A Very High Prevalence of Low HDL Cholesterol in Spanish Patients With Acute Coronary Syndromes

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ABSTRACT

Background: Total and low-density lipoprotein cholesterol (LDL-C) concentrations in coronary artery disease have progressively declined, although high-density lipoprotein cholesterol (HDL-C) has not always been evaluated. The prevalence and related factors of low HDL-C in a cohort of Spanish patients with acute coronary syndromes (ACS) were assessed.

Methods: Clinical and laboratory data registered at admission and at discharge of 648 patients admitted to coronary care units of 6 Spanish hospitals for ACS between January 2004 and September 2007 were analyzed.

Results: Low HDL-C (HDL-C <1.04 mmol/L) was observed in 367 (56.6%) patients. Male gender, smoking, hypertension, diabetes, high body mass index, and triglycerides were related to low HDL-C. Female gender was the strongest protective factor against low HDL-C (0.619; 95% confidence interval [CI]: 0.410–0.934; $P = 0.022$), whereas high triglycerides (1.653; 95% CI: 1.323–2.064; $P < 0.001$) followed by previous ischemic disease (1.504; 95% CI: 1.073–2.110; $P = 0.018$) were the strongest factors associated with low HDL-C. One-third of patients were taking statins at admission, but only 2% were on fibrate therapy. A large increase in statin therapy, but not in other hypolipemiant drug therapy, between admission and discharge was noted in the whole cohort and among patients with low HDL-C.

Conclusion: Spanish patients with ACS have a very high prevalence of low HDL-C. Male gender, high triglycerides, and previous ischemic disease are strong, independent factors associated with this disorder. As low HDL-C remains almost completely untreated in ACS, strategies to enhance the treatment of this lipoprotein abnormality are urgently required.

Introduction

In accordance with the different international guidelines, low-density lipoprotein cholesterol (LDL-C) is the main therapeutic target in cardiovascular disease prevention.[1,2] As a consequence, statin therapy is the cornerstone of cholesterol management, supported by extensive evidence from major prospective clinical trials on both primary and secondary prevention of cardiovascular disease.[3] However, despite intensive therapy with statins, the risk of a major cardiovascular event in patients with established coronary artery disease (CAD) remains high, approaching an annual risk of 9%.[4] In addition, a high percentage of patients with CAD and desirable LDL-C levels have low high-density lipoprotein cholesterol (HDL-C) levels.[5] Low HDL-C concentration is a major coronary risk factor.[6,7] In this respect, numerous prospective studies support a strong inverse correlation between HDL-C levels and cardiovascular risk and clinical studies using pharmacologic intervention such as fibrates or nicotinic acid to raise HDL-C levels have demonstrated beneficial effects in terms of clinical outcomes and atherosclerosis regression.[8–10] Thus, isolated low HDL-C is a key issue in clinical practice since it identifies a significant subgroup of patients who have already achieved their LDL-C goals, but are still in need of additional therapy to increase their HDL-C concentrations. Epidemiologic studies in recent years have shown a marked decline in the prevalence of hypercholesterolemia together with LDL-C levels. In this respect, analysis of the National Health and Nutrition Examination Survey

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(NHANES) database reveals that, whereas cholesterol levels in CAD patients have declined in recent decades,[11] HDL-C levels remain unchanged. Moreover, HDL-C levels declined significantly from 43 mg/dL in 2000 to 39 mg/dL in 2006.[12] This decrease has been attributed to the growing rates of obesity, insulin resistance, and diabetes; however, the lack of HDL-C-increasing therapy must also be taken into account. Given that the Mediterranean population has a differential lipid profile with higher HDL-C levels than other populations,[13] and that lipid-lowering agents used in most ischemic patients to lower LDL-C may also increase HDL, the prevalence of low HDL-C in patients in the hospital care setting has not always been evaluated. The aim of the present study was to assess the prevalence, main related factors, and level of treatment of low HDL-C in a cohort of Spanish patients hospitalized with acute coronary syndromes (ACS).

Methods

Study Population

A total of 648 medical records of patients admitted to coronary care units of 6 Spanish tertiary hospitals for ACS between January 2004 and September 2007 were examined. Acute coronary syndrome was defined according to European/American recommendations.[14,15] Age, gender, anthropometric parameters, previous ischemic disease (coronary artery disease, stroke, or peripheral arterial disease), hypertension, diabetes, smoking, and the number of patients taking statins, fibrates, or omega-3 fatty acids at admission and at discharge were retrospectively assessed from the clinical records. Nicotinic acid was not available in Spain during the time of the study. Hypertension and diabetes were considered present if they were registered in the medical records or when the patients were on antihypertensive or antidiabetic drug therapy. Smoking was classified as: non-smokers, including those who had never smoked and those who were ex-smokers, and current smokers. Serum glucose, measured by the oxidase method, and lipid profile were recorded. Total cholesterol and triglycerides were determined using enzymatic methods in a Cobas Mira automatic analyzer (Baxter Diagnostics AG, Düdingen, Switzerland). High-density lipoprotein cholesterol was measured using separation by precipitation with phosphotungstic acid and magnesium chloride. LDL-C concentration was calculated using the Friedewald formula. Non-HDL-C was calculated as total cholesterol minus HDL-C. Low HDL-C was defined as a serum concentration <1.04 mmol/L (40 mg/dL), according to the Adult Treatment Panel III of the National Cholesterol Education Program.[6] Furthermore, we compared the prevalence of low HDL-C for LDL-C and triglyceride concentrations. For this purpose the following categories were defined: for LDL-C, <1.813 mmol/L (70 mg/dL), 1.813 to 2.59 mmol/L (70–100 mg/dL) and >2.59 mmol/L (100 mg/dL), and for triglycerides, <1.68 mmol/L (150 mg/dL), 1.68 to 2.24 mmol/L (150–200 mg/dL) and >2.24 mmol/L (200 mg/dL).

Statistical Analysis

A Student *t* test was performed to assess differences between means. When data were not normally distributed, a Mann-Whitney test was used. Either an χ^2 test or Fisher's exact test was used to test the degree of association of categorical variables. Computed factors in the univariate analysis were age, gender, body mass index, previous ischemic disease, smoking, hypertension (dichotomized as present vs absent), diabetes mellitus (dichotomized as present vs absent), serum fasting glucose, total cholesterol, LDL-C, triglycerides, non HDL-C, statin, fibrate, and omega-3 fatty acid therapies at admission and at discharge. Variables demonstrating a univariate relationship ($P < 0.05$) with the outcome variable were included in the model to assess the effect of independent variables on low HDL-C. A P value <0.05 was considered statistically significant. All statistical analyses of database results were performed with SPSS software (SPSS for Windows, v.11.5, Chicago, IL).

Results

The clinical characteristics of the study sample are shown in Table 1. A total of 43% of patients had had previous ischemic disease, and the percentage of patients on statin therapy at admission was one-third. The use of fibrates and omega-3 fatty acids was rare (<3%) and did not differ in patients with prior CAD compared with those without. Low HDL-C was observed in 367 (56.6%) patients and was more prevalent in CAD patients with recurrent disease than in those presenting with a first acute coronary syndrome (46.2% vs 39.5%, respectively, $P = 0.09$). Patients with low HDL-C were more frequently male; had a higher body mass index and triglyceride concentrations; a higher prevalence of smoking, hypertension, and diabetes; and lower total cholesterol concentrations. Overall, no differences in the number of patients taking statins, fibrates, or omega-3 fatty acids were observed between those with and without low HDL-C (Table 2).

A great increase in statin therapy between admission and discharge was noted; however, no increase in fibrate and omega-3 fatty acid therapies in the whole cohort and among patients with low HDL-C was observed during this period. When comparing the prevalence of low HDL-C for LDL-C and triglyceride subsets, low HDL-C was similarly prevalent across all LDL-C levels, whereas low HDL-C was more frequent among patients with borderline-high or high triglycerides (Figure 1).

A logistic regression model was fitted to determine factors associated with low HDL-C in patients with ACS. The variables that did not enter the equation were age ($P = 0.689$), smoking status ($P = 0.073$), hypertension ($P = 0.149$), diabetes mellitus ($P = 0.117$), serum fasting

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Table 1. Characteristics of the 648 Spanish Patients With Acute Coronary Syndromes

	n = 648
Female	132 (20.4%)
Age (yrs)	63 ± 12
Body mass index	28.42 ± 4.2
Previous ischemic disease	274 (43.3%)
Smoker	252 (39.6%)
Hypertension	387 (60.9%)
Diabetes mellitus	207 (32.9%)
Glucose (mmol/L)	7.19 ± 3.32
Total cholesterol (mmol/L)	4.87 ± 1.19
LDL cholesterol (mmol/L)	3.13 ± 1.08
<1.813 mmol/L	72 (11.2%)
1.813–2.59 mmol/L	146 (22.7%)
>2.59 mmol/L	426 (66.1%)
Triglyceride (mmol/L)	1.70 ± 0.95
<1.68 mmol/L	385 (59.4%)
1.68–2.24 mmol/L	137 (21.1%)
>2.24 mmol/L	126 (19.4%)
Non-HDL cholesterol (mmol/L)	3.82 ± 1.2
Previous therapy	
Statins	215 (33.2%)
Fibrates	13 (2.0%)
Omega-3 fatty acids	1 (0.2%)
Therapy at discharge	
Statins	545 (88.7%)
Fibrates	17 (2.6%)
Omega-3 fatty acids	3 (0.5%)

Abbreviations: HDL, high-density lipoproteins; LDL, low-density lipoproteins.

Table 2. Characteristics of Patients With Acute Coronary Syndromes According to HDL-Cholesterol Concentration

	HDL-Cholesterol ≥1.04 mmol/L 281 (43.4%)	Low HDL-Cholesterol (<1.04 mmol/L) 367 (56.6%)	P
Female	70 (24.9%)	62 (16.9%)	0.012
Age (yrs)	64 ± 12	62 ± 12	0.056
Body mass index (Kg/m²)	28.04 ± 4.3	28.73 ± 4.1	0.050
Smoker	95 (34.5%)	157 (43.5%)	0.022
Hypertension	156 (56.5%)	231 (64.3%)	0.045
Diabetes mellitus	77 (27.9%)	130 (36.8%)	0.018
Glucose (mmol/L)	7.03 ± 3.18	7.31 ± 3.42	0.289
Total cholesterol (mmol/L)	5.08 ± 1.17	4.71 ± 1.18	<0.001
LDL cholesterol (mmol/L)	3.14 ± 1.1	3.12 ± 1.1	0.820
<1.813 mmol/L	30 (10.7%)	42 (11.5%)	
1.813–2.59 mmol/L	64 (22.9%)	82 (22.5%)	0.947
>2.59 mmol/L	186 (66.4%)	240 (65.9%)	
Triglyceride (mmol/L)	1.49 ± 1.0	1.85 ± 0.88	<0.001
<1.68 mmol/L	201 (71.5%)	184 (50.1%)	
1.68–2.24 mmol/L	46 (16.4%)	91 (24.8%)	<0.001
>2.24 mmol/L	34 (12.1%)	92 (25.1%)	
Non-HDL cholesterol (mmol/L)	3.77 ± 1.2	3.87 ± 1.2	0.293
Previous therapy			
Statins	83 (29.5%)	132 (36.0%)	0.085
Fibrates	3 (1.1%)	10 (2.7%)	0.136
Omega-3 fatty acids	0 (0%)	1 (0.3%)	1.000

glucose ($P = 0.707$), previous therapy with statins ($P = 0.284$), fibrates ($P = 0.305$), and omega-3 fatty acids ($P = 0.353$). Female gender was the strongest protective factor against low HDL-C (0.619; 95% CI: 0.410–0.934; $P = 0.022$), whereas high triglyceride concentration (1.653; 95% CI: 1.323–2.064; $P < 0.001$) followed by previous

Table 2. (*continued*)

	HDL-Cholesterol ≥1.04 mmol/L 281 (43.4%)	Low HDL-Cholesterol (<1.04 mmol/L) 367 (56.6%)	*P*
Therapy at discharge			
Statins	246 (87.5%)	329 (89.6%)	0.402
Fibrates	6 (2.1%)	11 (3.0%)	0.496
Omega-3 fatty acids	0 (0%)	3 (0.8%)	0.262

Abbreviations: HDL, high-density lipoproteins; LDL, low-density lipoproteins.

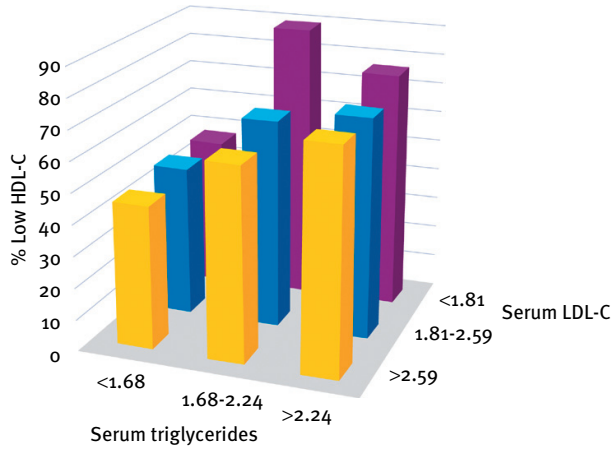

Figure 1. Relationship between the percentage of patients with low HDL-C, serum triglycerides, and LDL-C. Abbreviations: HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

ischemic disease (1.504; 95% CI: 1.073–2.110; $P = 0.018$) were the strongest associated factors with low HDL-C.

Discussion

The main findings of this study were: first, patients admitted to tertiary hospitals with ACS had a very high prevalence of low HDL-C; second, a strong and independent relationship existed between male gender, previous ischemic disease, and high triglyceride concentrations and low HDL-C levels; third, although statin therapy was prescribed in the vast majority of patients during hospitalization, strategies to increase HDL-C concentrations were scarcely used.

High-density lipoprotein is gaining increasing importance in the prevention and treatment of atherosclerosis. Since the first observational study of Barr et al more than 60 years ago,[16] in which plasma HDL-C concentrations were found to be lower in patients with CAD, many observational and prospective studies have confirmed the association between low HDL-C and coronary risk.[7] The Veterans Affairs High-Density Lipoprotein Intervention Trial (VA-HIT),[17] and the Bezafibrate Infarction Prevention (BIP) study showed that increasing HDL-C with a fibrate resulted in a significant reduction in coronary events in secondary-prevention patients.[18] In the long-term analysis of the BIP study and other fibrate trials, patients with low HDL-C and high triglyceride concentrations were those who benefited most in terms of cardiovascular prevention.[18,19] HDL-C level-raising therapy was associated with long-term mortality reduction and this was apparently related to the degree of HDL-C treatment response.[18] In addition, angiographic studies have also demonstrated that raising HDL-C with different drugs delays the progression of atherosclerosis.[20]

The findings of this study are consistent with previous observations of prevalent low HDL-C in CAD patients.[21] In a recent study, more than 50% of patients hospitalized with CAD had admission HDL-C levels <40 mg/dL.[5] Rubins et al showed that in a population of 8500 men at Veterans Affairs Medical Centers throughout the United States,[22] 63% had HDL-C concentrations under 40 mg/dL, and a similar percentage was seen in the BIP study population of 6741 men and 1509 women with CAD.[23]

The prognostic significance of HDL-C in cardiovascular outcomes is independent of total or LDL-C levels,[12,24] even in patients with low LDL-C.[25] Furthermore, in a prospective analysis of the Physicians Health Study, the greatest increase in risk of myocardial infarction associated with low HDL-C was seen in patients with below-average total cholesterol (<212 mg/dL).[26] The results of the Prospective Cardiovascular Münster (PROCAM) study also showed the risk associated with low HDL-C to be independent of triglyceridemia.[27] In addition, it has been reported that statin monotherapy does not attenuate the increased risk associated with low HDL-C and the need for management of patients with low-HDL and low-LDL lipid profile is likely to increase in coming years with the availability of safe and effective LDL-C lowering drug strategies.[28,29]

Among patients hospitalized with CAD who had low HDL-C levels, a lower prevalence was found of female gender and a higher prevalence of smoking, hypertension, diabetes, and hypertriglyceridemia. In multivariate analysis, male gender, high triglycerides, and previous ischemic disease were independently associated with low HDL-C. Variations in HDL-C concentrations can be largely explained by variations in triglyceride levels and reflect the close links between the metabolisms of these 2 lipid species.[30,31] We found low HDL-C to be more prevalent in CAD patients with recurrent disease than in those who present with a first ACS, as observed in other studies.[32] Moreover, previous coronary heart disease was, after hypertriglyceridemia, the factor more strongly associated with low HDL-C.

A considerable proportion of CAD patients were not on lipid-lowering medication during follow-up. In the present

study, only one-third of patients were on lipid-lowering therapy before hospitalization despite 43% having a history of CAD. Although a great increase was observed in the number of patients on statin therapy during hospitalization, the use of other drug therapies for raising HDL-C, both at admission and at discharge, was negligible. Moreover, the use of fibrates and omega-3 fatty acids did not differ in patients with prior ischemic disease when compared with those without nor in patients with low HDL-C compared with those with desirable HDL-C levels. Our results concur with those of other studies in which a clear increase in the percentage of ischemic patients on cholesterol-lowering therapy has been observed in recent years,[33] but not with respect to the undertreatment of low HDL-C. This finding could likely reflect the contrast between the robust evidence for LDL-C lowering therapy vs the more nebulous area of HDL-C raising therapy and therefore a general reluctance to treat low HDL-C in current practice. The development of more potent HDL-C raising therapies and the results of outcomes studies underway to analyze the possible preventive benefit of combined therapies to reduce LDL-C and increase HDL-C will be fundamental for reducing cardiovascular disease.

Several limitations of the present analysis should be mentioned. The lipid levels obtained in this study were measured in the first 6 days of admission. There is evidence that, as a part of the acute phase response, lipid metabolism is altered in patients with unstable coronary syndromes.[34] However, a recent study found little change in lipid levels measured serially in the first days of hospitalization for an acute coronary event.[35] This real-world study compiled results of laboratories from different hospitals rather than a single central laboratory. Although this approach may introduce variability into lipid testing results, it renders these findings more applicable to clinical practice.

In conclusion, low HDL-C in Spanish patients hospitalized for ACS is highly prevalent. Male gender, high triglyceride concentrations, and previous ischemic disease are strong and independent factors associated with this lipoprotein abnormality. Since low HDL-C is a key cardiovascular risk factor that remains almost completely untreated in patients with both first and recurrent ACS, strategies to improve this situation are urgently required.

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