

Original article

Prevalence and Characteristics of Lipid Abnormalities in Patients Treated With Statins in Primary and Secondary Prevention in Spain. DYSIS-Spain Study

José R. González-Juanatey,^{a,*} Jesús Millán,^b Eduardo Alegría,^c Carlos Guijarro,^d Jose V. Lozano,^e and Gustavo C. Vitale^f

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

^b Servicio de Medicina Interna, Hospital General Universitario Gregorio Marañón, Madrid, Spain

^c Servicio de Cardiología, Clínica Universitaria de Navarra, Pamplona, Navarra, Spain

^d Servicio de Medicina Interna, Fundación Hospital Alcorcón, Alcorcón, Madrid, Spain

^e Centro de Salud Serrera 2, Valencia, Spain

^f Departamento Médico, MSD España, Merck, Sharp and Dohme, Merck & Co., Barcelona, Spain

ARTICLE INFO

Article history:

Received 18 May 2010

Accepted 22 October 2010

Available online 15 March 2011

Keywords:

Cardiovascular prevention

DYSIS

High-density lipoprotein cholesterol

Low-density lipoprotein cholesterol

Triglycerides

ABSTRACT

Introduction and objectives: Patients at high risk of suffering cardiovascular events require medical treatment to optimize their lipid profile. The present analysis evaluates the lipid profiles among Spanish patients receiving statin therapy in the international DYSIS study.

Methods: DYSIS is a multinational cross-sectional study carried out in Canada and Europe (n = 22,063). In Spain, 3710 patients treated with statin therapy for at least 3 months were included. We compared data relating to demographic parameters and cardiovascular risk profile.

Results: Complete lipid profiles of 3617 patients were recorded. Regarding the high cardiovascular risk patients with complete lipid profiles (n = 2273), 78.9% had a disorder in at least one of the three main lipid parameters: low-density lipoprotein cholesterol (LDLc), high-density lipoprotein cholesterol (HDLc) and/or triglycerides. LDLc was not within target levels in 61.4% of these high risk patients; HDLc was abnormal in 25.3%, and triglycerides were elevated in 37.8%. Overall, LDLc was outside the target range in 63.1%, and 20.7% (n = 668) of those treated with statins were normal for all parameters.

Conclusions: Most patients in this study who received statin therapy, particularly those at high cardiovascular risk, were not at the normal lipid parameter levels according to cardiovascular guidelines. Although it is necessary to wait for the final results of current studies on the use of combined lipid-modifying treatments, the management of lipid levels in Spain still has potential for improvement.

© 2010 Sociedad Española de Cardiología. Published by Elsevier España, S.L. All rights reserved.

Prevalencia y características de la dislipemia en pacientes en prevención primaria y secundaria tratados con estatinas en España. Estudio DYSIS-España

RESUMEN

Introducción y objetivos: Los pacientes con alto riesgo de sufrir eventos cardiovasculares requieren tratamiento médico para optimizar su perfil lipídico. Dentro del estudio internacional DYSIS, se evaluaron las alteraciones del perfil lipídico de pacientes tratados con estatinas en España.

Métodos: DYSIS es un estudio multinacional y transversal llevado a cabo en Canadá y Europa (n = 22.063). En España se incluyó a 3.710 pacientes tratados con estatinas durante al menos 3 meses. Se compararon los datos demográficos y el perfil de riesgo cardiovascular.

Resultados: Se obtuvo el perfil lipídico de 3.617 pacientes. De los pacientes con alto riesgo cardiovascular con perfil lipídico completo (n = 2.273), el 78,9% presentaba concentraciones alteradas de alguno de los tres parámetros lipídicos principales: colesterol de las lipoproteínas de baja densidad (cLDL), colesterol de las lipoproteínas de alta densidad (cHDL) y/o triglicéridos. Dentro de este grupo, el cLDL no se encontraba en objetivo en el 61,4%, el cHDL estaba por debajo de lo normal en el 25,3% y los triglicéridos estaban elevados en el 37,8%. En general, el cLDL se encontraba fuera de objetivo en el 63,1% y sólo el 20,7% (n = 668) presentaba concentraciones normales o las recomendadas para los tres parámetros.

Conclusiones: La mayoría de los pacientes tratados con estatinas, sobre todo aquellos con alto riesgo cardiovascular, no alcanzan los objetivos propuestos por las guías para los parámetros lipídicos. Aunque se deberá esperar a los resultados finales de estudios actuales sobre el uso de tratamientos combinados modificadores de lípidos, el manejo de los lípidos en España es mejorable.

© 2010 Sociedad Española de Cardiología. Publicado por Elsevier España, S.L. Todos los derechos reservados.

Palabras clave:

Prevención cardiovascular

DYSIS

Colesterol unido a lipoproteínas

de alta densidad

Colesterol unido a lipoproteínas

de baja densidad

Triglicéridos

* Corresponding author: Servicio de Cardiología y UCC, Hospital Clínico Universitario, Travesía de A Choupana s/n, 15706 Santiago de Compostela, A Coruña, Spain.

E-mail address: jose.ramon.gonzalez.juanatey@sergas.es (J.R. González-Juanatey).

Abbreviations

DM: diabetes mellitus
 IC: ischemic cardiopathy
 HDLc: high-density lipoprotein cholesterol
 LDLc: low-density lipoprotein cholesterol
 TC: total cholesterol
 TG: triglycerides

INTRODUCTION

Lipid metabolism disorders are one of the main determinants of cardiovascular risk.¹ A significant proportion of patients, particularly those with ischemic cardiopathy (IC), metabolic syndrome, type 2 diabetes mellitus (DM), and diverse risk factors, have complex lipid disorders which are not limited to high levels of low-density lipoprotein cholesterol (LDLc) or total cholesterol (TC). These patients also have reduced levels of high density lipoprotein cholesterol (HDLc) and/or high triglyceride (TG) levels.^{2–4} The INTERHEART⁵ study showed the central role of dyslipidemia as one of the determinants of cardiovascular risk, mainly from myocardial infarction. In our field, Medrano et al⁶ estimated that dyslipidemia is responsible for 20% of coronary disease cases.

Many clinical trials have shown that treatment aimed at reducing LDLc, especially statins, effectively reduces the risk of cardiovascular disease in patients with a high risk of suffering vascular disease, in particular myocardial infarction.^{7–9} However, even with appropriate levels of LDLc, there is a high residual risk of atherothrombotic complications related to low HDLc and high TG. According to the recommendations of the United States National Cholesterol Education Program (NCEP-ATP III), drug treatment should be started to correct these lipid disorders, especially in high risk cases.¹⁰ Epidemiological studies have shown that a 1% reduction in HDLc values leads to a 2% to 3% increase in the risk of IC. Those studies agreed that low HDLc levels represent an independent risk factor for IC.^{11,12} The United Kingdom Prospective Diabetes Study (UKPDS) showed that an increase in HDLc of 4 mg/dL is associated with a 15% decrease in the number of cardiovascular events.¹³

In Spain, several epidemiological studies have analyzed the prevalence of lipid disorders.^{14,15} However, there is very little information on persistent dyslipidemia in patients treated with statins.

The present study, the Dyslipidemia International Survey-Spain (DYSIS-Spain), is part of a multinational cross-sectional cohort study (DYSIS) carried out in 11 European countries and Canada,¹⁶ with the following aims:

- To estimate the prevalence of persistent lipid disorders (not meeting the target levels of LDLc, TC, HDLc, and TG) in patients treated with statins.
- To describe the cardiovascular risk profile and lipid-lowering treatment of different groups: patients with IC, DM, and patients with a high cardiovascular risk.
- To investigate the predictors of persistent lipid abnormalities.

METHODS

Study Design

Data were analyzed from the DYSIS-Spain study, which included a total of 22,063 patients. DYSIS-Spain is a multi-center,

non-interventional, observational study performed in 477 Spanish healthcare centers (3710 patients; lipid profile was obtained from 3617 patients and the complete profile from 3225). Only data that was in the patients' medical records was obtained, and the management of participating patients was not changed. The protocol was approved by the Galicia Ethics Committee. All patients gave their written consent before participating in the study. The protection of personal data was guaranteed and randomized audits were carried out in 1% of the centers to check the data.

Doctors

Doctors were chosen from outpatient departments that included a mean of 7 consecutive patients in the study who met the eligibility criteria. The specialty of the participating doctors was recorded (primary care, internists, cardiologists and endocrinologists).

Patients

Patients were included who were over 45 years of age, had been treated with statins for at least 3 months at the time of the medical visit, and whose lipid profile (for at least one of the 3 lipid parameters) had been documented within the previous 6 months. The data requested in the case report form were obtained from the clinical examination or a review of patient medical records. The data were recorded in a single medical visit. Given the study's observational design, safety assessments were not carried out as part of the protocol.

Documented Parameters

Participating doctors were asked to document the following parameters during the medical visit: sex, age, race, weight, height, and waist circumference. Lipid parameters were taken from the most recent lipid analysis performed during the last 6 months and when the patient had been under treatment with statins for at least 3 months. The following parameters were collected: TC, LDLc, HDLc and TG; in addition, risk factors were documented and a record was made of whether the doctor was from primary care, internal medicine, cardiology, or endocrinology. Patients were defined as diabetic if they had been previously diagnosed, had glycemia ≥ 126 mg/dL in the last available analysis, or if they were being treated with antidiabetic drugs and/or insulin. High fasting glycemia was defined as glycemia ≥ 100 mg/dL in the last available analysis. Metabolic syndrome was defined in accordance with the definition of the International Diabetes Federation.¹⁷ Waist circumference was measured in a standing position, at the mid-point between the iliac crest and the last rib on the mid-axillary line (cut-off values: ≥ 102 cm for men and ≥ 88 cm for women). Patients were defined as hypertensive if they had been previously diagnosed, were under anti-hypertension treatment, or had a blood pressure $\geq 140/90$ mmHg. Current smokers were those who smoked at that time or had given up smoking within the last year, and ex-smokers were those who had given up smoking over 1 year earlier. Patients were considered to have a family history of premature cardiovascular disease if any first-degree relative (parents, brothers or sisters) had suffered early atherosclerotic cardiovascular disease (<55 years old in men and <65 years old in women). Patients were considered to have a sedentary lifestyle if they did not perform regular physical activity (walking for a minimum of 20 to 30 min 3 to 4 days per week, or equivalent).

Alcohol consumption was recorded as the mean number of units of alcohol per week.

Patient history of cardiovascular disease was recorded: IC (previous myocardial infarction or coronary by-pass, surgery, or percutaneous angioplasty), cerebrovascular disease (previous stroke or transient ischemic attack), peripheral arteriopathy (intermittent claudication with or without revascularization), chronic heart failure (class II-IV of the New York Heart Association [NYHA]).

Medication

The information regarding chronic medication focused on treatment with statins. The indication was recorded, along with the name of the drug, daily dose taken at the time of the medical visit, and when the last lipid analysis was performed. Furthermore, other lipid-modifying treatments (cholesterol absorption inhibitors, bile acid sequestrants, fibrates, and nicotinic acid) taken at the time of the visit and before the last lipid analysis were recorded. Treatment with anti-hypertensive, anti-diabetic and antiplatelet drugs was also registered.

Data Analysis

The categorical variables were presented as absolute values and percentages, the continuous variables as means (standard deviation) or medians [interquartile interval].

A multivariate regression analysis was performed to detect predictors of abnormal LDLc, HDLc and TG values. The odds ratio (OR) was adjusted for age, sex, family history of premature cardiovascular disease, tobacco smoking, sedentary lifestyle, alcohol consumption >2 units/week, body mass index ≥ 30 (obesity), waist circumference >102 cm in men and >88 cm in women, hypertension, DM, IC, cerebrovascular disease, heart failure, peripheral arteriopathy, blood pressure $\geq 140/90$ mmHg, equivalent to simvastatin 20–40 mg/day compared with simvastatin 10 mg/day, equivalent to simvastatin ≥ 80 mg/day compared with simvastatin 10 mg/day, ezetimibe, and the doctor's medical specialty. A retrospective selection was used ($\alpha=.05$) to identify the parameters associated with the dependent variables. All the statistical analyses were two-tailed and significance was set at $P < .05$. Analysis was carried out with the SAS 9.1 software.

Due to the descriptive aim of the study, a formal test of the hypothesis was not performed. The sub-groups were defined before the study: patients only with IC, only with DM, with DM or IC but without cardiovascular risk $\geq 5\%$ according to their European Society of Cardiology (ESC) SCORE,¹ and patients without DM or IC but with a cardiovascular risk $< 5\%$. A post-hoc analysis was performed to assess the differences in patient characteristics and in treatment between the sub-groups.

RESULTS

Of the 477 participating doctors, 68.8% were from primary care, and 31.2% were specialists (internists, cardiologists and endocrinologists).

Patient Characteristics and Level of Risk

The baseline characteristics are shown in Table 1. Of the 3710 patients, 98.4% were Caucasian, and the mean age was 64.8 years. There were slightly more men (52.7%) and a high prevalence of

cardiovascular risk factors. The women (47.2%) were older, and had a higher prevalence of obesity and metabolic syndrome.

Most of the patients (71.2%, with a higher frequency of men) had a risk of $\geq 5\%$ according to the ESC SCORE, and had been diagnosed with clinical cardiovascular disease or DM.

Treatment

Nearly half of the patients (45.7%) were receiving chronic treatment with atorvastatin. The proportion of other statins used is shown in Figure 1A. Most received a moderate-potency statin (equivalent to simvastatin 20–40 mg/day) (Fig. 1B). Regarding the use of other lipid-lowering drugs, 17.4% were taking ezetimibe, 3.6% fibrates, 0.1% nicotinic acid, and 0.3% resins.

Lipid Disorders

The lipid parameters were obtained from 3617 patients who had one or more parameters in their medical records; a complete lipid profile was obtained from 3225 of these patients. Despite statin treatment, 68% did not meet TC targets (< 200 mg/dL), and 63.1% did not meet LDLc targets (< 100 mg/dL in high-risk patients and < 120 mg/dL in low-risk patients). High TG levels (≥ 150 mg/dL) were recorded in 36.8% and low HDLc levels (< 40 mg/dL in men and < 50 mg/dL in women) in 23.2% (Table 2).

Table 1
Patient Characteristics

<i>Patients</i>	3710
<i>Age (years) (media $\pm$ DE)^a</i>	64.8 (10.1)
<i>Caucasian (%)</i>	98.4
<i>Family history of premature IC (%)</i>	19.9
<i>Smokers (%)</i>	18.6
<i>Hypertension (%)</i>	69
SBP (mm Hg) (media $\pm$ DE) ^b	134.2 (14.5)
DBP (mm Hg) (media $\pm$ DE) ^c	78.2 (9.6)
<i>Waist circumference (cm) (media $\pm$ DE)^d</i>	98.3 (12.4)
<i>BMI (kg/m²) (media $\pm$ DE)</i>	28.9 (4.5)
<i>BMI ≥ 30 (kg/m²) (media $\pm$ DE)</i>	35.1
<i>Metabolic syndrome (IDF) (%)</i>	61.2
<i>ESC risk level</i>	
High risk (CVD, diabetes and/or risk SCORE $\geq 5\%$) (%)	71.2
CVD (%)	35.7
Diabetes mellitus	39
Risk SCORE $\geq 5\%$ (%) without CVD and diabetes	11.3
Risk SCORE $< 5\%$ (%) without CVD and diabetes	28.8
<i>Lipid parameters</i>	
LDLc (mg/dL) (media $\pm$ DE) ^e	119.6 (38.6)
HDLc (mg/dL) (media $\pm$ DE) ^f	50.2 (15.4)
Total cholesterol (mg/dL) (media $\pm$ DE) ^g	200.7 (46.3)
Triglycerides (mg/dL) (mediana [RIQ]) ^h	124.6 [98–178]

BMI, body mass index; IC, ischemic cardiopathy; CVD, cardiovascular disease; DBP, diastolic blood pressure; ESC, European Society of Cardiology; HDLc, high density lipoprotein cholesterol; IDF, International Diabetes Federation; LDLc, low density lipoprotein cholesterol; SBP, systolic blood pressure; RIQ, interquartile interval.

^a Data available from 3654 patients.

^b Data available from 3702 patients.

^c Data available from 3702 patients.

^d Data available from 3535 patients.

^e Data available from 3504 patients.

^f Data available from 3496 patients.

^g Data available from 3681 patients.

^h Data available from 3612 patients.

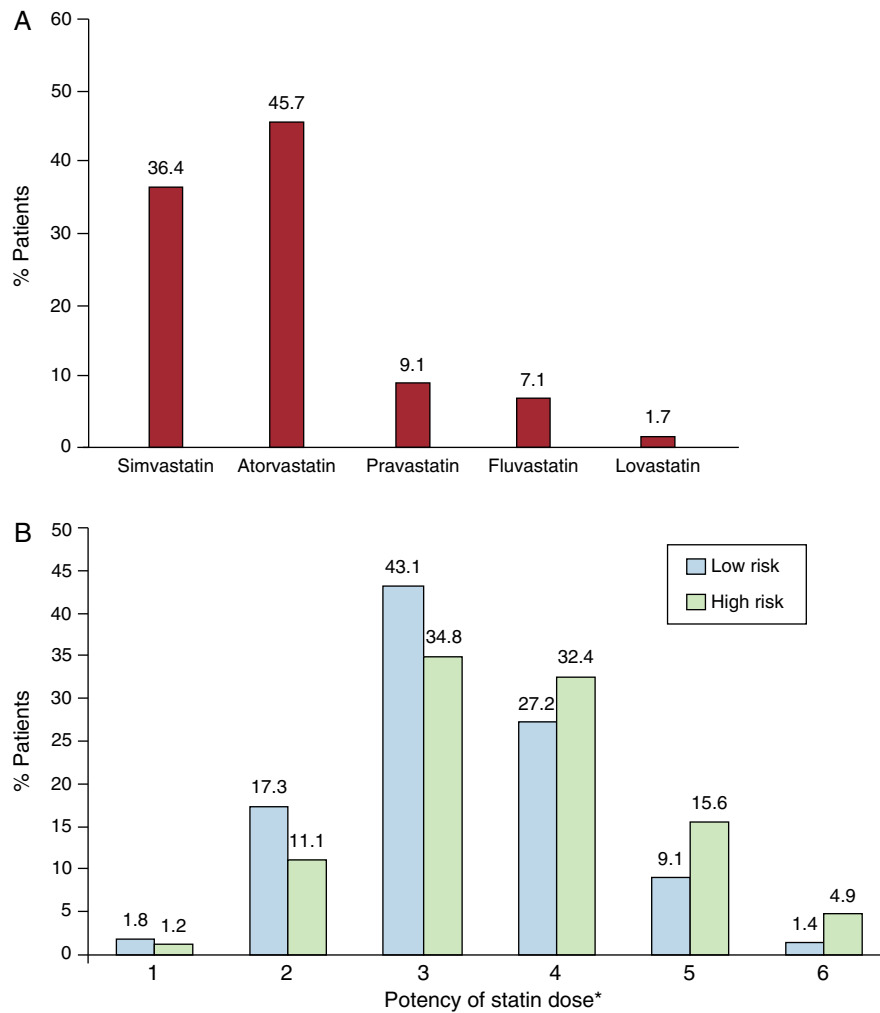


Figure 1. A: percentage of patients receiving baseline treatment with different types of statins. B: potency of the statin dose according to the patients' cardiovascular risk. *Statin dose: potency 1 is equivalent to simvastatin 5 mg/day; potency 2: simvastatin 10 mg/day; potency 3: simvastatin 20 mg/day; potency 4: simvastatin 40 mg/day; potency 5: simvastatin 80 mg/day; and potency 6: simvastatin ≥ 160 mg/day.

There was a high frequency of combined disorders: 35.1% had 2 or 3 simultaneous lipid disorders, while 8.2% had abnormal levels in the 3 lipid parameters (Fig. 2A).

Of the 2,273 high-risk patients for whom a complete lipid profile was available, 78.9% had abnormal concentrations of one of the 3 main lipid parameters. Figure 2 summarizes the individual and combined lipid abnormalities of this group (high risk with at least one abnormal level of the lipid parameters). In this group, 61.4% did not achieve the target levels of LDLc, 25.3% were not within the target levels of HDLc, and 37.8% had high TG. As for combined lipid disorders, non-target levels of LDLc, low HDLc, and/or high TG were found in 30.8% of the patients, and target LDLc, low HDLc and/or high TG levels were detected in 17.6% (Fig. 2B).

When analyzed by risk sub-groups, the patients with cardiovascular disease showed a better control of lipid parameters, except for HDLc, than the diabetic group or those with an ESC SCORE $\geq 5\%$ (Table 2).

Among the diabetic patients, 33.1% showed no lipid abnormalities, 49% had non-target levels of LDLc with normal concentrations of HDLc and TG, 32.7% had non-target LDLc, low HDLc and/or high TG, and 20.2% had target LDLc and/or low HDLc and/or high TG. Among the patients with IC but without DM, 48.5% showed no

lipid alterations, 39.5% had non-target levels of LDLc with normal concentrations of HDLc and TG, 21.4% had non-target LDLc, low HDLc and/or high TG, and 23% had target LDLc and/or low HDLc and/or high TG (Fig. 3).

Predictors of Lipid Abnormalities

The multivariate analysis identified several variables that were independently associated with abnormal lipid levels (Table 3). Being female, a family history of premature cardiovascular disease, tobacco smoking, a sedentary lifestyle, high alcohol consumption, and blood pressure $>140/90$ mm Hg were independently associated with having non-target levels of LDLc. On the other hand, a history of IC, cerebrovascular disease, and being seen by a specialist were associated with a better control of LDLc and inadequate control of HDLc. Treatment with high doses of statins was associated with a greater control of LDLc levels and low HDLc values. DM was associated with a worse control of HDLc and TG. A family history of premature cardiovascular disease, a sedentary lifestyle, and tobacco smoking were independent risk factors for having abnormal levels in the 3 lipid parameters.

Table 2

Lipid Abnormalities (Percentage of Patients) According to the European Society of Cardiology in All the Patients

	Total patients n = 3617	High risk ^a n = 2574	CVD n = 1321	Diabetes without CVD n = 846	ESC-SCORE $\geq 5\%$ n = 407	ESC-SCORE $< 5\%$ n = 1043
TC outside target levels ^b	68	65.5	56.4	70.2	85.3	74.1
LDLc outside target levels ^c	63.1	60.7	51.3	64.7	83.2	68.9
Low HDLc (< 40 mg/dL [men] and 50 mg/dL [women]) ^d	23.2	25.7	30.9	23.6	13.8	17
High TG (> 150 mg/dL) ^e	36.8	38.1	36.1	42.1	36.3	33.7

CVD, cardiovascular disease; ESC: *European Society of Cardiology*; HDLc, high-density lipoprotein cholesterol; LDLc, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides.

^a High risk: CVD, diabetes, and/or ESC-risk SCORE $\geq 5\%$.

^b TC ≥ 200 mg/dL in patients with ESC-risk SCORE $< 5\%$, and TC ≥ 180 mg/dL in patients with ESC-risk SCORE $\geq 5\%$, diabetes and/or CVD; data available for 3594 patients.

^c LDLc ≥ 115 mg/dL in patients with ESC risk SCORE $< 5\%$, and LDLc ≥ 100 mg/dL in patients with ESC risk SCORE $\geq 5\%$, diabetes and/or CVD; data available from 3420 patients.

^d Data available from 3346 patients.

^e Data available from 3525 patients.

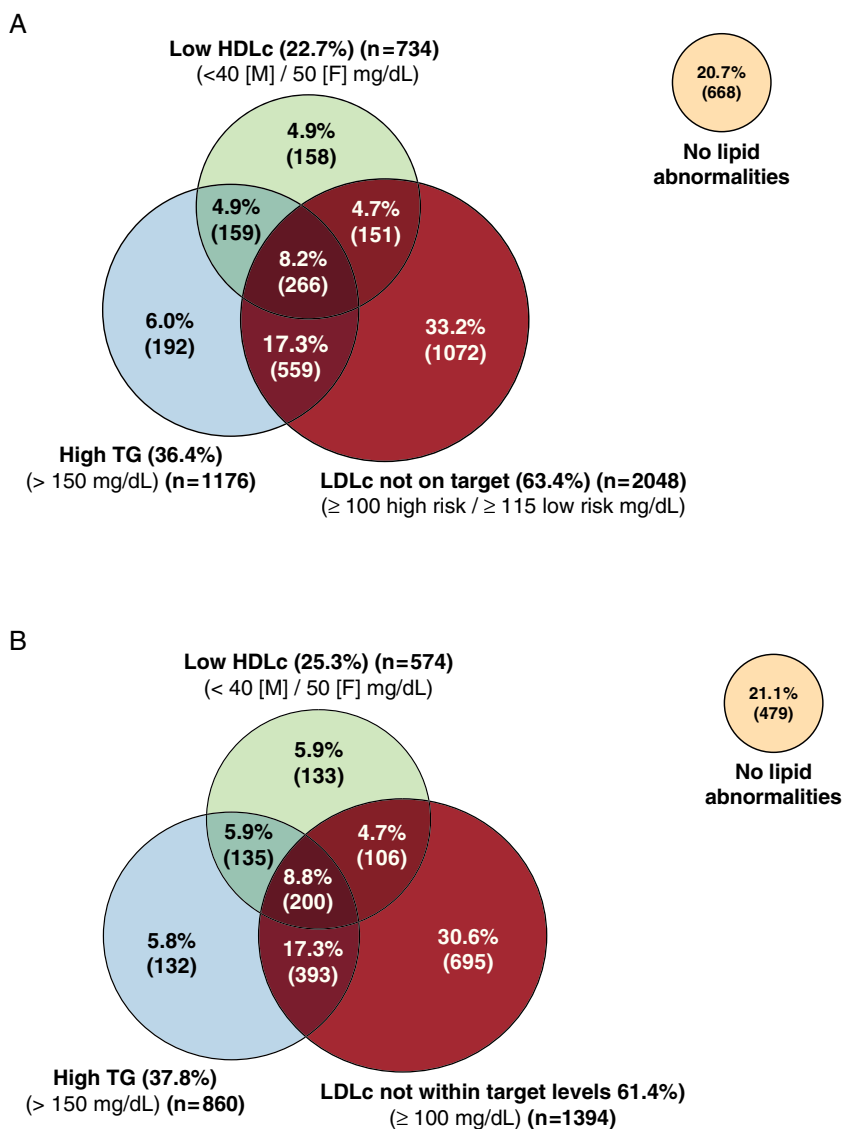


Figure 2. A: individual and combined lipid abnormalities in all the Spanish patients included in the DYSIS study. B: individual and combined lipid abnormalities in the patients with a high cardiovascular risk. Definition of levels of risk in accordance with the European Society of Cardiology; guidelines for the prevention of cardiovascular disease. HDLc, high-density lipoprotein cholesterol; LDLc, low-density lipoprotein cholesterol; F: female; M: male; TG, triglycerides.

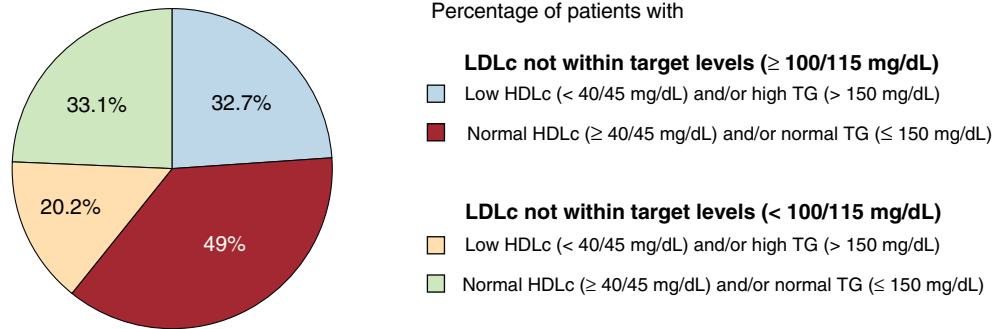
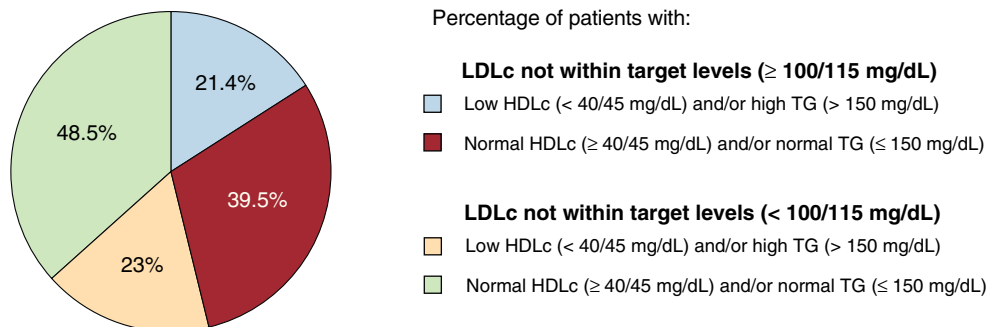
Diabetic patients**Patients with ischemic cardiopathy without DM**

Figure 3. Lipid profile in diabetic patients and in patients with ischemic cardiopathy but with concomitant diabetes mellitus. Data calculated from 1702 Spanish patients with a complete lipid profile (LDLc, HDLc and TG). DM, diabetes mellitus; HDLc, high-density lipoprotein cholesterol; LDLc, low-density lipoprotein cholesterol; TG, triglycerides.

DISCUSSION

The results of this extensive study (DYSIS-Spain) show that, despite treatment with statins, only a fifth of patients achieve normal lipid values, or those recommended by current clinical practice guidelines.^{1,10,11} Furthermore, the large majority of high-risk patients continue to have one or more of the parameters of dyslipidemia.

Although many cross-sectional epidemiological studies have analyzed the prevalence of dyslipidemia in populations with different levels of cardiovascular risk,^{14,15,18–20} this is the first study in Spain to analyze the characteristics of a large cohort of patients with cardiovascular risk treated with statins. Furthermore, previous studies usually focused on LDLc, without performing a more complete analysis of the patients' lipid profile. In addition to observing that a high proportion of patients do not meet target levels of LDLc, a significant proportion of cases are seen to have low HDLc and high TG. This was seen both when LDLc levels were under control and when they were not, which highlights the importance of trying to improve patients' overall lipid profile, particularly in high-risk cases.

In recent years, several studies have analyzed the target lipid levels in the general population and among patients in primary care settings.^{21–24} In the US NHANES study of 1111 patients with dyslipidemia, 85% had abnormal values of LDLc, HDLc and/or TG; 35% showed more than 2 abnormal lipid levels, while 42% had abnormal values of HDLc and/or TG with or without high LDLc.²⁵

While most studies into dyslipidemia have centered on LDLc in accordance with the recommendations of the NCEP ATP III,²⁶ our study takes a wider perspective and also considers HDLc, TG, and TC values.

Our results show that there is often more than one disturbance in the plasma level of lipids; in the whole group of Spanish patients, 35.1% had 2 or 3 simultaneous abnormalities, and 1 in 12 (8.2%) had 3 abnormal parameters. Furthermore, the presence of other risk factors and comorbidities such as DM and IC lead to a significant increase in the overall cardiovascular risk.

The recommended target lipid levels are achieved more often in patients with clinical cardiovascular disease, and in particular with IC, than in diabetic patients without IC and other high-risk cardiovascular patients (SCORE $> 5\%$). However, 78.9% of the high-risk patients included in the study failed to achieve the recommended targets for LDLc, and 38.9% also had abnormal levels of HDLc and/or TG despite lipid-lowering treatment, mainly with statins. It is important to remember what several authors have highlighted with regard to the efficacy of doubling the dose of statins after treatment with an initial dose: this double dose only results in a 6% decrease in LDLc levels, with a slight effect or no effect on HDLc and TG.^{27,28}

We observed a high prevalence of low HDLc and high TG levels in our study. A reciprocal relationship has been described between plasma concentrations of HDLc and the incidence of IC.^{29,30} The PROCAM cohort confirmed this association, even after adjusting for other risk factors.^{31,32} Although several studies have observed a linear relationship between levels of TG and the incidence of IC, a multivariate analysis did not confirm this.³¹ This could be due to the significant biological and analytical variability within and between subjects,³³ as well as the high prevalence of additional anomalies in HDLc and LDLc levels.⁶ However, in accordance with the recent consensus on the management of dyslipidemia in high-risk patients, treatment to raise HDLc and lower TG is classified as having secondary importance.⁷

Table 3Independent Predictors of Abnormalities in High Density Lipoprotein Cholesterol, Low Density Lipoprotein Cholesterol and Triglycerides Levels in Multivariate Logistic Regression Models^a

	LDLc outside target levels (≥100/115 mg/dL)		Low HDLc (<40/50 mg/dL)		High TG (>150 mg/dL)		LDLc outside target levels, low HDLc and high TG	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Age ≥70 years	NS	NS	0.64 (0.52–0.79)	<.0001	0.6 (0.5–0.72)	<.0001	0.46 (0.31–0.67)	<.0001
Female	1.25 (1.03–1.51)	.0211	NS	NS	0.64 (0.53–0.76)	<.0001	NS	NS
Family history of premature IC	1.32 (1.07–1.63)	.0109	1.33 (1.06–1.66)	.0123	1.31 (1.07–1.59)	.0081	1.51 (1.07–2.12)	.0179
Smokers	1.35 (1.07–1.7)	.0115	NS	NS	1.31 (1.07–1.61)	.0105	1.77 (1.26–2.49)	.001
Sedentary lifestyle	1.24 (1.05–1.47)	.0122	NS	NS	1.39 (1.18–1.64)	<.0001	1.76 (1.28–2.43)	.0005
Alcohol consumption > 2 units/week	1.38 (1.14–1.67)	.0011	NS	NS	NS	NS	NS	NS
BMI > 30 (obesity)	0.76 (0.64–0.91)	.0025	NS	NS	NS	NS	NS	NS
Waist circumference > 102 (men) or >88 cm (women)	NS	NS	1.27 (1.05–1.54)	.0144	1.43 (1.2–1.69)	<.0001	NS	NS
Hypertension	0.73 (0.6–0.88)	.0013	NS	NS	NS	NS	NS	NS
Diabetes mellitus	NS	NS	1.58 (1.31–1.92)	<.0001	1.42 (1.21–1.68)	<.0001	1.44 (1.06–1.97)	.0208
IC	0.59 (0.48–0.72)	<.0001	1.56 (1.25–1.93)	<.0001	0.81 (0.66–0.98)	.035	NS	NS
Cerebrovascular disease	0.62 (0.45–0.84)	.0024	1.54 (1.11–2.14)	.0094	NS	NS	NS	NS
Heart failure	NS	NS	NS	NS	NS	NS	NS	NS
Peripheral artery disease	NS	NS	NS	NS	NS	NS	NS	NS
20–40 mg/day equivalent compared with simvastatin 10 mg/day	0.71 (0.56–0.89)	.0038	1.64 (1.23–2.18)	.0007	NS	NS	NS	NS
≥80 mg/day equivalent compared with simvastatin 10 mg/day	0.42 (0.31–0.57)	<.0001	1.77 (1.24–2.53)	.0018	NS	NS	NS	NS
Ezetimibe	NS	NS	NS	NS	NS	NS	0.52 (0.3–0.89)	.018
Specialist (cardiologist/ endocrinologist/ internist/other)	0.52 (0.43–0.62)	<.0001	1.4 (1.15–1.71)	.0009	NS	NS	1.4 (1.02–1.92)	.0388

BMI, body mass index; CI, confidence interval; HDLc, high-density lipoprotein cholesterol; IC, ischemic cardiopathy; LDLc, low-density lipoprotein cholesterol; NS, non significant; OR, odds ratio; TG, triglycerides.

The models contain the following variables: age, sex, first-degree relative with history of premature cardiovascular disease, tobacco smoking, sedentary lifestyle, alcohol consumption >2 units/week, BMI ≥30 (obesity), waist circumference >102 cm in men and >88 cm in women, hypertension, diabetes mellitus, IC, cerebrovascular disease, heart failure, peripheral arteriopathy, blood pressure ≥140/90 mmHg (systolic/diastolic), 20–40 vs 10 mg/day simvastatin equivalent, ≥ 80 vs 10 mg/day simvastatin equivalent, ezetimibe, and medical specialty. A retrospective selection was made ($\alpha=.05$).

The multivariate analysis identified numerous variables associated with one or more lipid abnormalities. Tobacco smoking, a sedentary lifestyle, and an increase in waist circumference were associated with poor control of at least one of the 4 lipid abnormalities analyzed. Although DM was associated with target levels of LDLc being achieved more often, nearly two-thirds of diabetic patients did not achieve them. Furthermore, there was a significant association between DM and a worse control of HDLc and TG levels. These findings are not uncommon in diabetic patients treated with statins; they often have relatively low levels of LDLc but abnormal HDLc and TG levels.^{34,35} Although these abnormalities are characteristic of diabetic patients, these results lead us to believe that not all the necessary measures are taken to reduce lipid levels.

In this study, being treated by a specialist was associated with a greater control of LDLc and TG, mainly due to the use of higher doses of statins and the combined use of ezetimibe. The fact that high doses of statins are associated with low HDLc may indicate that the doctor is trying to achieve a greater decrease in LDLc to mitigate the risk from low HDLc levels, the treatment options for which are more limited. In our study, the moderate doses of statins, equivalent to simvastatin at 20 to 40 mg/day, were the most commonly used. This factor undoubtedly affects the results. Of the high-risk patients, over 50% were treated with doses equivalent to simvastatin 40 or 80 mg/day. Nonetheless, within the international DYSIS study, Spain has more deficient control of LDLc

compared with the overall mean values obtained from all the countries involved.¹⁶

In the recent 2L Registry, which included patients hospitalized for high-risk cardiovascular events, the mean initial dose of simvastatin used was 25 mg/day, and 31 mg/day on discharge. In our study, ezetimibe combined with statins was used in 14.7% of patients, compared with 13% in the 2L Registry at the baseline visit.³⁶

We observed a high prevalence of abnormalities in HDLc and TG levels, independent of LDLc levels, in this group of patients treated with statins. Similar data were found in a recent analysis of the NHANES, in which the use of therapy targeting HDLc and TG was <12%.²⁵

Four earlier studies, all focusing on LDLc target levels, analyzed the determinants of lipid control in clinical practice. In the Vascular Protection Registry and Guidelines Oriented Approach to Lipid Lowering,³⁷ which included high-risk outpatients, the factors associated with therapeutic success were: elderly patients, DM, IC, previous angioplasty or coronary surgery, and statins. These results are in agreement with those published by other studies.^{38–40}

The DYSIS-Spain study has several strengths and limitations. It is a cross-sectional observational study including data from the consecutive patients of 477 doctors. Therefore, it provides a more representative view of usual clinical practice. However, the participating doctors are particularly motivated and have greater knowledge of lipid-lowering treatments, and this could lead to a higher degree of compliance with the recommended guidelines.

Also, it cannot be ruled out that the data from the patients who refused to participate in the study could have affected our results. Furthermore, other variables could be valid predictors of achieving lipid targets. The register in this study does not take into account possible modifications in the lipid-lowering therapy; furthermore, treatment compliance is often worse in “real life” settings.

CONCLUSIONS

Most of the patients treated with statins in Spain, especially those with a high cardiovascular risk, do not meet recommended lipid targets and/or have a high frequency of abnormal HDLc and TG levels. The results of the DYSIS-Spain study show that significant differences exist between the recommendations in the guidelines and clinical practice, as well as highlighting the need for a more intensive and integrated management of dyslipidemia in high-risk patients. In particular, in secondary prevention and in diabetic patients, therapy should not focus solely on meeting the targets for TC and LDLc, but also achieving the right levels of TG and HDLc to reduce the risk as much as possible.

FUNDING

This study received funding from Merck & Co. Inc.

CONFLICTS OF INTEREST

Dr Gustavo Vitale is employed by Merck, Sharp and Dohme in Spain, and the authors of this article have collaborated with this company as scientific advisers.

REFERENCES

- Fourth Joint Task Force of the European Society of Cardiology and other Societies on Cardiovascular Disease Prevention in Clinical Practice. European guidelines on cardiovascular disease prevention in clinical practice. *Eur Heart J*. 2007;28:2375–414.
- Cordero A, Bertomeu V, Mazón P, Quiles J, Aznar J, Bueno H. Differences in medical treatment of chronic coronary heart disease patients according to medical specialties. *Cardiovasc Ther*. 2009;27:173–80.
- Gabriel R, Alonso M, Segura A, Tormo MJ, Artigao LM, Banegas JR, et al. Prevalencia, distribución y variabilidad geográfica de los principales factores de riesgo cardiovascular en España. Análisis agrupado de datos individuales de estudios epidemiológicos poblacionales: estudio ERICE. *Rev Esp Cardiol*. 2008;61:1030–40.
- Haffner S, Taegtmeier H. Epidemic obesity and the metabolic syndrome. *Circulation*. 2003;108:1541–5.
- Yusuf S, Hawken S, Ounpuu S, Dans T, Avenanzu A, Lanas F, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet*. 2004;364:937–52.
- Medrano MJ, Pastor R, Boix R, Del Barrio JL, Damián J, Álvarez R, et al. Riesgo coronario atribuible a los factores de riesgo cardiovascular en población española. *Rev Esp Cardiol*. 2007;60:1250–6.
- Brunzell JD, Davidson M, Furberg CD, Goldberg RB, Howard BV, Stein JH, et al. Lipoprotein management in patients with cardiometabolic risk: consensus conference report from the American Diabetes Association and the American College of Cardiology Foundation. *J Am Coll Cardiol*. 2008;51:1512–15124.
- Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet*. 2005;366:1267–78.
- Lee JMS, Choudhury RP. Prospects for atherosclerosis regression through increase in high-density lipoprotein and other emerging therapeutic targets. *Heart*. 2007;93:559–64.
- Expert Panel on Detection and Treatment of High Blood Cholesterol in Adults. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP). Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA*. 2001;285:2486–97.
- Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Final Report. *Circulation*. 2002;106:3143.
- Gordon DJ, Probstfield JL, Garrison RJ, Neaton JD, Castelli WP, Knoke JD, et al. High-density lipoprotein cholesterol and cardiovascular disease: four prospective American studies. *Circulation*. 1989;79:8–15.
- Turner RC, Millns H, Neil HA, Stratton IM, Manley SE, Matthews DR, et al. Risk factors for coronary artery disease in non-insulin-dependent diabetes mellitus: United Kingdom prospective diabetes study (UKPDS). *BMJ*. 1998;316:823–8.
- Cea-Calvo L, Lozano JV, Fernández-Pérez C, Listerri JL, Martí-Canales JC, Aznar J, et al. Prevalence of low HDL cholesterol, and relationship between serum HDL and cardiovascular disease in elderly Spanish population: the PREV-ICTUS Study. *Int J Clin Prac*. 2009;63:71–81.
- González-Juanatey JR, Grigorian L, Juiz MA, Sánchez M, Rodríguez E, Dopico J, et al. Impacto pronóstico de la localización de la enfermedad aterosclerótica previa en pacientes diabéticos. Estudio Barbanza-Diabetes. *Rev Esp Cardiol*. 2008;61:1168–77.
- Gitt AK, Kastelein JP. High prevalence of dyslipidemia in 18,574 patients treated with statins in Europe and Canada: Results of the dyslipidemia international study. *Eur Heart J*. 2009;30 Suppl 1:303.
- Magliano DJ, Shaw JE, Zimmet PZ. How to best define the metabolic syndrome. *Ann Med*. 2006;38:34–41.
- Grant RW, Meigs JB. Prevalence and treatment of low HDL cholesterol among primary care patients with type 2 diabetes: an unmet challenge for cardiovascular risk reduction. *Diabetes Care*. 2007;30:479–84.
- Goff Jr DC, Bertoni AG, Kramer H, Bonds D, Blumenthal RS, Tsai MY, et al. Dyslipidemia prevalence, treatment, and control in the Multi-Ethnic Study of Atherosclerosis (MESA): gender, ethnicity, and coronary artery calcium. *Circulation*. 2006;113:647–56.
- Daly CA, Clemens F, López-Sendón JL, Tavazzi L, Boersma E, Danchin N, et al. The impact of guideline compliant medical therapy on clinical outcome in patients with stable angina: findings from the Euro Heart Survey of stable angina. *Eur Heart J*. 2006;27:1298–304.
- Nichols GA, Nag S, Chan W. Intensity of lipid-lowering therapy and low-density lipoprotein cholesterol goal attainment among the elderly before and after the 2004 National Cholesterol Education Program Adult Treatment Panel III update. *Am Heart J*. 2007;154:554–60.
- Assmann G, Benecke H, Neiss A, Cullen P, Schulte H, Bestehorn K. Gap between guidelines and practice: attainment of treatment targets in patients with primary hypercholesterolemia starting statin therapy. Results of the 4E-Registry (Efficacy Calculation and Measurement of Cardiovascular and Cerebrovascular Events Including Physicians' Experience and Evaluation). *Eur J Cardiovasc Prev Rehabil*. 2006;13:776–83.
- Persell SD, Lloyd-Jones DM, Baker DW. Implications of changing national cholesterol education program goals for the treatment and control of hypercholesterolemia. *J Gen Intern Med*. 2006;21:171–6.
- Ose L, Skjeldstad FE, Bakken IJ, Levorsen A, Alemao EA, Yin DD, et al. Lipid management and cholesterol goal attainment in Norway. *Am J Cardiovasc Drugs*. 2006;6:121–8.
- Ghandehari H, Kamal-Bahl S, Wong ND. Prevalence and extent of dyslipidemia and recommended lipid levels in US with and without cardiovascular comorbidities: the National Health and Nutrition Examination Survey 2003–2004. *Am Heart J*. 2008;156:112–9.
- NCEP-ATP III Guidelines At-A-Glance Quick Desk Reference. Available at: <http://www.nhlbi.nih.gov/guidelines/cholesterol/atglance.pdf>
- Jones P, Kafonek S, Laurora I, Hunninghake D. Comparative dose efficacy study of atorvastatin versus simvastatin, pravastatin, lovastatin, and fluvastatin in patients with hypercholesterolemia (the CURVES study). *Am J Cardiol*. 1998;81:582–7.
- Leitersdorf E. Cholesterol absorption inhibition: filling an unmet need in lipid lowering management. *Eur Heart J Suppl*. 2001;3 Suppl E:E17–23.
- Sharrett AR, Ballantyne CM, Coady SA, Sharrett AR, Ballantyne CM, Coady SA, et al. Coronary heart disease prediction from lipoprotein cholesterol levels, triglycerides, lipoprotein(a), apolipoproteins A-I and B, and HDL density sub-fractions: The Atherosclerosis Risk in Communities (ARIC) Study. *Circulation*. 2001;104:1108–13.
- Stampfer MJ, Sacks FM, Salvini S, Willett WC, Hennekens CH. A prospective study of cholesterol, apolipoproteins, and the risk of myocardial infarction. *N Engl J Med*. 1991;325:373–81.
- Assmann G, Schulte H. Relation of high-density lipoprotein cholesterol and triglycerides to incidence of atherosclerotic coronary artery disease (the PROCAM experience). Prospective Cardiovascular Munster study. *Am J Cardiol*. 1992;70:733–7.
- Assmann G, Schulte H, Von Eckardstein A, Huang Y. High-density lipoprotein cholesterol as a predictor of coronary heart disease risk. The PROCAM experience and pathophysiological implications for reverse cholesterol transport. *Atherosclerosis*. 1996;124:S11–20.
- Wild S, Byrne CD. Time to rethink high-density lipoprotein? *Heart*. 2008;94:692–4.
- Ninomiya JK, L'Italien G, Criqui MH, Whyte JL, Gamst A, Chen RS. Association of the metabolic syndrome with history of myocardial infarction and stroke in the Third National Health and Nutrition Examination Survey. *Circulation*. 2004;109:42–6.
- Alsheikh-Ali AA, Lin JL, Abourjaily P, Ahearn D, Kuvlin JT, Karas RH. Prevalence of low high-density lipoprotein cholesterol in patients with documented coronary

- heart disease or risk equivalent and controlled low-density lipoprotein cholesterol. *Am J Cardiol.* 2007;100:1499–501.
36. Gitt AK, Juenger C, Jannowitz C, Karmann B, Senges J, Bestehorn K. Guideline-oriented ambulatory lipid-lowering therapy of patients at high risk for cardiovascular events by cardiologists in clinical practice: the 2L cardio registry. *Eur J Cardiovasc Prev Rehabil.* 2009;16:438–44.
37. Yan AT, Yan RT, Tan M, Hackam DG, Leblanc KL, Kertland H, et al. Contemporary management of dyslipidemia in high-risk patients: targets still not met. *Am J Med.* 2006;119:676–83.
38. Pearson TA, Laurora I, Chu H, Kafonek S. The lipid treatment assessment project (L-TAP): a multicenter survey to evaluate the percentages of dyslipidemic patients receiving lipid-lowering therapy and achieving low-density lipoprotein cholesterol goals. *Arch Intern Med.* 2000;160:459–67.
39. Mosca L, Merz NB, Blumenthal RS, Cziraky MJ, Fabunmi RP, Sarawate C, et al. Opportunity for intervention to achieve American Heart Association guidelines for optimal lipid levels in high-risk women in a managed care setting. *Circulation.* 2005;111:488–93.
40. Davidson MH, Maki KC, Pearson TA, Deedwania PC, McKenney JM, Fonarow GC, et al. Results of the National Cholesterol Education (NCEP) Program Evaluation Project Utilizing Novel E-Technology (NEPTUNE) II survey and implications for treatment under the recent NCEP Writing Group recommendations. *Am J Cardiol.* 2005;96:556–63.