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Original article

Degree of Lipid Control in Patients With Coronary Heart Disease and Measures Adopted by Physicians. REPAR Study

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ABSTRACT

Introduction and objectives: Lipid control is insufficient in patients with coronary heart disease but this situation may be improving with the implementation of the latest clinical practice guidelines. The aim of this study was to analyze whether target values of low-density lipoprotein cholesterol are achieved and to identify associated factors and physicians' attitudes to deficient control.

Methods: We conducted a national, multicenter, prospective, observational study of 1103 patients with stable coronary heart disease, analyzing lipid values and a broad set of clinical variables. The statistical analysis involved a binary logistic regression model using backward stepwise elimination.

Results: Low-density lipoprotein cholesterol was < 70 mg/dL in only 26% of patients, even though 95.3% were receiving cholesterol-lowering agents, 45% of which were high-intensity therapies. Independent predictors of low-density lipoprotein cholesterol < 70 mg/dL were diabetes mellitus, wholegrain bread, shorter history of dyslipidemia, and, especially, high-intensity cholesterol-lowering therapies. Physicians increased therapy in only 26% of poorly controlled patients. The main predictor of increased therapy was low-intensity baseline therapy (odds ratio = 5.05; 95% confidence interval, 3.3-9.2). A more proactive approach was observed in older physicians ($P = .019$) and longer physician practice ($P = .02$).

Conclusions: Despite the new guidelines, only 26% of patients with coronary heart disease have adequate lipid control. In 70% of patients, physicians continue the same therapy, even though high-intensity cholesterol-lowering therapies are a key factor in good control.

Grado de control lipídico en pacientes coronarios y medidas adoptadas por los médicos. Estudio REPAR

Palabras clave:
Dislipemia
Enfermedad coronaria
Estudio observacional
Valores objetivo

RESUMEN

Introducción y objetivos: El control lipídico es insuficiente en los pacientes coronarios, aunque las últimas guías de práctica clínica podrían haberlo modificado. El objetivo del estudio es analizar la consecución de los valores objetivo de colesterol unido a lipoproteínas de baja densidad, los factores asociados y las actitudes de los médicos ante un control deficiente.

Métodos: Estudio observacional, prospectivo, multicéntrico y nacional de 1.103 pacientes con enfermedad coronaria estable, incluyendo determinaciones lipídicas y un amplio conjunto de variables clínicas. Estudio estadístico: modelo de regresión logística binaria con el procedimiento de eliminación secuencial progresiva paso a paso.

Resultados: Solo el 26% de los pacientes tenían cifras de colesterol unido a lipoproteínas de baja densidad < 70 mg/dl pese a que el 95,3% recibían hipolipemiantes, el 45% de ellos de alta intensidad. Los factores independientes asociados a cifras < 70 mg/dl fueron la diabetes mellitus, el consumo de pan integral, las dislipemias de menor duración y, especialmente, el tratamiento de alta potencia. De los pacientes mal controlados, el médico solo aumentó el tratamiento al 26%. El principal factor asociado a escalada de tratamiento fue un tratamiento basal de baja potencia (*odds ratio* = 5,05; intervalo de confianza del 95%, 3,3-9,2). Tuvieron actitud más proactiva los médicos de más edad (p = 0,019) y más largo ejercicio (p = 0,02).

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Conclusiones: Pese a los cambios en las guías, solo un 26% de los pacientes coronarios presentan un adecuado control lipídico, y aun así en un 70% de los casos el médico mantiene el tratamiento pese a que, precisamente, es el tratamiento de alta intensidad el factor fundamental de un buen control.

Abbreviations

CV: cardiovascular
LDL-C: low-density lipoprotein cholesterol
MOR: median odds ratio

INTRODUCTION

The degree of lipid control has been the subject of heated debate in the medical community in recent years and is the source of differences between the recommendations in the European Guidelines on cardiovasvular (CV) disease prevention in clinical practice[1] and the ACC/AHA guideline on the treatment of blood cholesterol.[2] The European guidelines recommend a low-density lipoprotein cholesterol (LDL-C) target of < 70 mg/dL for patients at very high risk and the American guideline simply recommend the use of high-intensity statin therapy. Considerable evidence in the literature shows that intensive lowering of LDL-C provides benefit in these patients.[3–6]

Several authors have reported that these ambitious targets were not being achieved in Spain.[7–9] However, this situation could have changed with the new guidelines and knowledge, as suggested by the results of the IMPROVE-IT trial, which report lower LDL-C values with the addition of ezetimibe.[10]

The aims of the REPAR (Spanish Register for Lipid Control in Patients at Very High Risk) Study were to evaluate to what extent target LDL-C levels are achieved in patients at very high CV risk in Spain, to identify associated factors, measures taken by treating physicians when their patients are off target, and variability of such measures by autonomous community.

METHODS

The study had a national, multicenter, prospective, observational design. The protocol was approved by the ethics committee of *Unitat d'Avaluació, Suport i Prevenció* at Hospital Clínic, Barcelona. All patients gave their written informed consent.

Study Population and Sample Size

Inclusion criteria were patients aged ≥ 18 years recruited consecutively at cardiology clinics, at very high CV risk based on the European Society of Cardiology[11] defined as any one of the following: *a)* documented CV disease and at least 6 months since the last CV event; *b)* type 2 diabetes mellitus or type 1 diabetes mellitus with target organ damage; *c)* moderate to severe chronic kidney disease, or *d)* risk score > 10%. Another criterion was blood test results in the 3 months prior to recruitment. Patients were excluded if they had cancer or other disease that could confound study results.

We calculated the sample size from a previous study,[8] in which 31.3% of high-risk patients achieved therapeutic targets. Using a binomial distribution, we estimated a sample size of 1360 patients, with ± 2.5% accuracy, to identify the percentage of patients at very high CV risk who achieve the therapeutic targets for LDL-C, with a 95% confidence interval (95%CI). Assuming that 2.5% of patients would not be evaluable, we therefore needed to recruit 1395 patients.

Study Supervision

A total of 140 cardiologists were selected randomly from all the Spanish autonomous communities (Appendix). Each cardiologist was responsible for recruiting 10 consecutive patients. The recruitment period was from November 6, 2013 to July 31, 2014. The investigators collected study data in an electronic case report form. The data from the case report forms were entered in a database with internal consistency rules and ranges to ensure data quality, and data cleaning was performed.

Variables

We grouped patients by intensity of lipid-lowering therapy[2]: *a)* low-intensity (no treatment or daily dose of simvastatin 10 mg, pravastatin 10 to 20 mg, lovastatin 20 mg, fluvastatin 20 to 40 mg, pitavastatin 1 mg or ezetimibe 10 mg alone); *b)* moderate-intensity (atorvastatin 10-20 mg or rosuvastatin 5-10 mg, simvastatin 20-40 mg, pravastatin 40-80 mg, lovastatin 40 mg, fluvastatin XL 80 mg or pitavastatin 2-4 mg, or a low-intensity statin plus ezetimibe), and *c)* high-intensity (atorvastatin 40-80 mg, rosuvastatin 10-40 mg or any moderate-intensity statin plus ezetimibe).

The study primary endpoint was "adequate lipid control". Following the European guideline criteria for CV prevention,[1] we defined adequate control as LDL-C < 70 mg/dL and divided the study population into 2 groups: LDL-C < 70 mg/dL and LDL-C ≥ 70 mg/dL.

Under the healthy habits section, alcohol consumption was defined in units (1 unit = 1 beer, 1 glass of wine, 1/2 shot of liqueur or 1/2 whisky). More than 2 units/d was considered as excessive. Physical exercise was defined as walking for at least 30 minutes per day or more than 2 sports sessions per week.

A short dietary intake questionnaire was used to analyze adherence to a Mediterranean diet.[12]

"Treatment after first visit" was reported as a variable to identify whether cholesterol-lowering therapy was up titrated.

Statistical Analysis

The study was designed with 2 cross-sectional time points: at inclusion and at 1 year of follow up. This article refers to the first point only, because the second is still under way.

The sample was described using absolute and relative frequencies for dichotomous variables, and mean ± standard deviation or median [interquartile range] for continuous variables, depending on whether or not they followed a normal distribution. For the between-group comparison (LDL-C < 70 mg/dL and LDL-C ≥ 70 mg/dL, subdivided into up titration and no titration), we used the chi-square test for categorical variables and the Student *t* test for continuous variables.

We analyzed independent predictors of therapeutic target achievement (primary endpoint) using a binary logistic regression model and LDL-C < 70 mg/dL as the dependent variable. Our initial

model included all variables showing a statistically significant association with the dependent variable in the bivariate analysis. Statistical significance was defined as $P < .1$. We used backward stepwise elimination and P entrance/exit tolerances of $< .05$ and $> .1$, respectively (with automated variable selection), to progressively eliminate variables until the model included only potential predictors of LDL-C < 70 mg/dL with a statistical significance of $P < .05$. Potential effect modifiers were assessed using first-order interactions.

We then used the same procedure to analyze independent predictors of up titration after the first visit (increased intensity of the cholesterol-lowering therapy) in patients with LDL-C ≥ 70 mg/dL.

Finally, we examined variability by Spanish autonomous community in the prescription of high-intensity cholesterol-lowering therapy after the first visit, and whether such variability could be explained by the characteristics of the patients seen in each autonomous community or by the autonomous community size, expressed as total population. This analysis was performed only in autonomous communities that had enrolled at least 20 patients. We constructed a 3-step multilevel regression model[13]: in the first step we included a random constant only, to measure inter-community variability in patient rates with high-intensity cholesterol-lowering therapy. Second, we added various individual patient characteristics, to investigate whether the prescription differences by community could be explained by the characteristics of the patients seen in each community. We tested all the baseline characteristics that showed between-group differences with a statistical significance of $P < .1$. If autonomous community variability in the rate of patients with high-intensity cholesterol-lowering therapy fell to zero after we had adjusted by patient characteristics, variability would be due solely to the differences in the patients seen. Finally, in the third step we included the total population for each autonomous community. We estimated odds ratio (OR) as a measure of association. The multilevel regression models were constructed assuming independent covariance calculated with the R statistical package, version 0.98.953.

To measure the change in variability by autonomous community, at each step we calculated the percentage change in variance among autonomous communities in the most complex model vs the simplest. To measure the magnitude of the variance among autonomous communities, we estimated the intraclass correlation coefficient (ICC) and median OR (MOR). The ICC can be interpreted as the proportion of total variance in a selected variable that can be attributed to differences among autonomous communities. The MOR is defined as the median value of the estimated OR in the autonomous communities at "highest risk" and "lowest risk" after randomly selecting 2 autonomous communities repeated times. In this study, the MOR shows the extent to which the individual probability of receiving high-intensity cholesterol-lowering therapy is determined by the autonomous community where the patient is seen. A MOR equal to 1 would mean that there are no differences between autonomous communities in prescription rates. A MOR significantly greater than 1 would mean that there is some characteristic of the autonomous community that is relevant for explaining variations in the individual probability of receiving high-intensity cholesterol-lowering therapy, ie, some variability among autonomous communities remains unexplained. We used a 95%CI for ICC estimations and the Bayesian approach for MORs.

Analyses were calculated with the statistical packages SPSS 13.0 (Chicago, Illinois, United States) and R, version 0.98.953.

RESULTS

A total of 116 physicians recruited 1291 patients, 1103 of whom had coronary heart disease and the remainder fulfilled other inclusion criteria. To increase sample homogeneity, we focused on patients with coronary heart disease since they were a majority, and finally analyzed only the 1055 patients with available baseline LDL-C values. The general characteristics of this final study population are shown in Table 1.

Serum Lipid Values and Cholesterol-lowering Therapies

The most relevant serum lipid values for the entire study population (Table 1) were total cholesterol, 175 ± 46 mg/dL; high-density lipoprotein cholesterol, 46 ± 13 mg/dL; LDL-C, 94 ± 44 mg/dL; triglycerides, 138 ± 72 mg/dL; glycated hemoglobin, $6.4\% \pm 1.1\%$; ultrasensitive C-reactive protein, 2.5 ± 4.2 mg/dL, and creatinine clearance (Cockroft), 87.2 ± 58.5 mL/min/1.73 m^2.

Figure 1 shows the use of cholesterol-lowering agents by active substance. The most commonly-used drug was atorvastatin (47%), followed by rosuvastatin (20%) and simvastatin (19%). Among nonstatin cholesterol-lowering agents, ezetimibe was prescribed to 14% of the patients. A small number of patients, 4.7%, did not receive any cholesterol-lowering agent.

By therapy intensity, 45%, 45%, and 10% of patients received high-, moderate-, and low-intensity cholesterol-lowering therapy, respectively.

Table 1
Baseline Characteristics of the Study Population

Patients, No.	1055
Clinical variables	
Age, y	67 ± 10
Women	196 (18.6)
Abdominal girth, cm	99.1 ± 12.1
SBP, mmHg	137 ± 18
DBP, mmHg	78 ± 11
HR, bpm	66 ± 11
Time since dyslipidemia diagnosis, y	8.3 ± 7.3
Active smoker	163 (15.5)
HT	605 (57.3)
Diabetes mellitus	366 (34.7)
Myocardial infarction (history)	684 (64.8)
Previous coronary revascularization	762 (72.2)
Cerebrovascular disease	65 (6.2)
Peripheral arterial disease	101 (9.6)
Laboratory variables	
Total cholesterol, mg/dL	175 ± 46
LDL-C, mg/dL	94 ± 44
HDL-C, mg/dL	46 ± 13
Triglycerides, mg/dL	138 ± 72
Creatinine, mg/dL	1.05 ± 0.48
Glycated hemoglobin, %	6.4 ± 1.1
Ultrasensitive CRP, mg/dL	2.5 ± 4.2
Albumin to creatinine ratio	126 ± 206
Creatinine clearance (Cockroft), mL/min/1.73 m^2	87.2 ± 58.5
Creatinine clearance < 60 mL/min/1.73 m^2*	226 (22.2)

CRP, C-reactive protein; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; HR, heart rate; HT, hypertension; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure.
Unless otherwise indicated, data are expressed as No. (%) or mean ± standard deviation.
* Determined in 1017 patients.

Lipid Control and Associated Factors

In the baseline blood tests for the entire study set, 279 patients (26%) had adequate LDL-C control, while the remaining 776 (74%) had LDL-C ≥ 70 mg/dL. The clinical variables associated with LDL-C < 70 mg/dL are shown in Table 2. The following variables were of particular note: diabetes mellitus, coronary revascularization, better blood pressure control, lower heart rate, and, above all, high-intensity cholesterol-lowering therapy. In contrast, active smoking, a family history of dyslipidemia and concomitant carotid artery disease were associated with poor lipid control (LDL-C ≥ 70 mg/dL). Table 2 also lists diet and exercise factors, and shows an association between good lipid control and gentle daily exercise, fruit, and wholegrain bread intake.

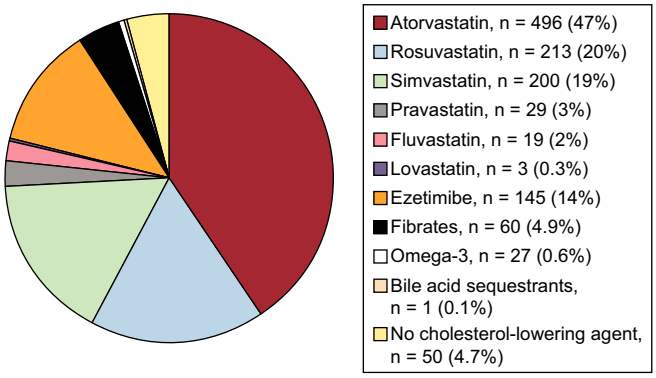

Figure 1. Distribution of the prescription of cholesterol-lowering agents in the study patient population.

Table 2
Factors Associated With Good Lipid Control (Low-density Lipoprotein Cholesterol < 70 mg/dL)

	Valid patients, No.	LDL-C < 70 mg/dL (n = 279)	LDL-C ≥ 70 mg/dL (n = 776)	*P*
Age, y	1055	67 ± 10	67 ± 10	.890
Women	1055	44 (15.8)	152 (19.6)	.160
HT	1055	154 (55.2)	451 (58.1)	.400
Diabetes mellitus	1055	121 (43.2)	245 (31.6)	< .001
Smoker	1055			.320
Nonsmoker		91 (32.6)	258 (33.2)	
Exsmoker		152 (54.5)	391 (50.4)	
Smoker		36 (12.9)	127 (16.4)	
Family history of dyslipidemia		50 (17.9)	216 (27.8)	.001
Time since dyslipidemia diagnosis, y	889	7.1 ± 6.0	8.7 ± 7.6	.003
Myocardial infarction, history	1055	194 (69.5)	490 (63.1)	.055
Coronary revascularization	1055	215 (77.1)	547 (70.5)	.036
Heart failure	1055	31 (11.1)	65 (8.4)	.170
Atrial fibrillation	1055	36 (12.9)	80 (10.3)	.230
Peripheral arterial disease	1055	31 (11.1)	70 (9.0)	.310
Carotid artery disease	1055	5 (1.8)	35 (4.5)	.041
Ischemic stroke	1055	11 (3.9)	24 (3.1)	.500
Weight, kg	1032	81.3 ± 14.0	81.1 ± 13.0	.890
Abdominal girth, cm	970	98.9 ± 13.1	99.1 ± 11.8	.780
Systolic blood pressure, mmHg	1055	134.0 ± 17.2	137.5 ± 19.0	.012
Diastolic blood pressure, mmHg	1055	76.0 ± 10.3	78.0 ± 11.2	.009
Heart rate, bpm	1037	63.8 ± 11.5	66.7 ± 11.2	< .001
Intensity of cholesterol-lowering therapy	1055			< .001
High intensity		167 (59.9)	309 (39.8)	
Moderate intensity		102 (36.6)	375 (48.3)	
Low intensity or none		10 (3.6)	92 (11.9)	
At least 30-min daily walk	1030	182 (66.9)	430 (56.7)	.003
Alcohol consumption	803	72 (34.3)	185 (31.2)	.410
Diet				
Olive oil (≥ 1 tbsp/d)	1010	241 (89.9)	671 (90.4)	.810
Fruit (≥ 1 serving/d)	992	230 (87.5)	596 (81.1)	.034
Vegetables or salad (≥ 1 serving/d)	985	197 (74.6)	552 (76.6)	.530
Fruit and vegetables (≥ 1 piece/d)	985	197 (74.1)	504 (70.1)	.220
Pulses (≥ 2 servings/wk)	998	207 (77.8)	556 (76.1)	.570
Fish (≥ 3 servings/wk)	1003	162 (60.7)	471 (64.0)	.330
Wine (≥ 1 glass/d)	1005	140 (52.6)	424 (57.4)	.180
Meat (< 1 serving/d)	1002	164 (61.2)	456 (62.1)	.790
White bread (< 1 serving/d) or rice (< 1 serving/wk) or wholegrain bread (> 5 d/wk)	1000	146 (54.5)	450 (61.5)	.046

HT, hypertension; LDL-C, low-density lipoprotein cholesterol.
Data are expressed as No. (%) or mean ± standard deviation.

Table 3
Independent Predictors of Low-density Lipoprotein Cholesterol < 70 mg/dL. Logistic Regression

	OR (95%CI)	*P*
Initial HR (for every 10 beats +)	0.8 (0.67-0.90)	.002
Time since diagnosis (for every 5 y +)	0.9 (0.76-0.98)	.024
Diet low in white bread and rice, or rich in wholegrain bread	1.4 (1.01-1.90)	.041
Diabetes mellitus	1.9 (1.35-2.60)	< .001
Cholesterol-lowering therapy		
Moderate intensity	1.8 (0.85-3.80)	.120
High intensity	3.1 (1.48-6.50)	.003

95%CI, 95% confidence interval; HR, heart rate; LDL-C, low-density lipoprotein cholesterol; OR, odds ratio.
C-statistic = 0.67 (0.63-0.71).
P value for Hosmer-Lemeshow goodness of fit = .23.

The independent predictors of LDL-C < 70 mg/dL in the multivariable analysis are shown in Table 3. The highest OR was associated with high-intensity cholesterol-lowering therapy. Lipid control was also better among diabetic patients, patients with diets containing less white bread and/or rice, and, finally, patients with a shorter history of dyslipidemia.

Physician Attitude to Poor Control

We analyzed prescription changes that physicians made for the 776 patients who had LDL-C ≥ 70 mg/dL. No change was made in 70% of patients. Therapy intensity was increased in 26% and was reduced in 3%. The main variables associated with up titration of therapy were low-strength therapy at baseline (OR = 5.05; 95%CI, 3.3-9.2) and the LDL-C value itself (OR = 1.2; 95%CI, 1.01-1.02). Specifically, of the patients with baseline LDL-C ≥ 70 mg/dL, an LDL-C value of 140 ± 43 mg/dL was found among patients whose therapy was up titrated vs a value of 104 ± 36 mg/dL among those whose therapy remained unchanged ($P < .001$). We also analyzed physician characteristics and found a more proactive attitude to up titration among older physicians ($P = .02$).

Analysis by Autonomous Community

Figure 2 shows a major difference in baseline LDL-C values by autonomous community. We also found differences when we investigated variability among autonomous communities in high-intensity cholesterol-lowering therapy prescription rates (Figure 3). In the unadjusted multilevel model, this variability was 75%, with ICC = 0.14 (95%CI, 0.05-0.32) and MOR = 4.02 (95%CI, 1.22-6.65) (Table 4). Various baseline patient characteristics were associated with a higher prescription rate of high-intensity cholesterol-lowering therapy: age, hypertension, smoking, history of myocardial infarction, and baseline LDL-C. Variability among autonomous communities remained unchanged after adjustment for these variables (ICC = 0.14; 95%CI, 0.05-0.31; MOR = 2.45; 95%CI, 1.21-6.4), showing there must be another factor unrelated to patient profiles that would explain this prescription rate. Finally, we adjusted by the "global population" variable by autonomous communities, and found that variability persisted (ICC = 0.16; 95%CI, 0.05-0.35; MOR = 3.28; 95%CI, 1.25-9.41), suggesting variability in the care process unexplained by individual patient characteristics or autonomous community population size.

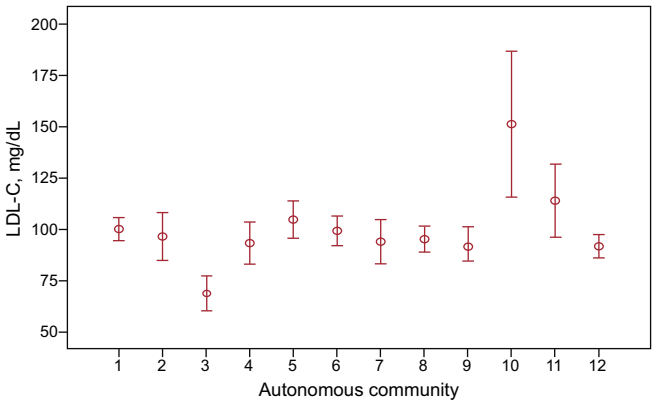

Figure 2. Low-density lipoprotein cholesterol values (mean ± standard deviation) of study patients with coronary heart disease based on laboratory test results before the baseline visit by autonomous community of residence. LDL-C, low-density lipoprotein cholesterol.

DISCUSSION

The degree of LDL-C control in patients with chronic coronary heart disease in Spain is still very low. Indeed, we observed adequate lipid control, which was the primary endpoint in this study, in only 26% of patients. This low figure is a cause for concern, because strategies that produce marked LDL-C reduction are associated with significant reductions in major adverse cardiovascular events.[14] Compared with previous studies,[7–9,15] the degree of control is even lower in our study, although results are not necessarily comparable due to a higher cutoff point (LDL-C < 100) in one study[8] and inclusion of participants at cardiovascular risk but without coronary heart disease itself in another study.[7]

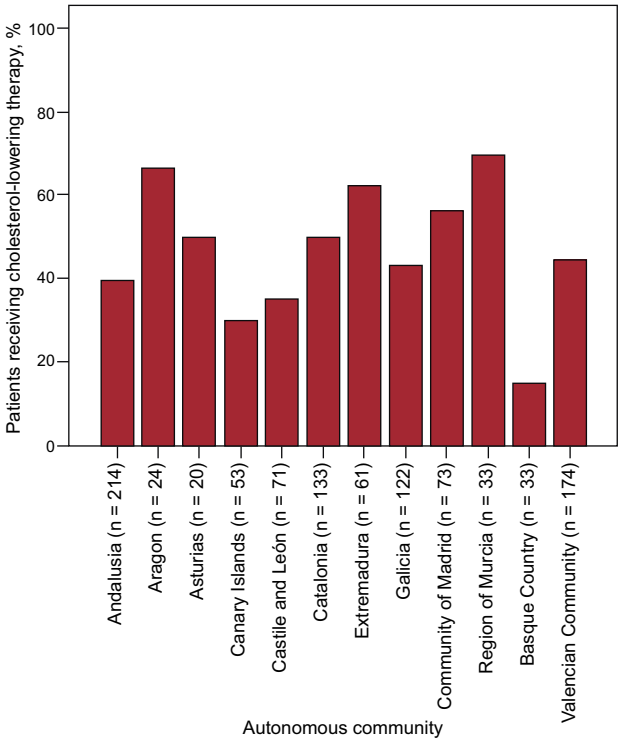

Figure 3. Variability in the prescription of cholesterol-lowering agents by Spanish autonomous community. Data collected at the baseline visit on therapy received until then.

Table 4
Variability by Autonomous Community

	Model 1		Model 2	
	OR (95%CI)	*P*	OR (95%CI)	*P*
Patient variables				
Age, for every 10 years	0.78 (0.65-0.92)	.001	0.77 (0.65-0.90)	.002
Hypertension	6.18 (1.27-20.0)	.022	5.58 (1.21-17.8)	.020
History of myocardial infarction	1.68 (1.17-2.32)	.004	1.68 (1.17-2.36)	.004
Active smoker	2.10 (1.25-3.35)	.002	2.15 (1.24-3.46)	.005
LDL-C (for every 10 mg/dL)	1.12 (1.08-1.17)	<.001	1.13 (1.08-1.17)	<.001
Autonomous community variables				
Population, 1 000 000 persons			1.00 (0.98-1.02)	.820

95%CI, 95% confidence interval; ICC, intraclass correlation coefficient; LDL-C, low-density lipoprotein cholesterol; OR, odds ratio.
Initial model without adjustment by variables (not shown in the Table): variance = 0.75; intraclass correlation coefficient = 0.14 (0.05-0.32); median odds ratio = 4.02 (1.22-6.65); goodness of fit = 1.51 (P = .9); discrimination = 0.63 ($P < .01$).
Model 1: variance = 0.75; intraclass correlation coefficient = 0.14 (0.05-0.31); median odds ratio = 2.45 (1.21-6.4); goodness of fit = 9.69 (P = .3); discrimination = 0.7 ($P < .001$).
Model 2: variance = 0.88; intraclass correlation coefficient = 0.16 (0.05-0.35); median odds ratio = 3.28 (1.25-9.41); goodness of fit = 8.8 (P = .35); discrimination = 0.7 ($P < .001$).

Furthermore, our study differs from others because we also investigated physician behavior and potential factors influencing physician actions, which provides a better overview of the problem.

The practice of administering cholesterol-lowering agents to patients with coronary heart disease is widely implemented (95.3% of patients received these drugs) and we should also note that there is a small percentage of patients with statin intolerance. Some 40% of patients received high-intensity cholesterol-lowering therapy (but not all were on maximum therapy because, for example, just 14% received ezetimibe). However, only 25% were well controlled, showing that adequate lipid control is hard to achieve. Doubling a statin dose reduces LDL-C by only 6.9% to 9.5%.[16] Therefore, considering general LDL-C values in a population with coronary heart disease (94 ± 44 mg/dL in this study), it is unlikely that this common change in therapy will reduce LDL-C values to < 70 mg/dL. As a result, therapy will need up titration and, in many cases, the addition of other drugs.[10] The use of novel, more potent cholesterol-lowering agents, such as PCSK9 inhibitors,[17,18] could help achieve lipid control targets.

One of the most striking findings of this study is the low proportion (26%) of increased therapy among poorly controlled patients. This concept, known as therapeutic inertia, has already been described in this patient population.[19] However, in our study, inertia should have been lower because the physicians knew they were participating in a lipid register.

The causes of therapeutic inertia include lack of consensus or knowledge of clinical practice guidelines,[20] physicians overestimating the number of their patients with good lipid control,[21] specialists being too focused on the acute disease stage, and extreme work load (although some studies were unable to find an association with the number of patients seen per week[19]). In our study, we found that older cardiologists prescribed significantly better treatment than their younger counterparts. Differences by autonomous community in high-intensity cholesterol-lowering therapy are another interesting finding, worthy of further reflection and investigation, but fall beyond the realms of this study. These differences in the care process remain unexplained by differences in patient characteristics, since variability scarcely changed when we adjusted the regression model by patient characteristics.

Underprescription could also be explained by lack of habit using drug combinations for dyslipidemias (combinations are very common in other fields) and even fear of using high-intensity cholesterol-lowering agents due to their potential adverse effects, although this is illogical because the undesired effects of cholesterol-lowering agents are readily reversed and a J-curve relationship in this field has yet to be demonstrated.

In addition, the health system itself further hinders the use of more potent or novel drugs and combinations by giving preference to lower-strength generics.[22] Another factor, which we did not analyze in this study, is the degree of medication adherence. Lack of adherence could explain poor lipid control. Alarming figures have been published in other settings on discontinuation of cholesterol-lowering agents after 1 year of treatment. Discontinuation rates were largely dependent on drug class: 68.3% for bile acid sequestrants, 55.4% for niacin, 39.9% fibrates, 33.0% ezetimibe, and 28.9% for statins ($P < .001$ for all cholesterol-lowering agents vs statins).[23]

These problems can be addressed through different initiatives, such as patient education, physician training, specialized units, multidisciplinary programs,[24] and even alternative therapies or intermittent dosing for statin-intolerant patients.[25]

Limitations

Although we instructed investigators to recruit patients consecutively to the study, as specified in the protocol, we did not check whether this requirement was fulfilled, and therefore we cannot rule out selection bias. Also, investigators were not selected or stratified at random by care level. We tried to ensure that all care levels were represented, but we cannot guarantee they were represented equally.

CONCLUSIONS

This study shows that despite changes in lipid control targets in official guidelines, a significant proportion of patients with coronary heart disease in Spain still has poor lipid control. In addition, most physicians take no action to correct poor lipid control. Our analysis of cholesterol-lowering therapies prescribed by physicians reveals room for improvement. In short, proactive policies should be implemented to encourage up titration of cholesterol-lowering therapies and the use of drug combinations when necessary, and to remove obstacles causing therapeutic inertia.

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Ferrer Internacional, Spain. The REPAR study is an initiative of the Vascular Risk and Cardiac Rehabilitation Section of the Spanish Society of Cardiology.

CONFLICTS OF INTEREST

E. Galve has received remuneration from Ferrer and E. Ruiz is on the staff of the medical department at Ferrer.

APPENDIX. CARDIOLOGISTS IN THE REPAR REGISTER

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WHAT IS KNOWN ABOUT THE TOPIC?

- In Spain, patients with coronary heart disease have insufficient lipid control but it is unknown whether new knowledge and guidelines have improved the situation.

WHAT DOES THIS STUDY ADD?

- This study shows that control remains inadequate (only 26% of patients have LDL-C $<$ 70 mg/dL); that there is room for improvement in current therapies because high-intensity statins are used in only 45% of patients and adjuvants such as ezetimibe are used in only 14%; that physicians show therapeutic inertia because they abstain from increasing therapy in 70% of patients, and that there are significant differences by autonomous community in Spain in terms of lipid control management.

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