A Six-Month, Multicenter, Open-Label, Noncomparative, Prospective, Observational Study of the Efficacy and Tolerability of Atorvastatin in the Primary Care Setting (*Estudio del Control de las Hiperlipidemias en Atención Primaria*): The CHEAP Study

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ABSTRACT

Background: A close relationship exists between high levels of total cholesterol (TC) (particularly low-density lipoprotein cholesterol [LDL-C]) and low levels of high-density lipoprotein cholesterol (HDL-C), which is associated with an increased risk for arteriosclerosis and cardiovascular disease (CVD). Evidence shows that atorvastatin produces significantly greater reductions in LDL-C and TC than other hydroxymethylglutaryl-coenzyme A reductase inhibitors. However, the results achieved in clinical studies could be different from those found in general clinical practice, where patient follow-up is less thorough and poorer compliance may reduce the effectiveness of the lipid-lowering therapy.

Objective: The aim of this study was to assess the effectiveness of atorvastatin in achieving the LDL-C levels recommended by several Spanish scientific societies, as well as its tolerability in standard clinical use.

Methods: This 6-month, open-label, noncomparative, prospective, observational study was conducted in 1351 primary care centers in Spain. All patients were aged 18 to 80 years and had primary hypercholesterolemia (TC >200 mg/dL and triglycerides [TG] <200 mg/dL) or combined hyperlipidemia (TC >200 mg/dL and fasting TG 200–400 mg/dL). All patients also had LDL-C levels higher than those established by the Spanish Society of Arteriosclerosis (*Sociedad Española de Arteriosclerosis* [SEA]) according to baseline cardiovascular risk and previous use of lipid-lowering therapy (for patients with low, moderate, or high cardiovascular risk, the recommended LDL-C goals are ≤175 mg/dL, ≤155

mg/dL, and ≤ 135 mg/dL, respectively; for patients with CVD, the LDL-C goal is ≤ 100 mg/dL). None of the patients had creatine kinase activity ≥ 540 U/L or alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels ≥ 60 U/L. Study visits occurred at months 0, 2, and 6 of treatment. Patients received atorvastatin calcium 10 mg/d for 2 months. The dosage was then doubled to 20 mg/d in patients who did not achieve the SEA LDL-C goal and also in those patients whose primary care physicians (PCPs) deemed this higher dosage necessary; this dosage was continued for at least 4 additional months, to complete at least a 6-month course of treatment. The percentage of patients who achieved their goals was used to measure atorvastatin effectiveness. Percentages of change in LDL-C, TC, TG, and HDL-C from baseline to the final study visit also were used as measures of effectiveness. The incidence of adverse events (AEs) per 10,000 patient-months was used for the primary tolerability analysis. A secondary tolerability analysis was performed in all patients treated with atorvastatin who had some recorded follow-up, regardless of whether the patient met inclusion criteria. Information was obtained from data recorded in the case-report forms.

Results: A total of 5317 outpatients (2715 women, 2598 men, 4 sex unknown; mean [SD] age, 58.7 [10.5] years) were enrolled. Among patients receiving known dosages of atorvastatin, 1580 of 4033 (39.2%) and 2378 of 3585 (66.3%) patients met the SEA LDL-C goal after 2 and 6 months of therapy, respectively ($P < 0.001$ for 2 months vs 6 months). Among the patients with low and moderate cardiovascular risk, 85.8% achieved the SEA LDL-C goal compared with 64.4% of high-risk patients ($P < 0.001$). Mean LDL-C decreased by 36.2%. Mean reductions in TC and TG levels were 26.9% and 19.2%, respectively. Mean HDL-C increased 17.0%. One hundred forty-eight patients (2.9%) experienced at least 1 AE and 25 (0.5%) had serious AEs. Eighty-nine patients had 134 AEs considered treatment related. Two of the serious AEs (phlebitis and a severe increase in ALT and AST activity) were considered treatment related. A total of 98.5% and 97.2% of PCPs and patients, respectively, reported excellent or good tolerability with atorvastatin.

Conclusions: In this study population, the use of atorvastatin in the primary care setting was associated with high achievement rates of the SEA LDL-C goals and with a substantial decrease in TG levels. In addition, a considerable increase in HDL-C levels occurred. Tolerability with atorvastatin was reported to be excellent or good by most of the patients and PCPs. The incidence of serious AEs was minimal, as reported by both patients and PCPs. (*Curr Ther Res Clin Exp.* 2003;64:338–354) Copyright © 2003 Excerpta Medica, Inc.

Key words: atorvastatin, hyperlipidemia, hypercholesterolemia, primary care.

INTRODUCTION

A close relationship exists between high levels of total cholesterol (TC) (particularly low-density lipoprotein cholesterol [LDL-C]) and low levels of high-density lipoprotein cholesterol (HDL-C), which is associated with an increased risk for

arteriosclerosis and cardiovascular disease (CVD).^{1,2} Reduction of LDL-C and TC levels can considerably decrease the risk for coronary morbidity and mortality in both primary and secondary prevention of CVD.³⁻⁷ The primary objective of drug therapy in patients with dyslipidemia is to reduce the risk for CVD or the progression of preexisting cardiac disease by achieving appropriate serum lipid levels. International scientific societies have established recommendations for the management of high lipid levels based on initial treatment with diet and guided by cardiovascular risk levels.^{8,9}

The Spanish Society of Arteriosclerosis (*Sociedad Española de Arteriosclerosis* [SEA]), the Spanish Society of Internal Medicine, and the Spanish League for the Campaign Against Arterial Hypertension have published recommendations for primary prevention of cardiovascular disease.¹⁰ In those recommendations, patients are classified into risk categories according to TC levels and the presence of other cardiovascular risk factors (Table I). Specific LDL-C goals are based on the baseline cardiovascular risk. For patients with low, moderate, or high risk, the recommended LDL-C goals are ≤ 175 mg/dL, ≤ 155 mg/dL, and ≤ 135 mg/dL, respectively. For patients with CVD, the LDL-C goal is ≤ 100 mg/dL.¹⁰

The drugs most often used to treat dyslipidemia are hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, fibric acid derivatives, nicotinic acid, and biliary acid uptakers. Statin drugs are HMG-CoA reductase inhibitors that substantially reduce LDL-C and TC levels in a dose-dependent manner. Many clinical trials^{5,6,11,12} in primary and secondary prevention have shown that statins also have beneficial effects on coronary morbidity and mortality and on overall mortality.

Statins are well tolerated and are considered to be the most effective drugs in lowering LDL-C levels.¹³ In placebo-controlled, dose-response studies¹⁴ in patients with primary hypercholesterolemia, atorvastatin produced 25% to 60% reductions in LDL-C levels. When given in equivalent doses (in milligrams), atorvastatin produced significantly greater reductions in LDL-C and TC than other HMG-CoA reductase inhibitors.¹⁵ This effect results in a greater number of patients achieving the therapeutic LDL-C goals recommended by scientific societies.

However, the results achieved in these well-controlled clinical studies could be different from those found in general clinical practice, where patient follow-up is less thorough and poorer compliance may reduce the effectiveness of the lipid-lowering therapy.

The aim of this study was to assess the effectiveness of atorvastatin in achieving the LDL-C levels recommended by several Spanish scientific societies, as well as its tolerability in standard clinical use.

PATIENTS AND METHODS

Study Design

The Study of Patients Receiving Atorvastatin in the Primary Care Setting (*Estudio del Control de las Hiperlipidemias en Atención Primaria*: the CHEAP Study) was

Table I. Study inclusion and exclusion criteria.**Inclusion criteria**

1. Patients assigned to start treatment with atorvastatin 10 mg/d per their primary care physicians' clinical criteria
2. Outpatients of both sexes, aged 18–80 years
3. Patients with primary hypercholesterolemia (TC >200 mg/dL and TG <200 mg/dL), or combined hyperlipidemia (TC >200 mg/dL and fasting TG 200–400 mg/dL), that was not controlled with diet
4. Patients with or without concurrent CVD
5. Patients with an LDL-C level higher than those established by the Spanish Society of Arteriosclerosis¹⁰ according to baseline cardiovascular risk and with previous use of lipid-lowering therapy, as follows:

Baseline Cardiovascular Risk	LDL-C in Patients Without Previous Lipid-Lowering Therapy, mg/dL	LDL-C in Patients With Previous Lipid-Lowering Therapy, mg/dL
Low	>190	>175
Moderate	>180	>155
High	>160	>135
CVD	>135	>100

Exclusion criteria

1. LDL-C level ≥ 250 mg/dL in patients without prior lipid-lowering therapy or LDL-C ≥ 200 mg/dL in patients with prior lipid-lowering therapy
2. Pregnant, possibly pregnant (ie, not using an adequate birth control method), or lactating women
3. Patients with known hypersensitivity to statins
4. Active hepatic disease/dysfunction (ALT or AST activity ≥ 60 U/L)
5. Rhabdomyolysis or creatine kinase elevation ≥ 540 U/L
6. Patients with potential adherence failure, including those who abuse alcohol or drugs
7. Patients with psychiatric or psychological conditions that could impair their ability to follow protocol instructions
8. Patients who participated in any other study involving study or marketed drugs within the previous month
9. Patients with TC <200 mg/dL or TG >400 mg/dL

TC = total cholesterol; TG = triglycerides; CVD = cardiovascular disease; LDL-C = low-density lipoprotein cholesterol; AST = aspartate aminotransferase; ALT = alanine aminotransferase.

conducted from November 1997 to April 1999. It was a 6-month, open-label, noncomparative, prospective, observational study conducted in 1351 primary care centers in Spain.

The CHEAP Study was conducted with atorvastatin following its authorized summary of product characteristics¹⁶ and under standard usage conditions. During the CHEAP Study, atorvastatin calcium was prescribed in a standard

fashion and according to conditions of general clinical practice. The assignment of a patient to a specific therapeutic approach was not decided beforehand by a clinical protocol but was determined by standard clinical practice. The decision to prescribe atorvastatin clearly was separated from the decision to include a patient in the study. No diagnostic or follow-up interventions were carried on during the study other than those of general clinical practice.

The CHEAP Study adhered strictly to legal and regulatory instructions¹⁷ for postauthorization observational studies for human-use drugs in Spain at the time the study was conducted and to the principles of the Declaration of Helsinki and its amendments.

Approval by a clinical investigation ethics committee was mandatory by Spanish law only when information was directly requested of patients, when diagnostic procedures were not part of the usual clinical practice, or when treatments were assigned in a systematic fashion. None of the prior conditions applied to the CHEAP Study. Written informed consent was not part of the Spanish legal requirements for postauthorization observational studies when the CHEAP Study was conducted.

Patients

The inclusion and exclusion criteria of this study are shown in [Table I](#). All patients had primary hypercholesterolemia (TC >200 mg/dL and triglycerides (TG) <200 mg/dL) or combined hyperlipidemia (TC >200 mg/dL and fasting TG 200–400 mg/dL), were aged 18 to 80 years, and had LDL-C levels higher than those established by the SEA according to baseline cardiovascular risk and previous use of lipid-lowering therapy. All patients also had creatine kinase (CK) levels <540 U/L and alanine aminotransferase (ALT) or aspartate aminotransferase (AST) activities <60 U/L. At enrollment patients were already following the National Cholesterol Education Program type I diet.⁸ They also had received recommendations about exercise from a primary care physician (PCP). No compliance follow-up was performed for these recommendations. The PCPs were involved in patient recruitment and data collection. Verbal informed consent was obtained from all patients. Nonretired patients partially paid for their treatment, whereas retired patients' treatment was fully covered by the Spanish Health System.

Methods

Patients began treatment with atorvastatin tablets at a dosage of 10 mg/d. Study visits occurred at months 0, 2, and 6 of treatment. Data collection is shown in [Table II](#). After 2 months of treatment, an increase in the dosage from 10 to 20 mg/d was made in most patients who did not meet the SEA therapeutic goal. The dosage also was titrated to 20 mg/d in some patients who met the SEA therapeutic goal after 2 months of treatment as per PCP criteria. This higher dosage was continued for at least 4 additional months, to complete at least a

Table II. Data collection at baseline and during follow-up study visits.

	Visit No.*		
	1 (Baseline)	2 (Month 2)	3 [†] (Month 6)
Information			
Date of birth	X		
Sex	X		
Cardiovascular risk factors	X		
Physical examination	X		
Inclusion/exclusion criteria	X		
Body weight	X	X	X [‡]
Blood pressure	X	X	X
Concomitant medication	X	X	X [‡]
Safety blood test profile [‡]	X	X	X [‡]
Lipid profile [§]	X	X	X [‡]
Assessment of treatment adherence		X	X [‡]
Adverse events		X	X [‡]
Global assessment of tolerance			X [‡]

*Time frame for blood withdrawal (the visit to the physician's office had to be within the subsequent week).

[†]Or at the time of a possible early discontinuation from the study.

[‡]Must include alanine aminotransferase, aspartate aminotransferase, and creatine kinase activities.

[§]Must include total cholesterol, triglycerides, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol. (The Friedewald formula¹⁸ was used to calculate low-density lipoprotein cholesterol.)

6-month course of treatment. Patients were not asked to bring empty drug blisters to the follow-up visits for purposes of compliance assessment.

All blood samples were drawn by a nurse after a minimum 12-hour fasting period. Because blood analyses were performed at local laboratories, quality control coefficients were not checked. The Friedewald formula¹⁸ was used to estimate LDL-C levels.

For quality control, some physicians were asked to clarify or complete case report forms by telephone, and others were asked at study centers. Letters were sent weekly by mail for data clarification purposes.

Efficacy Analysis

Data for efficacy analysis were obtained from all patients who completed at least a 6-month course of atorvastatin. Baseline TC levels and other risk factors were used to classify study patients according to their cardiovascular risk (Table III). The effectiveness of atorvastatin was calculated by assessing the percentage of patients who achieved the LDL-C therapeutic goal established by the SEA for their cardiovascular risk group. The percentages of change in LDL-C, TC, TG, and HDL-C levels from baseline to the final study visit also were used as efficacy parameters.

Table III. Spanish Society of Arteriosclerosis¹⁰ cardiovascular risk groups and low-density lipoprotein cholesterol (LDL-C) therapeutic goals.

Risk	TC, mg/dL	Other RFs*	Goal LDL-C, mg/dL
Low	200–300	None	≤175
Moderate	200–300	1 nonlipid RF or HDL-C <35 mg/dL	≤155
High	200–300 >300	≥2 nonlipid RFs or 1 serious RF –	≤135
Secondary prevention	–	–	≤100

TC = total cholesterol; RF = risk factor; HDL-C = high-density lipoprotein cholesterol.

*Hypertension or history of hypertension, smoking, HDL-C <35 mg/dL, male sex, postmenopause, diabetes, family history of early cardiovascular disease, and personal history of cardiovascular disease.

Tolerability Analyses

Data for the primary tolerability analysis were obtained from all patients with at least 1 follow-up study visit. An adverse event (AE) was defined as any clinical or laboratory abnormality (regardless of its causal relationship to the study drug) and was classified according to the World Health Organization guidelines.¹⁹ The number of AEs for every 10,000 patient-months was used for primary and secondary tolerability analyses.

An AE page was included in the case-report forms for visits 2 and 3. CK level ≥540 U/L and ALT or AST activities ≥60 U/L were considered AEs. Patients who had an AE during the study were followed up using additional laboratory studies, by telephone, or in person at the primary care center. Patients who discontinued treatment due to an AE were not challenged with atorvastatin later.

Serious AEs were defined as those that caused death, were life threatening, led to permanent disability, or prompted or extended hospitalization. The development of cancer and drug overdose also were considered serious AEs. All patients with serious AEs were monitored at their respective primary care centers. Serious AEs were reported within 24 hours to the drug manufacturer, which then notified the Spanish Pharmacovigilance System.

Tolerance was assessed at visit 3 or at the time of early discontinuation from the study. On the case-report forms, PCPs and patients had 4 options from which to choose in rating drug tolerance: excellent, good, borderline, or bad.

A secondary tolerability analysis was performed in all patients treated with atorvastatin who had some recorded follow-up, regardless of whether the patient met the inclusion criteria.

Statistical Analysis

The statistical analysis included incidences and percentages of the categorical variables and mean (SD) for the quantitative variables. Analysis of variance was

used to test for differences in mean percentages of reduction in LDL-C between all risk groups. The post hoc comparison test was used to look for significant differences in the mean percentages of reduction in LDL-C for all possible comparisons between 2 risk groups. The chi-square test was used to identify significant differences in the percentages of achievement of the SEA LDL-C goal between patients with different baseline risks. The chi-square test also was used to identify significant differences between the percentage of patients who achieved the SEA LDL-C goals after 2 and 6 months of treatment. The incidence of AEs was defined by the number of AEs per 10,000 patient-months of atorvastatin treatment. The binomial distribution test was used to compare the incidence of AEs between the first 2 months and the last 4 months of the study. Statistical significance was set at $P < 0.05$.

Sample size was calculated to ensure sufficient precision in the efficacy and tolerability analyses. It was assumed that the percentage of patients who experienced any AE could be $<2\%$; therefore, 0.4% is acceptable precision (absolute precision of 0.4% is equal to relative precision of $1/5$ of the quantity to estimate, 2%). Thus, with a 95% CI, a sample size of 4684 would be necessary to obtain sufficient precision in the tolerability analysis. Moreover, this calculated sample is sufficiently large to ensure that the efficacy analysis and both objectives would be met.

Statistical analysis was performed using SAS version 6.12 (SAS Institute Inc., Cary, North Carolina).

RESULTS

A total of 1351 PCPs participated in the study and provided data on 6769 patients. For quality control, 21% of the physicians were monitored by telephone; 13% were monitored at study centers. For the letters ($n = 1000$) sent weekly by mail for data clarification purposes, the response rate was 37% .

The mean (SD) age of the patients was 58.7 (10.5) years (range, 20 – 80 years). A total of 1452 patients (21.5%) eventually were excluded because of failure to meet study criteria. A total of 1400 patients (20.7%) were excluded for the following reasons: LDL-C lower than those established by the SEA according to baseline cardiovascular risk and previous use of lipid-lowering therapy, 891 patients (13.2%); fasting TG >400 mg/dL, 204 patients (3.0%); age <18 to >80 , 190 patients (2.8%); CK activity ≥ 540 U/L or ALT or AST activity ≥ 60 U/L, 88 patients (1.3%); and TC ≤ 200 mg/dL, 27 patients (0.4%). Fifty-two patients (0.8%) failed to meet other inclusion criteria.

A descriptive analysis (demographic characteristics, risk factors, and SEA risk group categories) of the remaining 5317 patients is shown in [Table IV](#).

A total of 4033 patients (75.9%) completed the study. Reasons for failing to complete the study were as follows: loss to follow-up, 1133 patients (21.3%) (906 [17.0%] had visit 2 as the only recorded follow-up and 227 [4.3%] had no recorded follow-up after visit 1); AEs, 81 patients (1.5%); lack of efficacy,

1 patient (0.02%); and miscellaneous reasons not related to the study, 69 patients (1.3%).

Efficacy Analysis

The rates of achievement of the SEA LDL-C goal at the end of the study according to baseline risk are shown in Table V. When broken down by risk group, the percentage of patients achieving the LDL-C goals at the end of the study increased as the risk level decreased. Five hundred forty-five of the 635 patients (85.8%) with low or moderate risk achieved the SEA LDL-C goals compared with 1879 of the 2919 patients (64.4%) with high risk ($P < 0.001$).

The mean baseline lipid levels and percentages of change in these levels are depicted in Table VI. The mean (SD) percentage of decrease in LDL-C level was 36.2% (13.8%). The mean (SD) percentages of decrease in reduction in TC and TG levels were 26.9% (10.3%) and 19.2% (33.1%), respectively. Importantly, the mean percentage of increase in HDL-C level was 17.0% (32.9%). In all risk groups, LDL-C decreased significantly from baseline (all $P < 0.001$). The post hoc

Table IV. Baseline characteristics of study patients (N = 5317). (Values are expressed as no. [%] of patients unless otherwise noted.)

Characteristic	Value
Age, mean (SD), y	58.6 (10.5)
Sex*	
Women	2715 (51.1)
Men	2598 (48.9)
Risk factors†	
Postmenopausal	2387 (44.9)
Male, aged ≥ 45 y	2222 (41.8)
High blood pressure	2076 (39.0)
Smoking	1677 (31.5)
Family history of CVD (before age 65 y)	1091 (20.5)
Diabetes mellitus	710 (13.4)
HDL-C < 35 mg/dL	609 (11.5)
Left ventricular hypertrophy	296 (5.6)
SEA cardiovascular risk group	
High	4154 (78.1)
Moderate	831 (15.6)
Low	49 (0.9)
CVD	283 (5.3)

CVD = cardiovascular disease; HDL-C = high-density lipoprotein cholesterol; SEA = Spanish Society of Arteriosclerosis (*Sociedad Española de Arteriosclerosis*).

*Sex was unknown in 4 patients.

†Some patients had > 1 risk factor.

Table V. Patients meeting the Spanish Society of Arteriosclerosis¹⁰ low-density lipoprotein cholesterol (LDL-C) goals* at the end of the study according to baseline risk.

Risk Group	No. (%) of Patients [†]
Low	34/34 (100.0)
Moderate	511/601 (85.0)
High	1879/2919 (64.4) [‡]
CVD	56/217 (25.8)
All risk groups	2480/3771 (65.8)

CVD = cardiovascular disease.

*For patients with low, moderate, or high cardiovascular risk, the recommended LDL-C goals are ≤ 175 mg/dL, ≤ 155 mg/dL, and ≤ 135 mg/dL, respectively; for patients with CVD, the LDL-C goal is ≤ 100 mg/dL.

[†]Percentages are based on 2480 risk-group samples receiving atorvastatin for 6 months and with known cardiovascular risk or established CVD.

[‡] $P < 0.001$ versus low- and moderate-risk patients.

comparison did not show any significant between-group differences in the mean percentages of change in LDL-C.

The rates of patients achieving the SEA LDL-C goals as a function of atorvastatin dosage are depicted in the [figure](#). Among patients receiving known dosages of atorvastatin, 1580 of 4033 (39.2%) and 2378 of 3585 (66.3%) patients met the SEA LDL-C goals after 2 and 6 months of therapy, respectively ($P < 0.001$ for 2 months vs 6 months).

Of the 445 patients unsuccessfully treated with other statins prior to study entry, 263 (59.1%) achieved the SEA LDL-C therapeutic goal at visit 3 ([Table VII](#)).

Tolerability Analyses

The primary tolerability analysis was conducted in 5090 of the 5317 study patients with at least 1 recorded follow-up study visit (95.7%). The mean (SD) treatment

Table VI. Mean percentages of change in lipid parameters.

Lipid Parameter	LDL-C	TC	TG	HDL-C
Mean (SD) baseline values, mg/dL	202.7 (26.5)	287.9 (27.8)	178.8 (70.2)	49.5 (14.1)
Decrease, %				
All study patients	36.2 (13.8)	26.9 (10.3)	19.2 (33.1)	–
Low-risk patients	33.3 (10.5)*	–	–	–
Moderate-risk patients	34.8 (14.2)*	–	–	–
High-risk patients	36.7 (13.6)*	–	–	–
Patients with CVD	33.4 (16.2)*	–	–	–
Increase, %	–	–	–	17.0 (32.9)

LDL-C = low-density lipoprotein cholesterol; TC = total cholesterol; TG = triglycerides; HDL-C = high-density lipoprotein cholesterol; CVD = cardiovascular disease.

* $P < 0.001$ versus baseline.

Figure. Algorithm of study dynamics and Spanish Society of Arteriosclerosis (*Sociedad Española de Arteriosclerosis* [SEA])¹⁰ low-density lipoprotein cholesterol (LDL-C) goal achievement rates. For patients with low, moderate, or high cardiovascular risk, the recommended LDL-C goals are ≤ 175 mg/dL, ≤ 155 mg/dL, and ≤ 135 mg/dL, respectively; for patients with cardiovascular disease, the LDL-C goal is ≤ 100 mg/dL. Percentages may not total 100% due to rounding. *Data unavailable in 148 patients (6.0%). Percentages do not total 100% due to rounding. †Data not recorded at final follow-up visit in 53 patients (3.4%). ‡SEA LDL-C global achievement rate: 66.3% (n = 3585 patients with known doses of atorvastatin after 6 months of therapy; this percentage is significantly higher than the percentage of patients who met SEA LDL-C goals after 2 months of therapy [$P < 0.001$]).

period in this group was 5.3 (1.7) months (range, 0.1–10.0 months). A total of 166 AEs developed in 148 patients (2.9%); 25 patients (0.5%) had serious AEs, 2 (0.04%) of whom developed an AE presumptively related to the study drug (phlebitis and a severe increase in ALT and AST activity). A total of 89 patients had 134 AEs considered treatment related. Eighty patients (1.6%) dropped out of the study due to AEs. The most common AEs were gastrointestinal (constipation, flatulence, dyspepsia, diarrhea, nausea; 45 patients [0.88%]) and musculoskeletal (41 patients [0.81%]) (Table VIII). Per the last laboratory follow-up, increases in ALT and AST activity to ≥ 60 U/L were seen in 23 patients (0.45%) and 41 patients (0.81%), respectively. Forty-eight patients (0.94%) had an increase in

Table VII. Number (%) of patients meeting the Spanish Society of Arteriosclerosis¹⁰ low-density lipoprotein cholesterol (LDL-C) goals* at visit 3 with atorvastatin versus prior lipid-lowering treatments.

Prior Lipid-Lowering Treatment [†]	No. (%) of Patients Meeting Therapeutic Goals with Atorvastatin
Statins	
Simvastatin	82/144 (56.9)
Lovastatin	78/139 (56.1)
Pravastatin	76/115 (66.1)
Fluvastatin	27/47 (57.4)
Total statins	263/445 (59.1)
Fibrates	178/267 (66.7)
Combinations	8/24 (33.3)
Resins	13/21 (61.9)
Other	13/15 (86.7)

*For patients with low, moderate, or high cardiovascular risk, the recommended LDL-C goals are ≤ 175 mg/dL, ≤ 155 mg/dL, and ≤ 135 mg/dL, respectively; for patients with cardiovascular disease, the LDL-C goal is ≤ 100 mg/dL.

[†]Patients who knew the lipid-lowering treatment they were receiving prior to study entry.

Table VIII. Clinical adverse events (AEs) according to the World Health Organization.^{19*}

AE Category	No. (%) of Patients [†]
Gastrointestinal	45 (0.88)
Musculoskeletal	41 (0.81)
Central and peripheral nervous system	17 (0.33)
Biliary and hepatic	15 (0.29)
Dermatologic	11 (0.22)
Cardiovascular	9 (0.18)
Psychiatric	5 (0.10)
Vestibular and auditory	4 (0.08)
Respiratory	4 (0.08)
Autonomic nervous system	3 (0.06)
Vision	2 (0.04)
Urinary	2 (0.04)
Reproductive	1 (0.02)
General	1 (0.02)

*AEs considered treatment related (134 AEs in 89 patients) included myalgia (17 patients); creatine kinase level ≥ 540 U/L (15 patients); alanine aminotransferase or aspartate aminotransferase activity ≥ 60 U/L (14 patients); headache (12 patients); dyspepsia (9 patients); stomachache (5 patients); constipation (4 patients); alopecia, asthenia, and pruritus (3 patients each); and miscellaneous (49 patients).

[†]Percentages are based on a population of 5090 patients with at least 1 follow-up visit.

ALT or AST activity. Two patients (0.03%) had an increase in CK to ≥ 540 U/L per the last available laboratory follow-up. Laboratory abnormalities were dose related and reversible with drug withdrawal in all patients.

The incidence of AEs at specific stages in the study and at different dosages of atorvastatin for patients who completed the study and those lost to follow-up after visit 2 are shown in Table IX. The incidence of AEs in the first 2 months of the study was significantly higher than the incidence in the last 4 months ($P < 0.001$).

In the secondary tolerability analysis ($n = 6413$), 190 patients (3.0%) developed at least 1 AE. Thirty-one patients (0.5%) had at least 1 serious AE, and 102 (1.6%) dropped out of the study due to an AE.

Of the 1452 patients excluded for not meeting the study criteria, 1323 (91.1%) had at least 1 follow-up study visit. Of these patients, 42 (3.2%) developed AEs and 22 (1.7%) dropped out of the study due to an AE.

Among the 906 patients who were lost to follow-up after visit 2, 9 patients (1.0%) developed AEs, none of which were serious. Of all patients completing the study ($n = 4033$), 100 (2.5%) had reported AEs by visit 2 ($P = 0.005$).

On the case-report forms, 4922 of 5064 patients (97.2%) reported excellent or good tolerability with atorvastatin. Among the 5089 forms returned by the PCPs, 5013 (98.5%) reported excellent or good tolerability with atorvastatin.

DISCUSSION

Atorvastatin became available in 1997, and 1 year later a comparative dose-efficacy study¹⁵ showed that atorvastatin decreased lipid and lipoprotein levels

Table IX. Incidence of adverse events (AEs) at different study stages and atorvastatin doses.

Months of Follow-up	Atorvastatin Dosage, mg/d	No. of AEs	No. of Patient-Months	Incidence of AEs per 10,000 Patient-Months, %*
Patients who completed the study				
1-2	10	108	10,485	103
3-6	10	23	12,109	19 [†]
3-6	20	18	3464	52
1-6	10	131	22,594	58
Patients lost to follow-up after visit 2				
1-2	10	8	2020	40

*Time weighted-fit estimation: 2/6 of the first period incidence plus 4/6 of the second period incidence.

[†] $P < 0.001$ versus 2 months.

more effectively than other HMG-CoA reductase inhibitors. In our study, 59.1% of patients whose disease was previously uncontrolled with other statins met the SEA LDL-C goals at visit 3.

The mean percentages of reduction in LDL-C, TC, and TG levels in our study were within the range reported in a previous double-blind clinical trial,¹⁴ but with a higher increase in HDL-C levels. Our study showed significant differences in the mean percentages of reduction in LDL-C in all risk groups, which confirms the overall effectiveness of atorvastatin. A significant difference was found in the SEA LDL-C achievement rates between patients with low and moderate risk and those with high cardiovascular risk. However, the group of patients with high risk represented the majority of the study population. The identification and aggressive treatment of patients with high risk for CVD is cost-effective and should be a high priority for clinicians because those patients can benefit from the greatest absolute decrease in morbidity and mortality.

Our study reflected Spanish outpatient practice in the primary care setting and showed that 39.2% of patients achieved their LDL-C goals with the initial 10-mg/d dosage of atorvastatin after 2 months of treatment. Our results compare favorably with achievement rates of 1% to 27% reported with other statins 12 to 16 weeks after initiation of therapy.^{20,21} After 6 months of treatment with atorvastatin, 66.3% of our patients achieved the recommended SEA LDL-C goal. This success rate compares favorably with that reported in the LIPI-WATCH study,²² in which 36% of 1664 dyslipidemic patients achieved the European Atherosclerosis Society LDL-C goals with monotherapy or a combination of lipid-lowering drugs during a 5-month period. In the Lipid Treatment Assessment Project,²³ 38% of patients achieved the LDL-C goals of the National Cholesterol Education Program while receiving lipid-lowering drugs as monotherapy or combination therapy for at least 3 months. In both studies,^{22,23} the goal LDL-C levels were achieved in 40% of patients receiving statins as their only drug therapy. However, the success rate of studies that target physicians with high lipid-lowering prescribing habits may not reflect what happens in routine primary care practice, where LDL-C goals may be met by as few as 14.7% of patients.²⁴

We found a significant difference in the percentage of patients who achieved the SEA LDL-C goals at visit 2 compared with visit 3. To maintain LDL-C within target levels, PCPs should frequently reassure patients about the benefits of sustained adherence to treatment that decreases LDL-C levels and subsequent risk of CVD. In addition, PCPs should be aware of the need for retesting at 3- to 6-month intervals to ensure that target LDL-C levels are sustained.

Dose titration in patients who had not met their goals by visit 2 increased the SEA LDL-C goal achievement rates from 34.9% to 50.0%. Patients with a high cardiovascular risk may especially benefit from dose titration in this scenario because their rates of morbidity and mortality are higher than those with a low or moderate risk.

Tolerance of atorvastatin was considered excellent or good by most patients and PCPs during our study. The discontinuation rate of 1.5% related to the AEs that occurred with atorvastatin treatment compares favorably with discontinuation rates of 88%, 69%, and 4.4% reported with the use of niacin, sequestrants, and other statins, respectively.^{21,25} The incidence of AEs at visit 3 was significantly lower than at visit 2 in patients without dose titration. This information can help to reassure patients who are experiencing early nonserious AEs and to optimize treatment compliance.

The incidences of AEs and serious AEs were not higher for patients lost to follow-up after visit 2 than those of patients who completed the study. These results validate our tolerability data and minimize the role of AEs in patients' failure to adhere to the treatment regimen. Sustained reassurance and education are essential in optimizing patients' compliance in the primary care setting.

The CHEAP study analyzed data only from those patients who attended the scheduled follow-up study visits. When a patient did not comply with the study visits, data could not be collected and analyzed, no matter how high the dropout potential. The bias related to dropouts in the study was unavoidable.

CONCLUSIONS

In this study population, the use of atorvastatin in the primary care setting was associated with high achievement rates of the SEA LDL-C goals and with a substantial decrease in TG levels. In addition, a considerable increase in HDL-C levels occurred. Tolerability with atorvastatin was reported to be excellent or good by most of the patients and PCPs, respectively. The incidence of serious AEs was minimal, as reported by both patients and PCPs.

REFERENCES

1. Castelli WP, Garrison RJ, Wilson PW, et al. Incidence of coronary heart disease and lipoprotein cholesterol levels. The Framingham study. *JAMA*. 1986;256:2835–2838.
2. Neaton JD, Blackburn H, Jacobs D, et al. Serum cholesterol level and mortality findings for men screened in the Multiple Risk Factor Intervention Trial. Multiple Risk Factor Intervention Trial Research Group. *Arch Intern Med*. 1992;152:1490–1500.
3. Levine GN, Keaney JF Jr, Vita JA. Cholesterol reduction in cardiovascular disease. Clinical benefits and possible mechanisms. *N Engl J Med*. 1995;332:512–521.
4. Superko HR, Krauss RM. Coronary artery disease regression. Convincing evidence for the benefit of aggressive lipoprotein management. *Circulation*. 1994;90:1056–1069.
5. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: The Scandinavian Simvastatin Survival Study (4S). *Lancet*. 1994;344:1383–1389.
6. Sacks FM, Pfeffer MA, Moye LA, et al, for the Cholesterol and Recurrent Events Trial investigators. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. *N Engl J Med*. 1996;335:1001–1009.
7. West of Scotland Coronary Prevention Study: Identification of high-risk groups and comparison with other cardiovascular intervention trials. *Lancet*. 1996;348:1339–1342.

8. Summary of the second report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II). *JAMA*. 1993;269:3015–3023.
9. Pyörälä K, De Backer G, Graham I, et al. Prevention of coronary heart disease in clinical practice: Recommendations of the Task Force of the European Society of Cardiology, European Atherosclerosis Society and European Society of Hypertension. *Atherosclerosis*. 1994;110:121–161.
10. Spanish Society of Arteriosclerosis, Spanish Internal Medicine Society and League Against Hypertension. Recommendations for the primary prevention of cardiovascular disease [in Spanish]. *Clin Invest Arteriosclerosis*. 1994;6:62–102.
11. Downs JR, Clearfield M, Weis S, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: Results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. *JAMA*. 1998;279:1615–1622.
12. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med*. 1998;339:1349–1357.
13. Dujovne CA, Moriarty PM. Clinical pharmacologic concepts for the rational selection and use of drugs for the management of dyslipidemia. *Clin Ther*. 1996;18:392–410.
14. Nawrocki JW, Weiss SR, Davidson MH, et al. Reduction of LDL cholesterol by 25% to 60% in patients with primary hypercholesterolemia by atorvastatin, a new HMG-CoA reductase inhibitor. *Arterioscler Thromb Vasc Biol*. 1995;15:678–682.
15. 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;81:582–587.
16. Spanish Agency of Medicine. Reference 61716. October 17, 1997.
17. Guide for the Pharmaceutical Companies in Spain. Law 31/95 of Farmaindustria, and Law 18/90 of the Management of Pharmacy and Health Products.
18. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem*. 1972;18:499–502.
19. WHO Collaborating Centre for International Drug Monitoring. *International Monitoring of Adverse Reactions to Drugs: Adverse Reaction Terminology*. Uppsala, Sweden: Collaborating Centre for International Drug Monitoring; 1992.
20. Brown AS, Bakker-Arkema RG, Yellen L, et al. Treating patients with documented atherosclerosis to National Cholesterol Education Program-recommended low-density-lipoprotein cholesterol goals with atorvastatin, fluvastatin, lovastatin and simvastatin. *J Am Coll Cardiol*. 1998;32:665–672.
21. Dart A, Jerums G, Nicholson G, et al. A multicenter, double-blind, one-year study comparing safety and efficacy of atorvastatin versus simvastatin in patients with hypercholesterolemia. *Am J Cardiol*. 1997;80:39–44.
22. Muls E, De Backer G, De Bacquer D, et al. LIPI-WATCH, a Belgian/Luxembourg Survey on achievement of European Atherosclerosis Society lipid goals. *Clin Drug Invest*. 2000;19:219–229.
23. 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;160:459–467.

24. Gómez J, Martínez J, Babín F, et al. A working-day evaluation of dyslipidaemia in a Spanish population (JADE study). *Clin Drug Invest.* 2000;19:131–142.
 25. Hiatt JG, Shamsie SG, Schectman G. Discontinuation rates of cholesterol-lowering medications: Implications for primary care. *Am J Manag Care.* 1999;5:437–444.
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