivos lipídicos;
Hipolipemiantes

Estrategia de tratamiento de la dislipemia y consecución de objetivos en la población española con diabetes tipo 2 sin enfermedad cardiovascular

Resumen

Objetivo: Evaluar la estrategia terapéutica y el grado de consecución de los objetivos lipídicos en la población española con diabetes y alto riesgo cardiovascular.

Sujetos y métodos: Estudio descriptivo, transversal y multicéntrico con inclusión mediante muestreo consecutivo de los 10 primeros pacientes que acudieron a consulta de Atención Primaria y que hubieran sido visitados durante los 12 meses previos al estudio. Se incluyeron pacientes con diabetes tipo 2 sin enfermedad cardiovascular, concentraciones de colesterol LDL (cLDL) ≤ 160 mg/dl y triglicéridos ≤ 600 mg/dl, y al menos uno de los siguientes: retinopatía, albuminuria, tabaquismo actual o hipertensión.

Resultados: Se evaluaron 2.412 pacientes (edad: $61,3 \pm 8,3$ años; 46,8% mujeres, duración de la diabetes de $8,6 \pm 7,4$ años). En comparación con la visita previa ($8,1 \pm 5$ meses antes), en el momento de la evaluación, la proporción de pacientes con cLDL < 100 mg/dl (22,7 vs 28,6%), c-noHDL < 130 mg/dl (27,7 vs 33,8%) y la combinación de ambos (17,6 vs 22,1%) aumentaron significativamente. Las estatinas eran los fármacos hipolipemiantes más prescritos (65,5%) y, desde la visita previa, en el 38,7% de los pacientes se cambió el fármaco hipolipemiente, en el 17,3% se aumentó la dosis y en un 5% se añadió otro fármaco.

Conclusión: La utilización de estatinas de mayor potencia y el incremento de la dosis es la estrategia terapéutica más utilizada para mejorar el control de la dislipemia en los pacientes con diabetes tipo 2, pero estos cambios resultan claramente insuficientes para alcanzar los objetivos lipídicos en la mayoría de los pacientes con diabetes tipo 2.

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Introduction

Diabetes is a disease with a major social and health impact, attributable to its high prevalence and morbidity and mortality particularly from cardiovascular disease (CVD). Diabetes is considered to be a coronary artery disease risk equivalent¹, and the association of diabetes with other cardiovascular risk factors (CVRFs) such as hypertension, dyslipidemia, and smoking causes a much higher risk of CVD than each risk factor alone². In addition, the benefit achieved with therapeutic measures indicated for cardiovascular prevention in diabetic patients is similar to the benefit seen in other populations with established cardiovascular disease³⁻⁷.

In patients with diabetes, dyslipidemia is characterized by moderate hypertriglyceridemia and low high density lipoprotein cholesterol (HDL-C) levels, while levels of low high density lipoprotein cholesterol (LDL-C) do not usually differ from those of the general population. However, LDL-C is the main CVRF in patients with diabetes⁸, and the level of evidence supporting the significance of LDL-C control in them^{3,9-12} is much higher than the data available regarding the control of triglycerides (TG), HDL-C, and hyperglycemia¹³⁻¹⁸. Despite this evidence and the fact that most recommendations give LDL-C levels < 100 mg/dL as the first goal for patients with diabetes, it is widely documented that the proportion of patients with type 2 diabetes who achieve lipid goals is very high¹⁹⁻²⁴.

The CARDS¹⁰ study was the first randomized, double-blind study with statins including patients with type 2 diabetes only. Its results conclusively showed the benefit of atorvastatin treatment and support statin therapy in

patients with type 2 diabetes and high CVR. Because of the impact of the results of that study on clinical practice in the diabetic population, the present study was undertaken in order to assess the treatment strategy and degree of goal achievement in a Spanish population with type 2 diabetes and with the characteristics of the CARDS study.

Patients and methods

Study design

The study was designed as a multicenter, descriptive, cross-sectional, non-interventional study of a population seen by primary care physicians from all over Spain. Physicians who participated voluntarily in the study had to include the first 10 patients attending their offices from the starting date of the study who had been seen during the 12 months prior to the visit and who met the inclusion criteria and none of the exclusion criteria. As this was a non-interventional study, data from the baseline visit reflected patient status at the time of selection for the study. Patients enrolled were subjects of both sexes with diagnosis of type 2 diabetes (medication intake and/or ADA criteria and/or WHO criteria), with ages ranging from 40 to 75 years, with no prior history of acute myocardial infarction (AMI), angina, coronary surgery, stroke/TIA (transient ischemic attack) or severe peripheral vascular disease, and at least one of the following: 1) arterial hypertension, defined as either the receiving of antihypertensive treatment or SBP ≥ 140 mmHg or DBP ≥ 90 mmHg on at least two consecutive occasions; 2) retinopathy, defined as any degree of prior retinopathy,

maculopathy, or photocoagulation; 3) microalbuminuria or macroalbuminuria, defined as a positive reactive strip result, or an albumin/creatinine ratio ≥ 30 mg/g (2.6 mg/mmol) or an albumin excretion ≥ 20 μ g/min in at least two consecutive occasions; 4) active smoking, regardless of the number of cigarettes/day; 5) LDL-C ≤ 160 mg/dL and triglycerides ≤ 600 mg/dL. Patients with secondary diabetes, arrhythmia treatment, or severe heart failure (class III or IV), HbA_{1c} > 12% at recruitment, active liver disease or transaminase (AST or ALT) levels ≥ 1.5 times the normal limit, severe renal impairment or nephrotic syndrome, plasma creatinine levels > 1.3 mg/dL or 150 μ mol/L or creatinine clearance < 60 mL/min (MDRD), CPK ≥ 3 times the normal limit, body mass index (BMI) > 35 kg/m², and alcoholism were excluded from the study.

Patients entered the study after reading the patient information sheet and giving their written informed consent.

Data collection and assessment criteria

The study was designed to collect all information at a single visit in the setting of standard clinical practice. Information was collected from the clinical history, patient interview, and physical examination. Demographic and anthropometric data (age, sex, height, weight, BMI, abdominal circumference), smoking status, and blood pressure were recorded for each recruited patient. Laboratory test data included: basal blood glucose (mg/dL), HbA_{1c} (%), creatinine (mg/dL), total cholesterol (TC) (mg/dL), triglycerides (TG) (mg/dL), LDL-C (mg/dL), HDL-C (mg/dL), and non-HDL-C (mg/dL), as well as liver enzymes and TSH when available. Data relating to diagnosis and the treatment of diabetes, dyslipidemia, and hypertension were also collected. Laboratory results were those obtained from the laboratory tests performed during the previous month or at the time of the visit. Data corresponding to the final visit and laboratory tests done during the previous year were also recorded.

In accordance with the Adult Treatment Panel III (ATP-III) criteria, levels of LDL-C < 100 mg/dL and non-HDL-C < 130 mg/dL were considered as lipid goals. Diabetes was considered to be well controlled when glycosylated hemoglobin (HbA_{1c}) was < 7%, and blood pressure was considered to be controlled if SBP and DBP values were less than 130 mmHg and 85 mmHg respectively. Obesity was defined as a BMI > 30 kg/m², and abdominal obesity as a waist circumference greater than 102 cm in males and 88 cm in females.

Variables from the laboratory tests performed in the previous month or at the time of the visit (current visit) were collected from a total of 2,412 patients. The results of the laboratory tests done during the previous year (prior visit) were also collected. The mean time between both laboratory tests was 8.1 ± 5 months.

Sample size calculation and statistical analysis

Sample size was calculated from the proportion of patients with controlled lipid levels according to the NCEP-ATP-III guidelines. With a sample size of 2,550 patients or greater, a two-tailed test with a 95% confidence interval, and using a

normal distribution for large samples, the observed percentage of patients achieving the therapeutic goals would have a $\pm 2\%$ precision from the expected 50%. A 50% expected prevalence of achievement of therapeutic goals was assumed. Finally, 2,541 patients were recruited. This sample size, with a 54.1% prevalence of patients with controlled total cholesterol, had a precision error of 2.0%.

The population used for analysis included all the selected patients who met all the inclusion criteria and none of the exclusion criteria.

Measures of central tendency and dispersion were performed for quantitative variables (including the 95% confidence interval), and absolute and relative frequencies were calculated for qualitative variables. The type of distribution of quantitative variables was studied, and their fit to a Gaussian distribution was assessed using a Kolmogorov-Smirnov test to check that they met the assumption of normality.

To see whether differences existed between the two separate groups, a Student's t test was used for quantitative variables, a Mann-Whitney's U test was used for quantitative variables not following a Gaussian distribution, and a Chi-square test or a Fisher's exact test was used for qualitative variables.

Statistical tests were performed with a 5% significance level and were two-sided. SAS version 8.2 statistical software was used for all statistical tests.

Results

A total of 297 physicians from all over Spain recruited 2,541 patients. Of these, 129 (5.1%) were excluded because they did not meet the screening criteria. A total of 2,412 (94.9%) subjects were therefore evaluable. Table 1 shows the clinical and biochemical characteristics of the study population (data are given as mean \pm standard deviation or as percentage). Obesity and abdominal obesity were found in 37.7% and 55.4% of patients respectively. Twenty percent of subjects were former smokers, and smokers smoked a mean of 20.0 ± 11.6 cigarettes/day. As regards hypertensive patients, age at diagnosis was 53.4 ± 9.5 years, and 96.2% of them were receiving antihypertensive drugs. Mean age at diagnosis of diabetes was 52.9 ± 9.7 years, mean known time since diabetes onset at study start was 8.6 ± 7.4 years, and 55% of patients had HbA_{1c} $\leq 7\%$. Treatment with oral hypoglycemic drugs was received by 87.1% of patients. The most commonly prescribed drug was metformin (in 61.1%), and 25% received insulin. In the overall study population, 13.4% had left ventricular hypertrophy, 18.3% albuminuria, and 17.3% a family history of early CVD. Among women, 83.2% were postmenopausal. Acetylsalicylic acid and clopidogrel were taken by 23.5% and 0.7% of patients respectively.

Characteristics and degree of control of dyslipidemia

Dyslipidemia had been diagnosed in 75.8% of patients. Mean age at diagnosis was 55.8 ± 8.9 years, and time from diagnosis of dyslipidemia to study start was 6 ± 5.4 years. Mean peak LDL-C and triglyceride levels recorded in the

Table 1 Clinical and biochemical characteristics of the 2,412 evaluated patients.

Age (years) (n = 2,412)	61.3 ± 8.3
Sex (% females) (n = 2,412)	46.8
BMI (kg/m ²) (n = 2,367)	29.2 ± 4.2
Waist circumference (cm) (n = 2,112)	98.1 ± 12.5
HBP (%) (n = 2,407)	74.6
Dyslipidemia (%) (n = 2,403)	75.8
Smoking (%) (n = 2,405)	22.1
Time since diabetes onset (years) (n = 2,112)	8.6 ± 7.4
Complications of diabetes (n = 2,412)	
Retinopathy (%)	15.4
Nephropathy (%)	8.9
Neuropathy (%)	5.6
Polyneuropathy (%)	3.9
HbA _{1c} (%) (n = 2,213)	6.9 ± 1.3
Total cholesterol (mg/dL) (n = 2,367)	198.1 ± 43.6
LDL-C (mg/dL) (n = 2,300)	119.7 ± 32.8
HDL-C (mg/dL) (n = 2,299)	50.4 ± 12.9
Triglycerides (mg/dL) (n = 2,334)	150.4 ± 80.2
TSH (mU/L) (n = 1,278)	2.0 ± 1.3
GOT (U/L) (n = 2,120)	25.8 ± 11.6
GPT (U/L) (n = 2,180)	28.4 ± 15

Table 2 Lipid-lowering treatment and mean dose prescribed at the assessment visit and the prior visit (8.1 ± 5 months before).

Treatment (n = 2,412)	Patients (%)	Mean dose (mg/day)
<i>Pre-assessment visit</i>		
Atorvastatin	22.0	21.2 ± 12.3
Simvastatin	21.5	23.1 ± 20.1
Pravastatin	8.0	20.4 ± 10.5
Fluvastatin	5.3	66.9 ± 22.1
Gemfibrozil	3.5	823.4 ± 265
Fenofibrate	3.1	171.9 ± 53.4
Lovastatin	2.7	24.5 ± 11.7
Ezetimibe	0.9	10.0 ± 0.0
Other	1.6	-
<i>Assessment visit</i>		
Atorvastatin	53.7	28.0 ± 15.9
Simvastatin	7.0	26.4 ± 30.9
Ezetimibe	4.2	10.3 ± 1.8
Fenofibrate	2.5	158.3 ± 34.9
Fluvastatin	2.4	73.5 ± 17.3
Pravastatin	2.0	34.0 ± 54.2
Gemfibrozil	1.4	847.3 ± 338.0
Omega fatty acids	1.1	1.725.3 ± 1.322.9
Other	0.1	-

clinical history of patients diagnosed with dyslipidemia were 173.2 ± 38.9 mg/dL and 231.4 ± 151.7 mg/dL respectively, while patients not diagnosed with dyslipidemia had lower levels (LDL-C 122.7 ± 30.4 mg/dL and triglycerides 150.5 ± 108.9 mg/dL, $p < 0.0001$).

At the time of evaluation, 83.8% of patients followed a low fat diet, and 65.5%, 4.2%, and 4.0% were being treated with statins, ezetimibe, and fibrates respectively. The most commonly used lipid-lowering drug was atorvastatin (53.7%), given at a mean dose of 28.0 ± 15.9 mg/day (Table 2). Table 1 shows the mean levels found in the laboratory tests performed in the previous month or at the study visit. Total cholesterol levels < 200 mg/dL were found in 54.1% of patients, LDL-C levels < 100 mg/dL in 28.6%, HDL-C levels

> 40 mg/dL in 82.0%, non-HDL-C levels < 130 mg/dL in 33.8%, and triglyceride levels < 150 mg/dL in 56.5%.

Changes from prior visit in dyslipidemia treatment and control

Figure 1 shows changes in lipid-lowering drug treatment from the prior visit and laboratory tests, occurring 8.1 ± 5 months before the study visit. The lipid-lowering drug was changed in 38.7% of patients, dosage was increased in 17.3%, and another drug was added in 5% of patients. Main changes were increased use (22.0% vs 53.7%) and dose (21 ± 12 mg/day vs 28 ± 16 mg/day) of atorvastatin, and increased use of

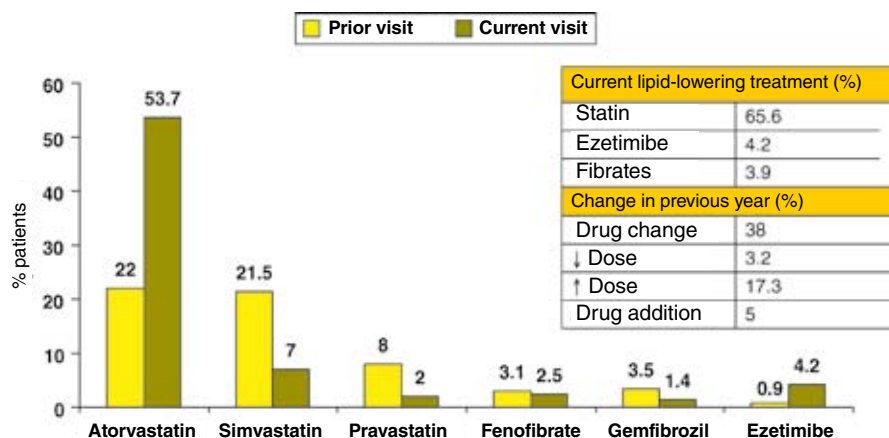


Figure 1 Main changes in lipid-lowering treatment from the prior visit, occurring 8.1 ± 5 months before the (current) study visit.

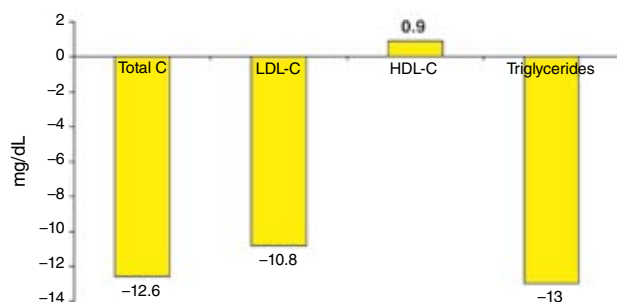


Figure 2 Changes in lipid levels from the visit made 8.1 ± 5 months before the study (prior visit) to the study visit (current visit).

ezetimibe (0.9% vs 4.2%). These changes were associated with decreased total cholesterol, LDL-C, and triglyceride levels (Fig. 2). Higher proportions of patients with LDL-C < 100 mg/dL (22.7% vs 28.6%), non-HDL-C < 130 mg/dL (27.7% vs 33.8%) and with LDL-C < 100 mg/dL and non-HDL-C < 130 mg/dL (17.6% vs 22.1%) were seen, while there were no changes in the proportions of patients with HDL-C > 40 mg/dL (80.5% vs 82.0%) and TG < 150 mg/dL (56.9% vs 56.5%) (Fig. 3).

Those patients who maintained LDL-C levels > 100 mg/dL differed from those achieving LDL-C levels < 100 mg/dL in proportion to the documented diagnosis of dyslipidemia (78% vs 73%; $p < 0.01$) and in peak LDL-C levels (177 ± 38 vs 164 ± 40 mg/dL; $p < 0.0001$), but not in HDL-C and triglyceride levels. When compared to patients who achieved this combined goal, patients with LDL-C > 100 mg/dL and non-HDL-C > 130 mg/dL had, in addition to higher peak LDL-C levels, higher peak triglyceride levels (238 ± 159 vs 205 ± 114 mg/dL; $p < 0.02$) and lower peak HDL-C levels (52 ± 19 vs 55 ± 20 mg/dL; $p < 0.02$). Among those patients who met and did not meet the combined goal, the proportions of patients treated with atorvastatin were 55% vs 50% and the proportions of those treated with fibrates and omega-3 fatty acids were 5.4% and 3.7% respectively.

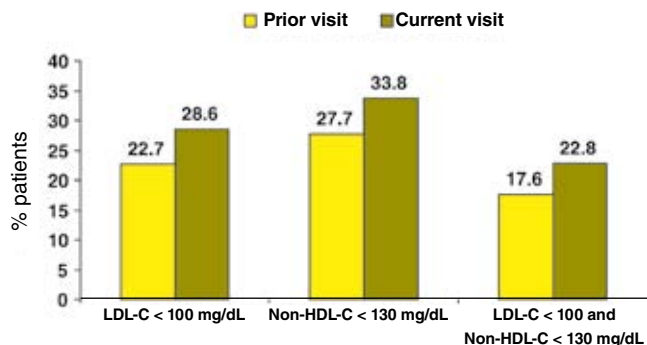


Figure 3 Proportion of patients achieving the different lipid goals at the visit made 8.1 ± 5 months before the study (prior visit) and at study visit (current visit).

Discussion

This study, conducted on a large sample of patients with type 2 diabetes seen in primary care, assessed the treatment strategy and degree of goal achievement in a Spanish population with type 2 diabetes and the characteristics of the CARDS study¹⁰. They were therefore patients with no cardiovascular disease but with a high cardiovascular risk in whom the efficacy of lipid-lowering treatment has been conclusively shown. Despite this, the results of this study show that the therapeutic goals recommended by the ATP III¹ are achieved in less than one third of patients. Such a degree of goal achievement is very modest and contrasts with the high prevalence of dyslipidemia and the fact that 70% of the patients were prescribed lipid-lowering drug treatment. This shows the difficulty in achieving lipid goals and faithfully reflects the actual clinical situation of inadequate treatment strategies and the undertreatment of dyslipidemia in patients with type 2 diabetes.

The benefits of statins for both primary and secondary prevention have been shown in diabetes²⁵. In patients with no prior cardiovascular disease, the CARDS study¹⁰ showed that atorvastatin 10 mg/day decreased LDL-C and TG levels by 40% and 19% respectively. Risks of a major cardiovascular event, acute coronary syndrome, the need for myocardial revascularization, and stroke were decreased by 37%, 36%, 31%, and 48% respectively. The number of patients who needed treatment to prevent a major coronary event was 38. The HPS study⁵ also showed that treatment with simvastatin 40 mg/day decreased by 33% the risk of cardiovascular disease. Thus, these two studies clearly showed statin therapy to be highly effective for the primary prevention of cardiovascular disease in patients with type 2 diabetes. Secondary prevention studies such as PROVE-IT²⁶ and TNT²⁷ also showed that more intensive statin therapy resulted in a greater reduction than less intensive therapy in patients with type 2 diabetes mellitus. Despite these data and the availability of clinical guidelines recommending the achievement of a LDL-C goal < 100 mg/dL in patients with type 2 diabetes and no cardiovascular disease, the results of this and other studies¹⁹⁻²¹ show that a very low proportion of patients achieve these lipid goals.

Several studies²⁸⁻³² have shown the difficulty of controlling CVRFs, particularly in the patient subgroup at high cardiovascular risk. In the EUROASPIRE I, II, and III studies²⁹, the proportion of patients with total cholesterol levels > 174 mg/dL decreased from 94.5% in 1991-1995 to 46.2% in 2006-2007, in parallel with an increased use of statins. Although this improvement was significant, almost half the patients did not achieve the recommended goals. This is also shown in several studies conducted in Spain³⁰⁻³² where the proportion of patients who achieved the goals was less than 50%.

In the present study, the lipid-lowering treatment received by most patients at the visit prior to the study visit was a statin in low-middle equipotent doses. The main change consisted of an increase in the equipotent dose of statin, either by increasing the dose or by using a more potent preparation. However, despite these positive changes in lipid-lowering treatment, and as occurred in other studies^{20,21}, treatment continued to be clearly suboptimal, as it did not achieve a relevant increase in the proportion of

patients achieving their therapeutic goals. The potential causes contributing to this difficulty in goal achievement are multiple and include aspects related to adherence^{33,34}, but also to the treatment strategy used. This is particularly relevant in conditions such as dyslipidemia and other chronic diseases where therapeutic inertia is widely documented and related to undertreatment³⁵. Statin preparations and doses recorded in the visit prior to the study visit suggest that the initial equipotent dose was predominantly low-middle in most patients. This strategy, which does not usually take into account baseline LDL-C levels and the reduction required to achieve the goals, is usual, and combined with clinical inertia with regard to a lack of adequate subsequent dose titration, has been related to difficulties in goal achievement^{20,36}. There is clear evidence showing the benefits to be derived from statin treatment in patients with diabetes, showing that the use of high doses is not associated with a significant increase in side effects³⁷, and demonstrating that a more intensive use of statin monotherapy achieves its goals in a substantial proportion of patients³⁸. All of this suggests that the most adequate strategy is to start treatment with a statin at the dose required to achieve the proposed LDL-C goal³⁹. Subsequently, if the goal is not achieved and knowing that an additional 6% reduction in LDL-C is achieved when the dose is doubled, the statin dose may be increased or an intestinal cholesterol absorption inhibitor or nicotinic acid may be added.

Even in studies where aggressive LDL-C reductions are achieved, a residual cardiovascular risk persists, which is particularly high in diabetic patients and has been related to low HDL-C levels and high triglyceride levels⁴⁰⁻⁴². In such situations, the calculation of non-HDL-C allows atherogenic cholesterol to be estimated and this is considered a secondary therapeutic goal after LDL-C goals in patients with high triglyceride levels (≥ 200 mg/dL)¹ have been achieved. In the present study, 33.8% of patients had non-HDL-C levels < 130 mg/dL, 56.5% had triglyceride levels < 150 mg/dL, and only 22.1% reached the combined goal of LDL-C < 100 mg/dL and non-HDL-C < 130 mg/dL. In these cases, in order to correct the existing impairments and achieve non-HDL-C goals, it was often necessary to add a fibrate, if hypertriglyceridemia was the most important disorder, or nicotinic acid if low HDL-C levels were the predominant problem^{43,44}. However, the use of lipid-lowering drugs other than statins was rare, and the use of fibrates even decreased in the year prior to evaluation. This is a normal situation in clinical practice⁴⁵ and is probably related to excess fear concerning the adverse effects of a combination of lipid-lowering agents and to a lack of evidence that this will prevent cardiovascular events.

The study had the limitation that a non-randomized physician sample was used, but we think this bias was minimized by its distribution throughout all the Spanish regions and the selection of a retrospective design using consecutive patients, which precluded the possibility of changing standard practice or prescription. In addition, the data from this study do not disagree with data reported in the literature regarding lipid levels and treatment schemes based on the use of the different statins at national level. This, in our opinion, supports the representativeness of the study sample.

To sum up, despite the wide evidence available concerning the efficacy of lipid-lowering treatment and goal achievement in patients with type 2 diabetes, most patients with diabetes and high cardiovascular risk do not achieve the goals proposed by the ATP III. The changes made in the year prior to evaluation consisted almost entirely of an increase in the equipotent statin dose and were clearly inadequate to achieve the therapeutic goals. These data suggest the need to improve our therapeutic strategy regarding dyslipidemia in patients with diabetes so that we can achieve the recommended goals in most patients and, in the setting of a multifactorial and global approach to the different cardiovascular risk factors, contribute to a reduction in the main cause of morbidity and mortality in the population with type 2 diabetes.

Conflict of interest

This study was supported by Pfizer. Dr. A. Pérez has received lecture and/or consultation fees from Pfizer, Merck Sharp & Dohme, Schering-Plough, and Solvay Pharma; Dr. C. González has received lecture fees from Pfizer, and Dr. M.A. Hernández-Presa and Dr. J. Chaves are Pfizer employees.

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