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CME

Lipoprotein(a) Levels in Familial Hypercholesterolemia

An Important Predictor of Cardiovascular Disease Independent of the Type of LDL Receptor Mutation

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Lipoprotein(a) Levels in Familial Hypercholesterolemia

An Important Predictor of Cardiovascular Disease Independent of the Type of LDL Receptor Mutation

Objectives The aim of this study was to determine the relationship between lipoprotein(a) [Lp(a)] and cardiovascular disease (CVD) in a large cohort of patients with heterozygous familial hypercholesterolemia (FH).

Background Lp(a) is considered a cardiovascular risk factor. Nevertheless, the role of Lp(a) as a predictor of CVD in patients with FH has been a controversial issue.

Methods A cross-sectional analysis of 1,960 patients with FH and 957 non-FH relatives recruited for SAFEHEART (Spanish Familial Hypercholesterolemia Cohort Study), a long-term observational cohort study of a molecularly well-defined FH study group, was performed. Lp(a) concentrations were measured in plasma using an immunoturbidimetric method.

Results Patients with FH, especially those with CVD, had higher Lp(a) plasma levels compared with their unaffected relatives ($p < 0.001$). A significant difference in Lp(a) levels was observed when the most frequent null and defective mutations in *LDLR* mutations were analyzed ($p < 0.0016$). On multivariate analysis, Lp(a) was an independent predictor of cardiovascular disease. Patients carrying null mutations and Lp(a) levels >50 mg/dl showed the highest cardiovascular risk compared with patients carrying the same mutations and Lp(a) levels <50 mg/dl.

Conclusions Lp(a) is an independent predictor of CVD in men and women with FH. The risk of CVD is higher in those patients with an Lp(a) level >50 mg/dl and carrying a receptor-negative mutation in the *LDLR* gene compared with other less severe mutations. (J Am Coll Cardiol 2014;63:1982–9) © 2014 by the American College of Cardiology Foundation

Heterozygous familial hypercholesterolemia (FH) is a frequent autosomal dominant inherited disorder associated with premature cardiovascular disease (CVD). Its genetic bases are rooted mainly in the low-density lipoprotein receptor (*LDLR*) gene (1). It has been shown that at least 50% of male subjects and 30% of female subjects with FH who do not receive effective treatment will experience a coronary event by 50 years of age (2). Expression of CVD in affected subjects varies considerably across cohorts and individual patients, suggesting that other factors contribute to the atherosclerotic burden in these patients (3–5).

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Lipoprotein(a) [Lp(a)] is a plasma lipoprotein consisting of a low-density lipoprotein–like particle with one additional protein, apolipoprotein(a), attached via a disulfide bond to apolipoprotein B100 (6). Several epidemiological and genetic studies have shown that high Lp(a) levels can increase the risk of CVD in the general population independent of low-density lipoprotein cholesterol (LDL-C) levels and other cardiovascular risk factors (6–8). However, the role of Lp(a) as a predictive factor of CVD in patients with FH has been a long-term controversial issue. Previous reports have shown either higher levels of Lp(a) in subjects with FH who had coronary heart disease or no differences when compared with subjects without FH (5,9–12). Recently, some differences in Lp(a) levels regarding the onset of CVD in male and female subjects with FH have been reported (13).

The aim of this study was to define the role of Lp(a) as a predictor of CVD and the relationship with the type of *LDLR* gene mutation in a large controlled cohort of patients with a molecular diagnosis of heterozygous FH.

Methods

Study design and patients. The study design and patient recruitment have been described previously (14). Briefly, SAFEHEART (Spanish Familial Hypercholesterolemia Cohort Study) is an open, multicenter, long-term, observational, cohort study in a molecularly well-defined population of subjects with FH in Spain. A list of SAFEHEART investigators appears in the Online Appendix. Six patients with homozygous FH and 11 patients receiving nicotinic acid were excluded from this analysis.

This study complies with the Declaration of Helsinki and was approved by the local ethics committee. Written informed consent was obtained from all participants before their inclusion in the registry.

Measures and blood samples. Data collected on the demographic and clinical characteristics of the subjects included age, history of CVD, hypertension, type 2 diabetes mellitus, smoking status, findings on physical examination, and current lipid-lowering treatment. Information on a history of CVD was obtained from medical charts provided by each subject's physician at inclusion in the study. Findings on physical examination included weight, height, body mass index (BMI), and waist circumference. Blood pressure was measured twice with each subject in a supine position using an Omron MX3 sphygmomanometer (Mannheim, Germany).

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Abbreviations and Acronyms

BMI = body mass index
CI = confidence interval
CVD = cardiovascular disease
FH = heterozygous familial hypercholesterolemia
HDL-C = high-density lipoprotein cholesterol
IQR = interquartile range
LDL-C = low-density lipoprotein cholesterol
LDLR = low-density lipoprotein receptor
Lp(a) = lipoprotein(a)
OR = odds ratio

It was determined that CVD was present if one of the following criteria was documented: 1) myocardial infarction proved by classic criteria; 2) classic symptoms of angina pectoris and one positive result on an ischemic test or >70% stenosis on coronary angiography; 3) percutaneous transluminal coronary angiography (PTCA) or coronary artery bypass grafting; 4) ischemic stroke or documented transitory ischemic attack; 5) intermittent claudication, which was defined as classic symptoms and at least one positive result of an ankle/arm index <0.9 or stenosis >50% on angiography or ultrasonography; 6) abdominal aortic aneurism; or 7) peripheral arterial bypass grafting or percutaneous transluminal angioplasty. Premature CVD was defined as the occurrence of the first event before 55 years of age in men and before 65 years of age in women.

Venous blood samples were obtained after the subjects fasted for 12 h. DNA was isolated from whole blood using standard methods, and FH was diagnosed using a DNA microarray (15). Plasma samples for measurement of Lp(a) were stored at −20°C and used within 3 weeks after they were obtained according to the recommendation of the manufacturer of the commercial assay. Serum total cholesterol, triglyceride, and high-density lipoprotein cholesterol (HDL-C) levels were measured using enzymatic methods. LDL-C levels were calculated using the Friedewald formula. Lp(a) levels were measured with a turbidimetric method using immunoglobulin G anti-human Lp(a) (Quantia Lp(a) 7K00-01) in an Architect autoanalyzer C16000 (Abbott Diagnostics, Lake Forest, Illinois) This assay is not influenced by apolipoprotein(a) isoform size (16) and was calibrated with the World Health Organization–approved, International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) reference standard apolipoprotein(a) with 21 kringle 4 repeats for standardization of Lp(a) (IFCC/SRM 2B). Interassay variation for samples in the centralized laboratory was <7%. Samples with hemolysis and/or lipemia were excluded.

Mutations in the *LDLR* gene were classified as receptor-negative (null) or receptor-defective (defective) depending on their functional class as reported previously (17). Mutations with an unknown biological effect were classified as "unknown" but were considered functional if the autosomal dominant trait was present in the family.

Statistical analysis. Statistical analyses were performed using the R programming language version 2.15.1 (2013, Vienna, Austria). For quantitative variables with normal distribution, a descriptive analysis was performed using mean ± SD. For qualitative variables, the total number of cases and percents were estimated. For quantitative variables lacking a normal distribution, the median and the interquartile range (IQR) were reported. Comparisons of frequencies between qualitative variables were performed using the chi-square test. Mean values of quantitative variables were compared with the Student *t* test for independent data, and median values were compared with the nonparametric Wilcoxon Mann Whitney rank sum test. The relationship between variables was considered statistically significant if the p value was <0.05.

Analysis of variance was conducted to identify interdependency among variables, including age, sex, BMI, hypertension, type 2 diabetes mellitus, xanthomas, smoking status, Lp(a) levels, lipid levels, and type of mutation. Over independent covariates, a Cox proportional hazards model was performed to examine the relationship between CVD and one or more variables. Significant covariates were selected using the Akaike information criterion method. A variable is selected when the p value is <0.05. The magnitude of the association was estimated using the odds ratio (OR) with a confidence interval (CI) of 95%.

A Kaplan-Meier estimate was performed to determine the overall CVD-free survival time due to Lp(a) levels (<50 mg/dl and >50 mg/dl) and the type of mutation (null and defective) as well as sex (male and female). The failure rate (the probability of a patient experiencing a CVD event during a particular time under some conditions) was used to plot the cumulative hazard. Comparison of Kaplan-Meier estimators was performed using the log-rank test.

Results

A total of 2,917 subjects (1,960 patients with FH and 957 non-FH relatives) were included in this analysis. The clinical

Table 1 Baseline Characteristics of Subjects (N = 2,917)

	Subjects With FH (n = 1,960)	Subjects Without FH (n = 957)	p Value
Male	921 (47.0)	443 (46.3)	0.7520
Age, yrs	44.4 ± 15.6	40.6 ± 15.9	<0.0010
Current tobacco use	540 (27.6)	330 (34.5)	<0.0010
BMI, kg/m^2	26.5 ± 5.2	26.0 ± 5.1	<0.0100
CVD	247 (12.6)	41 (4.3)	<0.0010
Premature CVD	193 (9.8)	25 (2.6)	<0.0010
Age at first event, yrs	48.3 ± 12.3	53.7 ± 10.2	<0.0030
Coronary artery disease	223 (11.4)	34 (3.6)	<0.0010
Type 2 diabetes mellitus	77 (3.9)	38 (4.0)	0.9610
Arterial hypertension	284 (14.5)	121 (12.6)	0.1950
Tendinous xanthomas	266 (13.6)	0 (0)	<0.0010
Total cholesterol, mg/dl	255 ± 67.2	207 ± 45.2	<0.0010
Triglycerides, mg/dl	83 (63–117)	85 (63–119.6)	0.6010
HDL-C, mg/dl	50 ± 12.9	55 ± 13.8	<0.0010
LDL-C, mg/dl	185 ± 63.8	131 ± 40.7	<0.0010
Lp(a), mg/dl	23.6 (9.6–59.2)	21.0 (7–47.2)	<0.0001
Lp(a) >50 mg/dl	574 (29.3)	212 (22.2)	<0.0001

Values are n (%), mean ± SD, or median (interquartile range).

BMI = body mass index; CVD = cardiovascular disease; FH = heterozygous familial hypercholesterolemia; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; Lp(a) = lipoprotein(a).

Table 2 Lipid Profile in the Study Group According to the Presence of CVD

	(A) FH+ CVD+ (n = 247)	(B) FH+ CVD− (n = 1,713)	(C) FH− CVD+ (n = 41)	(D) FH− CVD− (n = 916)
Total cholesterol, mg/dl	225 ± 54.8	260 ± 67.7*	185 ± 32.2†	208 ± 45.5*†
Triglycerides, mg/dl	97 (70–129)	81 (62–129)*	98 (80–129)	84 (62–129)*‡
HDL-C, mg/dl	46 ± 11.4	51 ± 11.4*	52 ± 15.0‡	55 ± 15.0‡
LDL-C, mg/dl	158 ± 49.2	189 ± 49.2*	109 ± 24.4†	132 ± 24.4*†
Non–HDL-C, mg/dl	179 ± 52.9	209 ± 67.8*	133 ± 29.6†	153 ± 44.2*†
Apo A1, mg/dl	133 ± 25.0	140 ± 27.6*	147 ± 26.6‡	151 ± 58.0†
Apo B, mg/dl	111 ± 30.0	122 ± 37.9*	83 ± 21.0†	91 ± 26.3†§
Lp(a), mg/dl	43.4 (18.2–84.3)	21.3 (8.9–53.9)*	21.5 (8.4–37)‡	20.8 (7–47.3)‡
Lp(a) >50 mg/dl	114 (46.2)	460 (26.9)*	6 (14.6)†	206 (22.5)‖

Values are mean ± SD, median (interquartile range), or n (%). *$p < 0.0001$ and §$p < 0.05$ between A and B and between C and D; †$p < 0.0001$; ‡$p < 0.005$, and ‖$p < 0.05$ between A and C and between B and D.
Abbreviations as in Table 1. Apo = apolipoprotein.

and biochemical characteristics of the subjects are shown in Table 1. The mean age was 44.4 years for patients with FH and 40.6 years for non-FH relatives ($p < 0.001$). In total, 159 different functional mutations were identified in the participants (data not shown). Almost 90% of patients with FH were receiving stable lipid-lowering treatment at inclusion in the study. In regard to the lipid profile, patients with FH had significantly higher total cholesterol, LDL-C, and Lp(a) levels and lower HDL-C levels ($p < 0.001$). In addition, the number of subjects with Lp(a) levels >50 mg/dl was significantly higher in the FH group ($p < 0.001$). Male patients with FH had significantly higher Lp(a) levels compared with non-FH male subjects (23.5 mg/dl [IQR: 9.5 to 57.2 mg/dl] vs. 19.5 mg/dl [IQR: 7.0 to 44.4 mg/dl]; $p < 0.001$), but there were no differences between female subjects (23.5 vs. 21.5 mg/dl, respectively).

Lp(a) levels and CVD. Patients with FH and CVD had significantly higher Lp(a) levels than patients with FH without CVD ($p < 0.001$) (Table 2). The percent of subjects with Lp(a) levels >50 mg/dl was significantly higher in those with FH and CVD than in those without CVD ($p < 0.0001$). Conversely, no differences in Lp(a) concentrations were noted in non-FH subjects according to CVD status.

There were no significant differences in Lp(a) levels (42.7 vs. 44.1 mg/dl, respectively) and in the number of subjects with Lp(a) levels >50 mg/dl between the premature CVD and non- premature CVD groups (45.6% vs. 48.1%, respectively; data not shown). Figure 1 shows the cumulative hazard curve for CVD according to Lp(a) levels, showing that the risk was significantly higher for patients with FH compared with non-FH subjects at any level beyond 50 mg/dl.

When analyzing Lp(a) levels and CVD according to sex, female subjects with FH and CVD had significantly higher Lp(a) levels and there was a higher percent of subjects with Lp(a) levels >50 mg/dl compared with male subjects with FH and CVD (58.4 mg/dl [IQR: 22.0 to 97.2 mg/dl] vs. 35.4 mg/dl [IQR: 15.1 to 81.9 mg/dl] [$p < 0.02$] and 56.4% vs. 41.1% [$p < 0.03$], respectively). Male subjects with FH and CVD had significantly higher levels of Lp(a) than non-FH male subjects with CVD (35.4 mg/dl [IQR: 15.1 to 81.9 mg/dl] vs. 21.5 mg/dl [IQR: 7.0 to 32.5 mg/dl]; $p < 0.003$) and there was a higher percent of subjects with an Lp(a) level >50 mg/dl (41.1% vs. 12.5%; $p < 0.004$). In female subjects, there were no differences in Lp(a) levels between subjects with FH and CVD and non-FH subjects with CVD. No differences were observed in male and female subjects with FH regarding Lp(a) levels and onset of CVD (data not shown). Figure 2 shows that CVD-free survival time was significantly reduced in male and female subjects with FH and Lp(a) levels >50 mg/dl than in subjects of the same sex and Lp(a) levels <50 mg/dl (log-rank p value = 0.0001).

Lp(a) levels and type of *LDLR* mutation. A nonsignificant higher level of Lp(a) and percent of subjects with Lp(a) levels >50 mg/dl was observed in patients carrying null mutations compared with defective mutations (24.4 mg/dl vs. 21.5 mg/dl and 30.2% vs. 28.1%, respectively). Because of the high molecular heterogeneity, subjects carrying the most

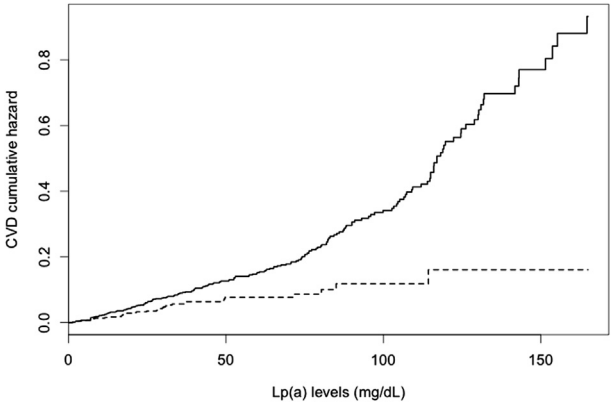

Figure 1 Cumulative Hazard for CVD and Lp(a) levels

The **solid line** indicates patients with FH, and the **dashed line** indicates non-FH subjects. CVD = cardiovascular disease; FH = heterozygous familial hypercholesterolemia; Lp(a) = lipoprotein(a).

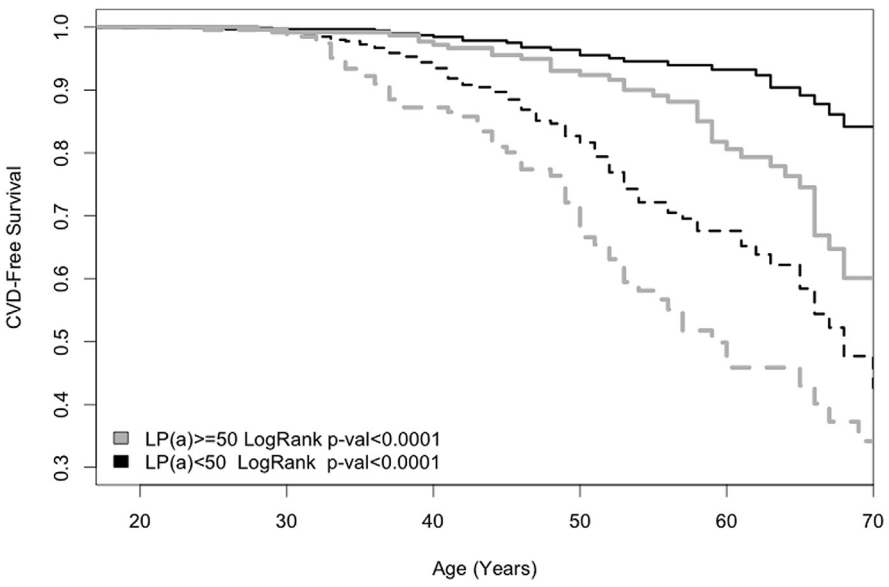

Figure 2 Kaplan-Meier Curves for CVD-Free Survival in Subjects With FH According to Lp(a) Levels and Sex

The **dashed gray line** indicates male subjects with Lp(a) levels >50 mg/dl, the **dashed black line** indicates male subjects with Lp(a) levels <50 mg/dl, the **gray solid line** indicates female subjects with Lp(a) levels >50 mg/dl, and the **black solid line** indicates female subjects with Lp(a) levels <50 mg/dl. Abbreviations as in Figure 1.

frequent null and defective mutations (>50 cases per mutation) were selected and analyzed. The 5 more common null mutations were found in 500 subjects, whereas the 4 most common defective mutations were found in 246 subjects. A significant difference in the median Lp(a) levels between null and defective mutations was observed ($p < 0.0016$) (Fig. 3).

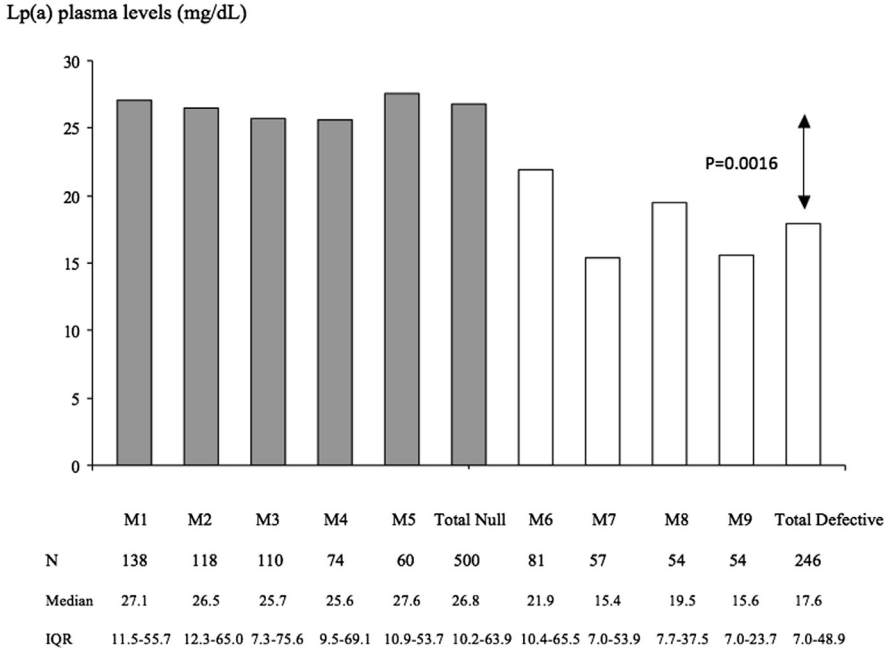

Figure 3 Median Lp(a) Levels in Subjects With the Most Frequent Null Mutations and Defective Mutations Included in the Analysis

Shaded bars indicate null mutations, and **open bars** indicate defective mutations. M1: c.1342C>T; M2: c.97C>T; M3: c.313+1G>C+c274C>G; M4: c.460C>T; M5: c.1358+1G>A; M6: c.2397_2405delCGTCTTCCT+c.1690A>C; M7: c.530C>T; M8: c.2475C>A ; M9: c.1285G>A. IQR = interquartile range; other abbreviations as in Figure 1.

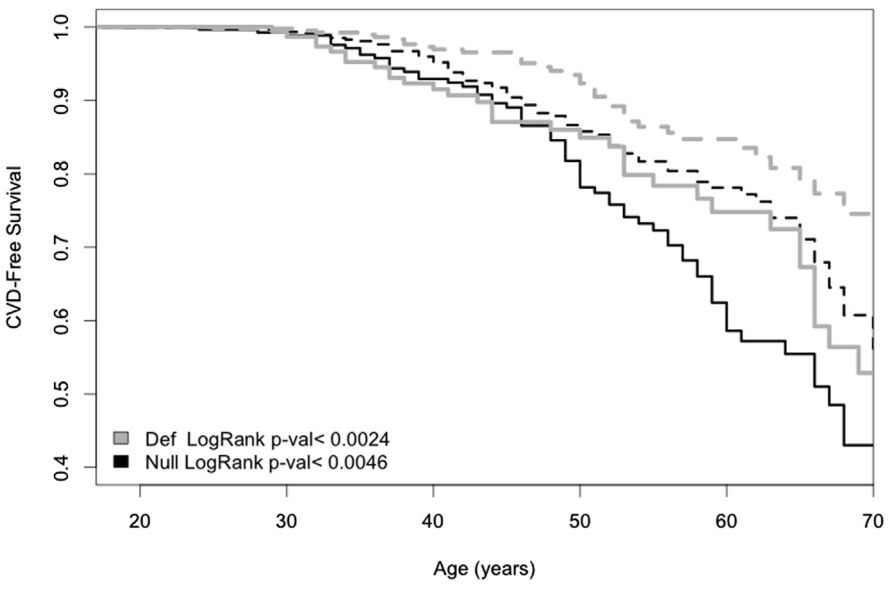

Figure 4 Kaplan-Meier Curves for CVD-Free Survival in Subjects With FH According to Lp(a) Levels and Type of Mutation

The **black solid line** indicates null mutations and Lp(a) levels >50 mg/dl; the **black dashed line** indicates null mutations and Lp(a) levels <50 mg/dl; the **gray solid line** indicates defective mutations and Lp(a) levels >50 mg/dl; and the **gray dashed line** indicates defective mutations and Lp(a) levels <50 mg/dl. Def = defective; other abbreviations as in Figure 1.

Figure 4 shows that CVD-free survival time was significantly lower in patients carrying null mutations who had Lp(a) levels >50 mg/dl (log-rank p value <0.0046) compared with patients carrying defective mutations (log-rank p value <0.0024). On the other hand, CVD-free survival time in patients carrying null mutations and Lp(a) levels <50 mg/dl and in those carrying defective mutations and Lp(a) levels >50 mg/dl was similar.

Lp(a) levels were analyzed in non-FH subjects with high cholesterol levels (total cholesterol level >250 mg/dl or LDL-C level >190 mg/dl or receiving lipid-lowering treatment) and CVD (n = 36) and compared with those of subjects with FH and CVD. Lp(a) levels were significantly lower in non-FH subjects with hypercholesterolemia compared with subjects with FH and CVD (21.5 mg/dl [IQR: 7.0 to 32.9 mg/dl] vs. 43.4 mg/dl [IQR: 18.2 to 84.3 mg/dl]; p < 0.0001; data not shown).

Table 3 Cox Proportional Hazards Model Showing Relationships Between Different Cardiovascular Risk Factors and CVD in Patients With FH

	Odds Ratio	95% Confidence Interval	p Value
Male	2.738	2.008–3.740	<0.0001
Current smoker	1.906	1.409–2.575	<0.0001
Xanthomas	1.488	1.089–2.032	<0.01
HDL-C <40 mg/dl	1.419	1.022–1.969	<0.03
BMI	1.035	1.006–1.066	<0.02
Lp(a) level	1.008	1.005–1.010	<0.0001
Triglyceride level	1.004	1.001–1.007	<0.02
Hypertension	1.287	0.964–1.719	0.08
Null mutation	1.282	0.962–1.710	0.09

Variables in the model included sex, tobacco use (current smokers), triglyceride levels, HDL-C level <40 mg/dl, hypertension, type 2 diabetes mellitus, BMI, Lp(a) level, type of mutation (null and defective), and xanthomas.

Abbreviations as in Table 1.

Multivariable analysis. The relationship of Lp(a) levels with other CVD risk factors and the type of mutation as risk predictors was assessed using the Cox proportional hazards model (Table 3). The most important risk factors contributing to CVD in this FH study group were male sex (OR: 2.738; p < 0.0001), smoking (OR: 1.906; p < 0.0001); xanthomas (OR: 1.488; p < 0.01); HDL-C level <40 mg/dl (OR: 1.419; p < 0.03); BMI (OR: 1.035; p < 0.02), and Lp(a) levels (OR: 1.008; p < 0.0001). In male subjects with FH, Lp(a) continued to be an independent predictor of CVD (OR: 1.007; 95% CI: 1.004 to 1.011; p < 0.0001) and in female subjects with an Lp(a) level >50 mg/dl (OR: 2.387; 95% CI: 1.46 to 3.90; p < 0.0005).

Discussion

This study shows that patients with FH, especially those with CVD, have significantly higher Lp(a) levels compared with their nonaffected relatives and that Lp(a) is an independent predictor of CVD in this study group. This effect seems to be independent of the type of mutation, although patients with Lp(a) levels >50 mg/dl who are carrying a null mutation have the highest risk of CVD.

Plasma Lp(a) levels are genetically determined, and it seems that the major determinant of plasma levels is the production, more than the clearance, of the lipoprotein (6).

The role of the *LDLR* in Lp(a) uptake and degradation remains unclear. Our findings are in agreement with some previous studies showing higher Lp(a) levels in patients with FH compared with healthy control patients and also compared with non-FH relatives (18–21). The fact that non-FH subjects with hypercholesterolemia have lower levels of Lp(a) supports the role of *LDLR* in the catabolism of Lp(a).

Regarding the type of *LDLR* mutation, we observed a nonsignificant trend toward higher Lp(a) levels in patients carrying null mutations compared with those carrying defective mutations. To decrease the variability, we restricted the analyses to the most prevalent null and defective mutations (38% of the cases). In this subset, we observed a significant difference in the median Lp(a) levels between both groups of mutations, suggesting a role of *LDLR* in Lp(a) plasma concentrations. Only one previous study has analyzed the role of the type of *LDLR* mutation in Lp(a) levels in FH. Leitersdorf et al. (22) showed in a small sample of cases with 4 different mutations that, despite the fact that the LDL-C levels were similar in all FH subgroups, the Lp(a) levels were significantly different among them. Also, it has been shown that patients with homozygous FH have higher Lp(a) levels than heterozygous subjects from the same families, suggesting that *LDLR* mutations also result in hyperlipoprotein(a) with a gene-dosage effect, although the mechanism is not clear (23).

Elevated Lp(a) levels have been associated with an increased risk of coronary, peripheral, and cerebrovascular disease in the general population and in patients with FH (10,18). Until now, the largest study analyzing Lp(a) levels and CVD in the context of FH was the Dutch cohort that showed a significant association between Lp(a) levels >30 mg/dl and CVD (5). Another recent study has shown that Lp(a) levels are different according to the onset of coronary heart disease only in women with FH (13).

Our data show that Lp(a) is an independent predictor of CVD in patients with FH. Patients with CVD had Lp(a) concentrations that were twice as high as those in patients with FH and non-FH relatives without CVD. Furthermore, the increased risk is independent of age, sex, smoking status, other lipoproteins, and the type of mutation in the *LDLR* gene. On the other hand, no differences in Lp(a) levels according to the onset of CVD were found.

According to the recent consensus in Lp(a) and CVD, we used a cutoff of 50 mg/dl in Lp(a) levels to classify the risk associated with this lipoprotein (6). To the best of our knowledge, this is the first study showing that subjects with FH carrying the null mutation and Lp(a) levels >50 mg/dl have the highest risk of CVD. Therefore, it may be advisable to measure Lp(a) levels once in all patients with FH and, if available, to perform DNA testing in *LDLR* to identify those patients with a very high risk of CVD. Lp(a) levels are resistant to most lifestyle interventions, and the efficacy of statins in reducing Lp(a) levels is still not well established (6). To attain the recommended Lp(a) levels <50 mg/dl, low-density lipoprotein apheresis may be useful in some patients with severe FH because of the effectiveness in removing Lp(a) (24). Moreover, emerging lipid-lowering treatments can reduce Lp(a) levels up to 40% (25).

Study limitations. This is a large cross-sectional study of patients with FH and their unaffected relatives. Therefore, no conclusions about Lp(a) as a risk factor can be obtained. Follow-up of the SAFEHEART population will provide information about the role of Lp(a) and new cardiovascular events and the relationship with other known cardiovascular risk factors. The study design allowed for samples for Lp(a) to be measured within 3 weeks in plasma stored at −20°C, thus avoiding problems of longer storage. Individual Lp(a) levels are stable because they are strongly genetically determined (6). The size heterogeneity of apolipoprotein(a) due to the presence of a multiple number of copies of kringle 4 type 2 affects the measurement of Lp(a) levels in plasma. Previous controversy in the Lp(a) field has been related to the use of nonstandardized immunologically based assays, differences in the composition and properties of antibodies or calibrators, and sample storage, among others, making comparison between different studies difficult. Current recommendations include the use of methods that are not affected by the isoform size and the calibration with an international standard (26). In this study, a validated assay shown to be independent of the apolipoprotein(a) isoform size used (16) and also was calibrated with the IFCC/SRM 2B standard, which will enable comparison of Lp(a) levels with other studies and laboratories.

Conclusions

Lp(a) is an independent predictor of CVD in men and women with FH, especially in those patients carrying the most severe type of *LDLR* mutations. Therefore, our results support the recent recommendations (6) that Lp(a) levels should be measured in all patients with FH as a marker that might help identifying high-risk subjects who could benefit from more aggressive lipid-lowering treatments.

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Key Words: cardiovascular disease ▪ familial hypercholesterolemia ▪ LDL receptor mutations ▪ lipoprotein(a).

APPENDIX

For a list of SAFEHEART investigators, please see the online version of this article.