JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
© 2016 BY THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION
PUBLISHED BY ELSEVIER

VOL. 67, NO. 11, 2016
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2016.01.008

Attainment of LDL-Cholesterol Treatment Goals in Patients With Familial Hypercholesterolemia

5-Year SAFEHEART Registry Follow-Up

Leopoldo Perez de Isla, MD,[a,b] Rodrigo Alonso, MD,[b,c] Gerald F. Watts, MD,[d,e] Nelva Mata, MD,[b,f] Adriana Saltijeral Cerezo, MD,[b,g] Ovidio Muñiz, MD,[h] Francisco Fuentes, MD,[i] José Luís Diaz-Diaz, MD,[j] Raimundo de Andrés, MD,[k] Daniel Zambón, MD,[l] Patricia Rubio-Marin, MD,[m] Miguel A. Barba-Romero, MD,[n] Pedro Saenz, MD,[o] Juan F. Sanchez Muñoz-Torrero, MD,[p] Ceferino Martinez-Faedo, MD,[q] José P. Miramontes-Gonzalez, MD,[r] Lina Badimón, MD,[s] Pedro Mata, MD,[b] for the SAFEHEART Investigators

ABSTRACT

BACKGROUND Familial hypercholesterolemia (FH) is the most common genetic disorder associated with premature atherosclerotic cardiovascular disease (ASCVD). There are sparse data on attainment of treatment targets; large registries that reflect real-life clinical practice can uniquely provide this information.

OBJECTIVES We sought to evaluate the achievement of low-density lipoprotein cholesterol (LDL-C) treatment goals in FH patients enrolled in a large national registry.

METHODS The SAFEHEART study (Spanish Familial Hypercholesterolemia Cohort Study) is a large, ongoing registry of molecularly defined patients with heterozygous FH treated in Spain. The attainment of guideline-recommended plasma LDL-C goals at entry and follow-up was investigated in relation to use of lipid-lowering therapy (LLT).

RESULTS The study recruited 4,132 individuals (3,745 of whom were ≥18 years of age); 2,752 of those enrolled were molecularly diagnosed FH cases. Mean follow-up was 5.1 ± 3.1 years; 71.8% of FH cases were on maximal LLT, and an LDL-C treatment target <100 mg/dl was reached by only 11.2% of patients. At follow-up, there was a significant increase in the use of ezetimibe, drug combinations with statins, and maximal LLT. The presence of type 2 diabetes mellitus, a defective allele mutation, ezetimibe use, and the absence of previous ASCVD were predictors of the attainment of LDL-C goals.

CONCLUSIONS Despite the use of intensified LLT, many FH patients continue to experience high plasma LDL-C levels and, consequently, do not achieve recommended treatment targets. Type of LDL-receptor mutation, use of ezetimibe, coexistent diabetes, and ASCVD status can bear significantly on the likelihood of attaining LDL-C treatment goals.
(J Am Coll Cardiol 2016;67:1278–85) © 2016 by the American College of Cardiology Foundation.

From the [a]Cardiology Department. Hospital Clínico San Carlos, IDISSC, Madrid, Spain; [b]Fundación Hipercolesterolemia Familiar, Madrid, Spain; [c]Clínica las Condes, Santiago de Chile, Chile; [d]Lipid Disorders Clinic, Centre for Cardiovascular Medicine, Royal Perth Hospital, Perth, Australia; [e]School of Medicine and Pharmacology, University of Western Australia, Perth, Australia; [f]Department of Epidemiology, Madrid Health Authority, Madrid, Spain; [g]Cardiology Department, Hospital del Tajo, Aranjuez, Madrid, Spain; [h]Department of Internal Medicine, Hospital Virgen del Rocío, Sevilla, Spain; [i]Department of Internal Medicine, Hospital Universitario, Reina Sofía, Córdoba, Spain; [j]Department of Internal Medicine, Hospital Abente y Lago, A Coruña, Spain; [k]Department of Internal Medicine, Fundación Jiménez Díaz, Madrid, Spain; [l]Department of Endocrinology, Hospital Clinic, Barcelona, Spain; [m]Department of Internal Medicine, Hospital SAS de Jerez de la Frontera, Cádiz, Spain; [n]Department of Internal Medicine, Complejo Hospitalario Universitario, Albacete, Spain; [o]Department of Internal Medicine, Hospital de Mérida, Extremadura, Spain; [p]Department of Internal Medicine, Hospital San Pedro de Alcántara, Cáceres, Spain; [q]Department of Endocrinology, Hospital Central, Asturias, Spain; [r]Department of Internal Medicine, Hospital Univeritario, Salamanca, Spain; and the [s]Instituto Catalán Ciencias Cardiovasculares, IIB-Sant Pau, Barcelona, Spain. This work was supported by Fundación Hipercolesterolemia Familiar; grant G03/181 and FIS PI12/01289 from Instituto de Salud Carlos III (ISCIII), grant 08-2008 Centro Nacional de Investigación Cardiovascular (CNIC). Dr. Perez de Isla has received speaker fees from Merck Sharp & Dohme, and AstraZeneca. Dr. Alonso has received speaker fees from AMGEN, AEGERION, and ISIS. Drs. Watts and P. Mata have received

Listen to this manuscript's audio summary by *JACC* Editor-in-Chief Dr. Valentin Fuster.

Heterozygous familial hypercholesterolemia (FH) is an autosomal codominant disorder with a prevalence of 1 per 300 to 500 cases in the general population (1). It is the most common genetic disorder associated with premature atherosclerotic cardiovascular disease (ASCVD). Observational studies show a reduction in coronary and total mortality in FH explained, in part, by use of statins and probably by following healthy lifestyles (2–4). The type of mutation in the low-density lipoprotein (LDL)-receptor (LDLR) gene is probably the most common predictor for the clinical expression of FH. Nevertheless, there are other genetic, environmental, and metabolic factors that might play a significant role in modulating the burden of ASCVD in these individuals (5–7). Although lipid-lowering therapy (LLT) has improved in the last few years, most FH patients do not achieve an optimal therapeutic LDL cholesterol (LDL-C) level (8) and therefore remain at high risk for premature ASCVD.

SEE PAGE 1286

International guidelines consider FH patients at high cardiovascular risk; therefore, the optimal LDL-C goal should be <100 mg/dl or <70 mg/dl with previous history of ASCVD, or at least a 50% reduction in LDL-C levels (9,10). Nevertheless, based on longitudinal studies, little is known about the use of LLT and the attainment of LDL-C goals and its determinants in real clinical practice. National registries can be utilized to provide this key information, necessary for improving models of care for FH, including physician and patient education, therapeutic protocols, health policy, and planning (11,12). SAFEHEART (Spanish Familial Hypercholesterolemia Cohort Study) was designed to improve insight into the prognostic factors, treatments, and mechanisms that influence the development of ASCVD and mortality in a well-defined FH population.

Our aim was to use information accrued by the SAFEHEART registry to investigate the achievement of LDL-C goals in relation to the use of LLT over time, as well as to assess factors that predict the likelihood of attaining these goals.

METHODS

The SAFEHEART study is an open, multicenter, nationwide, long-term prospective cohort study in a molecularly defined, heterozygous FH population in Spain (13). Recruitment of subjects from FH families began in 2004. Inclusion criteria were index cases with a genetic diagnosis of FH and their relatives older than 15 years with a genetic diagnosis of FH. In the present study, data were analyzed between January 2004 and November 2013, and only subjects ≥18 years old were included. This study was approved by the local ethics committees, and all eligible subjects gave written informed consent.

Treatment goals were initially defined according to consecutively released international guidelines (9,10,14). These guidelines were used to inform, educate, and train physicians who participated by including patients and families in this registry; details of best practices were reinforced at every annual meeting of the Fundación Hipercolesterolemia Familiar attended by relevant physicians. An electronically based and telephone advice system was also used to inform care, and a web-based training program was deployed to further support management.

A coordinating center based in Madrid was responsible for managing case follow-up. Patients were contacted annually using a standardized phone call to record relevant changes in lifestyle habits and medications, and development of cardiovascular events. Premature ASCVD was defined as the occurrence of the first event before 55 years of age in men and before 65 years of age in women. The same age thresholds were used to define premature familial ASCVD.

CLINICAL AND LABORATORY MEASUREMENTS. Demographic and clinical characteristics were recorded as described elsewhere and included age, classic cardiovascular risk factors, physical examination, and current treatment for hypercholesterolemia and other risk factors (13). Venous blood samples were taken after 12 h of fasting. Serum, plasma, and deoxyribonucleic acid (DNA) samples were aliquoted and preserved at −80°C. Serum total cholesterol, triglycerides (TG), and high-density lipoprotein cholesterol (HDL-C) levels were measured in a centralized

ABBREVIATIONS AND ACRONYMS

apo = apolipoprotein
ASCVD = atherosclerotic cardiovascular disease
CI = confidence interval
DNA = deoxyribonucleic acid
FH = heterozygous familial hypercholesterolemia
HDL-C = high-density lipoprotein cholesterol
IQR = interquartile range
LDL-C = low-density lipoprotein cholesterol
$LDL\text{-}C_{Lp(a)}$ = cholesterol adjusted by cholesterol content of lipoprotein (a)
LDLR = low-density lipoprotein receptor
LLT = lipid-lowering therapy
Lp(a) = lipoprotein (a)
OR = odds ratio
T2DM = type 2 diabetes mellitus
TC = total cholesterol
TG = triglycerides

honoraria for participation on advisory boards for Amgen and Sanofi; and have received research grants from Amgen and Sanofi. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received October 21, 2015; revised manuscript received December 17, 2015, accepted January 5, 2016.

laboratory using enzymatic methods. Serum LDL-C concentration was calculated using the Friedewald formula. Adjustment of LDL-C by cholesterol content of lipoprotein (a) (Lp(a)) (LDL-$_{CLp(a)}$) was made by using a modified version of the Friedewald formula (with TC = total cholesterol): LDL-$C_{Lp(a)}$ = TC − HDL-C − TG/5 − (Lp(a) × 0.45) that assumed that 45% of Lp(a) mass in mg/dl was cholesterol. DNA was isolated from whole blood using standard methods, and the genetic diagnosis of FH was made using a DNA microarray (15). Mutations were classified as previously described (5).

LLT CLASSIFICATION. Maximal statin dose was defined as atorvastatin 40 to 80 mg/day or rosuvastatin 20 to 40 mg/day, which were considered high-intensity statin doses. Maximal combined therapy was defined as maximal statin dose plus ezetimibe 10 mg/day. Maximal lipid-lowering therapy was defined as any LLT expected to produce at least a 50% reduction in LDL-C baseline levels: simvastatin 20, 40, or 80 mg/day plus ezetimibe 10 mg/day; pravastatin 40 mg/day in combination with ezetimibe 10 mg/day; fluvastatin 80 mg/day plus ezetimibe 10 mg/day; atorvastatin 40 or 80 mg/day with or without ezetimibe 10 mg/day; atorvastatin 10 or 20 mg/day plus ezetimibe 10 mg/day; rosuvastatin 20 or 40 mg/day with or without ezetimibe 10 mg/day; rosuvastatin 10 mg/day plus ezetimibe 10 mg/day; and pitavastatin 4 mg/day in combination with ezetimibe 10 mg/day (8,16).

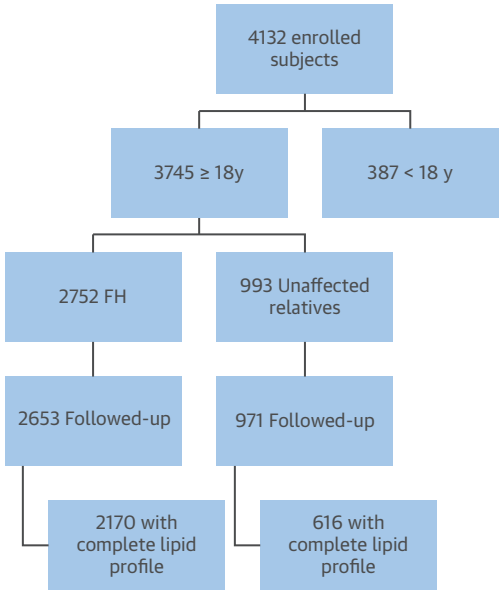
STATISTICAL ANALYSIS. Statistical analyses were carried out using SPSS version 18.0 (SPSS, Chicago, Illinois). Variables were analyzed for a normal distribution with the Kolmogorov-Smirnov test. Quantitative data were expressed as median and interquartile range (IQR) and qualitative data as absolute number and percentage. Two populations were defined: population at entry (N = 2,752) and population at follow-up (otherwise known as the cohort), which included those patients who had a full plasma lipid profile at follow-up (n = 2,170). All comparisons between entry and follow-up were carried out in the cohort study. Comparisons of frequencies between qualitative variables were carried out using the chi-square test. Changes in binary variables were analyzed by McNemar test. Median values of quantitative variables were compared with the Mann-Whitney nonparametric tests or the paired Wilcoxon signed rank test when appropriate. Differences were considered statistically significant with a p value <0.05.

A forward binary logistic regression analysis was conducted in the cohort study, excluding those patients who reached the goal at entry, to determine the variables associated with the attainment of LDL-C <100 mg/dl in patients without ASCVD and <70 mg/dl in those with ASCVD. We included variables that were statistically significant in univariate analyses, as well as a priori predictors and confounders: age, sex, type 2 diabetes mellitus (T2DM), presence of ASCVD, type of mutation (null or defective), use of ezetimibe, and follow-up in a primary/specialized setting. The same analysis was conducted for the achievement of LDL-$C_{Lp(a)}$ goals (LDL-$C_{Lp(a)}$ <100 mg/dl in patients without ASCVD and LDL-$C_{Lp(a)}$ <70 mg/dl in those with ASCVD). A similar analysis was carried out to explore variables associated with the use of high-intensity statins, but this was restricted to the cohort study.

RESULTS

We recruited 4,132 subjects, 769 of whom were index cases (18.6%). Of the total population, 3,745 were ≥18 years of age and 2,752 were FH cases (at-entry

FIGURE 1 SAFEHEART Registry Recruitment



One of the main strengths of the SAFEHEART (Spanish Familial Hypercholesterolemia Cohort Study) registry is the large size of the population studied and the unique longitudinal data presented because most studies on familial hypercholesterolemia (FH) present cross-sectional data. Furthermore, all patients were genetically characterized, and patients managed by general practitioners as well as medical specialists were equally represented in the study. The **left side** of the diagram represents the cohort patients in the current study.

population). Follow-up was attained for 2,653 participants, of whom 2,170 had a full plasma lipid profile at the follow-up (cohort population) (Figure 1). Follow-up was in a primary care setting for 764 patients (35.2%). Mean follow-up was 5.1 ± 3.1 years (age range: 1 to 9 years).

At enrollment (the at-entry population), 1,264 FH patients (45.9%) were male. Median age was 49.5 (IQR: 28.0 to 61.0) years. History of ASCVD was present in 358 (13.0%) patients, history of premature ASCVD in 260 (9.4%), and premature familial ASCVD in 617 (22.4%). Among baseline characteristics, T2DM was present in 132 (4.8%) patients, hypertension in 425 (15.4%), current tobacco smoking in 725 (26.3%), xanthomas in 367 (13.7%), and corneal arcus in 916 (33.3%). Median body mass index was 25.9 kg/m^2 (IQR: 23.0 to 29.1) and waist circumference 87.0 cm (IQR: 76.0 to 97.0). Median TC was 237.0 mg/dl (IQR: 205.0 to 280.0), LDL-C 165.0 mg/dl (IQR: 138.6 to 207.8), HDL-C 49.0 mg/dl (IQR: 41.0 to 57.2), TG 84.0 mg/dl (IQR: 63.0 to 229.5), non-HDL-C 185.0 mg/dl (IQR: 155.0 to 229.5), apolipoprotein (apo)-AI 135.0 mg/dl (IQR: 118.0 to 153.0), apo-B 109.0 mg/dl (IQR: 91.0 to 133.0), and Lp(a) 22.6 mg/dl (IQR: 8.8 to 55.6). Baseline characteristics at inclusion between cohort patients and those who were not followed-up are shown in Table 1. Significantly lower plasma concentrations of TC, LDL-C, and TG were seen in the cohort; HDL-C concentrations did not differ significantly between the groups; and Lp(a) was significantly higher in the cohort. Furthermore, a significantly lower proportion of cohort patients were managed in the primary care setting.

A reduction in the number of current smokers from 26.3% to 15.8% was observed. Thirteen patients developed T2DM, and 28 patients were diagnosed with high blood pressure during follow-up. There were significant reductions in the plasma concentrations of TC, LDL-C, and non-HDL-C; a significant increase in HDL-C was also observed (Table 2).

LLT, FUNCTIONAL MUTATIONS, AND GOAL ATTAINMENT. We identified 209 different functional mutations in LDLR (97.0%) and apo-B (3.0%) genes, of which 33% were classified as null mutations, 50% as defective mutations, and 17% as unknown mutations.

Table 3 shows the use of different LLT regimens at entry and follow-up. A significant increase in the use of statins, the use of maximal statin dose, the use of ezetimibe, the use of maximal combined therapy, and the use of maximal LLT can be seen. The most widely prescribed statin at entry (46.6%) and follow-up (38.5%) was atorvastatin (409 quitters and 231 starters; $p < 0.001$). The prescription of rosuvastatin increased at follow-up (from 12.5% at inclusion to 35.4% at follow-up; 44 quitters and 541 starters; $p < 0.001$). Fibrates and bile acid sequestrants were only used in 132 (6.08%) patients at inclusion and 106 (4.88%) at follow-up. Ezetimibe monotherapy without a statin was used in 29 (1.34%) and 18 (0.83%) patients at inclusion and follow-up, respectively.

Variables independently associated with the use of high-intensity statins in the multivariate analysis were: age (odds ratio [OR]: 1.02; 95% confidence interval [CI]: 1.01 to 1.03), female sex (OR: 0.77; 95% CI: 0.61 to 0.98), previous ASCVD (OR: 2.24; 95% CI: 1.39 to 3.60), defective LDLR mutation (OR: 0.69; 95% CI: 0.55 to 0.88), use of ezetimibe (OR: 2.23; 95% CI: 1.75

TABLE 1 Baseline Characteristics of the At-Entry Population

	FH Patients With Follow-Up (Cohort Group) (n = 2,170)	FH Patients Without Follow-Up (n = 582)	p Value
Age, yrs	45.0 (34.0-56.0)	42.0 (22.8-58.0)	0.95
Male	987 (45.5)	277 (47.6)	0.37
Type 2 diabetes mellitus	97 (4.5)	22 (3.8)	0.57
High blood pressure	312 (14.4)	85 (14.7)	0.84
Active tobacco smoker	560 (25.8)	165 (28.5)	0.20
Previous ASCVD	277 (12.8)	81 (14.0)	0.45
BMI, kg/m^2	26.0 (23.0-29.2)	25.4 (22.8-29.0)	0.77
Total cholesterol, mg/dl	234.0 (204.0-275.0)	246.0 (145.6-298.0)	<0.001
LDL-C, mg/dl	163.0 (136.4-203.0)	178.0 (145.6-222.2)	<0.001
HDL-C, mg/dl	49.0 (41.0-58.0)	48.0 (41.0-57.0)	0.79
TG, mg/dl	83.0 (63.0-114.0)	87.0 (65.0-123.0)	0.012
Non-HDL-C, mg/dl	183.0 (153.0-224.0)	198.1 (161.5-248.0)	<0.001
Lp(a), mg/dl	23.5 (9.2-57.7)	20.5 (7.0-49.3)	0.008
LDL-C$_{Lp(a)}$, mg/dl	149.1 (118.9-186.6)	160.8 (133.9-208.9)	<0.001
LDL-C goal achieved	75 (3.5)	18 (3.1)	0.80
LDL-C$_{Lp(a)}$ goal achieved	220 (10.1)	40 (6.9)	0.017
Null mutation	796 (47.3)	197 (43.9)	0.20
Managed in primary care setting	764 (38.7)	243 (49.7)	<0.001

Values are median (interquartile range) or n (%).

ASCVD = atherosclerotic cardiovascular disease; BMI = body mass index; FH = familial hypercholesterolemia; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; LDL-C$_{Lp(a)}$ = LDL-C adjusted by cholesterol content of lipoprotein (a); Lp(a) = lipoprotein (a); TG = triglycerides.

TABLE 2 Plasma Lipid and Lipoprotein Concentrations

	Cohort at Entry	Cohort at Follow-Up	p Value
Total cholesterol, mg/dl	234.0 (204.0-275.0)	210.0 (187.0-240.0)	<0.001
LDL-C, mg/dl	163.0 (136.0-203.0)	137.0 (116.0-162.1)	<0.001
HDL-C, mg/dl	49.0 (41.0-58.0)	53.0 (44.0-62.0)	<0.001
TG, mg/dl	83.0 (63.0-114.0)	85.0 (64.0-116.8)	0.22
Non-HDL-C, mg/dl	183.0 (153.0-224.0)	154.0 (132.0-179.0)	<0.001
LDL-C$_{Lp(a)}$, mg/dl	149.1 (118.9-186.6)	121.2 (97.4-148.4)	<0.001

Values are median (interquartile range).

Abbreviations as in Table 1.

TABLE 3 LLT and LDL-C Goal Achievement (Cohort)

	At-Entry−/Follow-Up−	At-Entry−/Follow-Up+	At-Entry+/Follow-Up−	At-Entry+/Follow-Up+	p Value
Patients on statins	136 (6.3)	244 (11.2)	88 (4.1)	1,702 (78.4)	<0.001
Patients on maximal statin dose	822 (37.9)	471 (21.7)	139 (6.4)	738 (34.0)	<0.001
Patients on ezetimibe	814 (37.5)	539 (24.8)	80 (3.7)	737 (34.0)	<0.001
Patients on maximal combined therapy	1,210 (55.8)	455 (21.0)	94 (4.3)	411 (18.9)	<0.001
Patients on maximal lipid-lowering therapy	523 (24.1)	542 (25.0)	90 (4.1)	1,015 (46.8)	<0.001
LDL-C goal achieved	1,927 (88.8)	168 (7.7)	48 (2.2)	27 (1.2)	<0.001
LDL-$C_{Lp(a)}$ goal achieved	1,578 (72.7)	372 (17.1)	84 (3.9)	84 (6.3)	<0.001

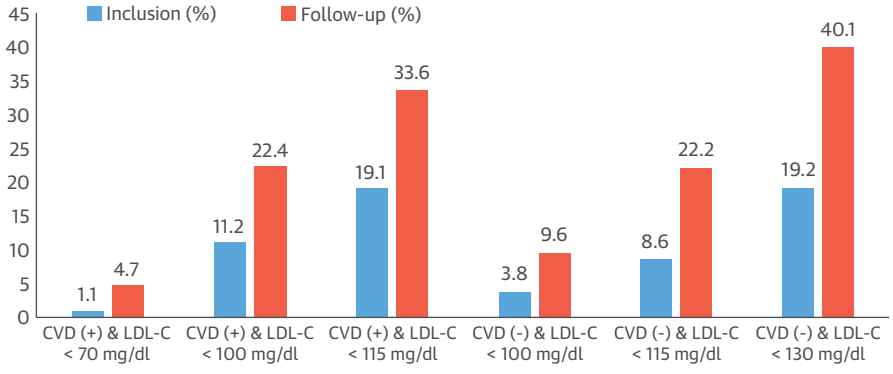
Values are n (%). A negative sign indicates not present; a plus sign indicates present.
LLT = lipid lowering therapy; other abbreviations as in Table 1.

to 2.84), and management in a specialized health care setting (OR: 2.09; 95% CI: 1.64 to 2.66).

Plasma LDL-C concentration decreased by an average of 16%, reaching a median value 137 mg/dl at follow-up. LDL-C goals, as defined by the recent international recommendations on FH, were reached in fewer than 10% of cases (9,10) (**Table 3**, **Figure 2**, **Central Illustration**). LDL-$C_{Lp(a)}$ goals are also shown in **Table 3**. Nevertheless, there was an increase in the percentage of subjects who reached the goals based on ASCVD status: of those with ASCVD, 4 patients (1.1%) had an LDL-C <70 mg/dl at inclusion and 13 (4.7%) at follow-up ($p = 0.03$ for difference); of those without ASCVD, 89 patients (3.8%) had an LDL-C <100 mg/dl at inclusion and 182 (9.6%) at follow-up ($p < 0.001$ for difference). With all FH patients combined, there was a significant increase in the proportion reaching an LDL-C <100 mg/dl at follow-up: 103 patients (4.7%) versus 244 patients (11.2%) at inclusion and follow-up, respectively ($p < 0.001$).

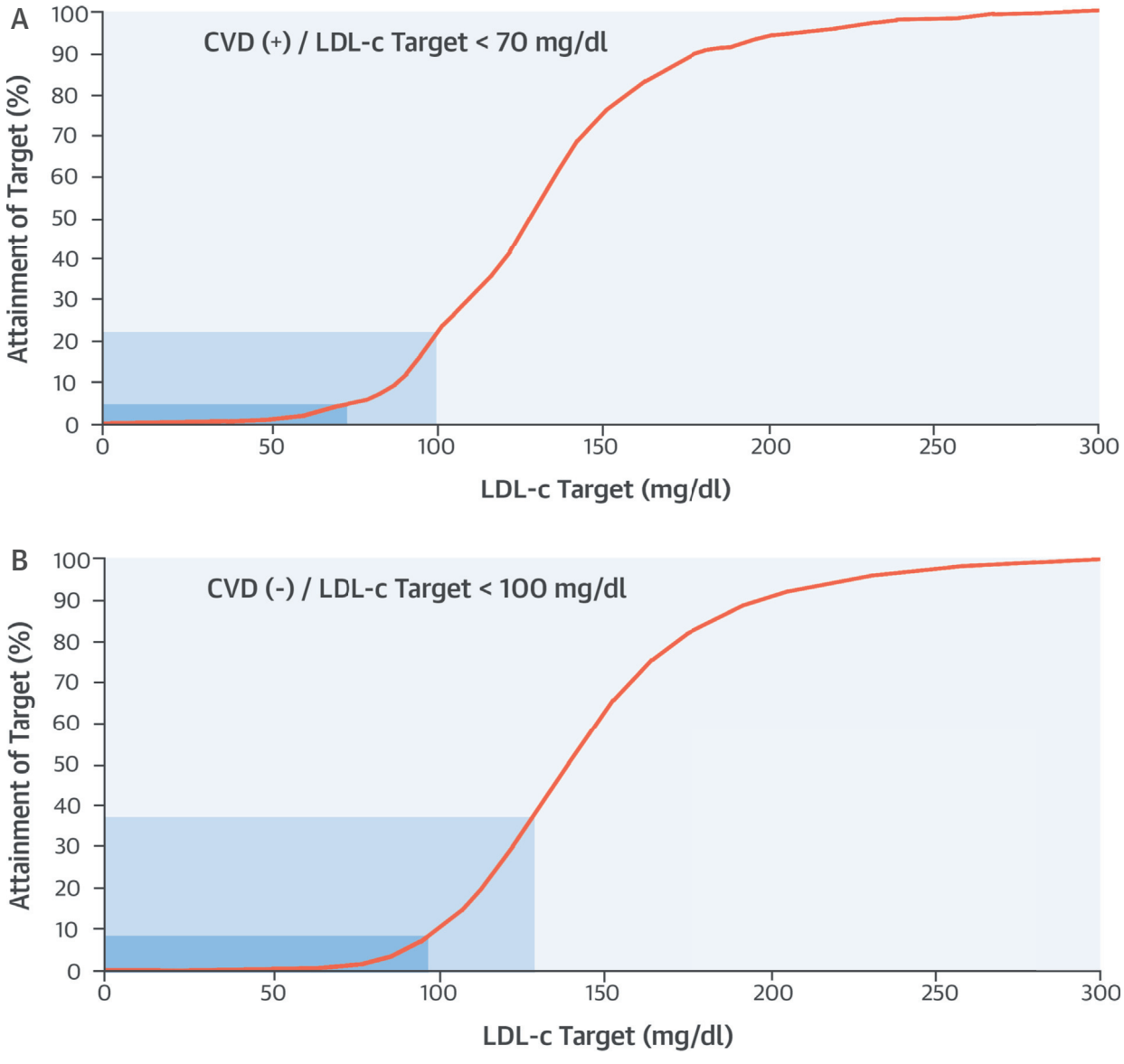
In the follow-up cohort, 2,095 (96.5%) did not reach the LDL-C goal at entry, and they were the population used to determine the predictors of attaining LDL-C goal. The presence of T2DM (OR: 3.70; 95% CI: 1.90 to 7.24), previous ASCVD (OR: 0.32; 95% CI: 0.15 to 0.68), defective LDLR mutation (OR: 2.01; 95% CI: 1.38 to 2.93), and ezetimibe use (OR: 1.91; 95% CI: 1.27 to 2.87) were independently associated in the multivariate analysis with achievement of LDL-C goal. The type of health care providers (specialist or general practitioner), age, and sex were not factors related to goal achievement. The presence of Lp(a) >50 mg/dl was not associated with LDL-C goal attainment (OR: 0.57; 95% CI: 0.17 to 1.88). When considering LDC-$C_{Lp(a)}$ goals, male sex (OR: 1.37; 95% CI: 1.04 to 1.81), previous ASCVD (OR: 0.47; 95% CI: 0.29 to 0.77), defective LDLR mutation (OR: 1.78; 95% CI: 1.36 to 2.34), and ezetimibe use (OR: 1.80; 95% CI: 1.31 to 2.36) were independently associated in the multivariate analysis with achievement of LDL-$C_{Lp(a)}$ goals.

FIGURE 2 Percentage of Patients Reaching Recommended Goals



Although plasma low-density lipoprotein cholesterol (LDL-C) concentration decreased at follow-up, LDL-C goals, as defined by recent international recommendations on familial hypercholesterolemia (FH), were reached in <10% of cases. Nevertheless, there was an increase in the percentage of subjects who reached recommended goals at follow-up compared with at study entry, whether the patient had a history of atherosclerotic cardiovascular disease (CVD [+]) or had no such history (CVD [−]).

CENTRAL ILLUSTRATION **Treatment Goals in FH: Proportion of Patients at LDL Target**



Perez de Isla, L. et al. J Am Coll Cardiol. 2016; 67(11):1278–85.

Despite a high percentage receiving maximal lipid-lowering therapy, most familial hypercholesterolemia (FH) patients still have high low-density lipoprotein cholesterol (LDL-C) levels and did not achieve the recommended LDL-C target for patients **(A)** with or **(B)** without cardiovascular disease (CVD). There is a clinical need for new lipid-lowering treatments in combination with current therapy to reach lower LDL-C levels in an effort to prevent the development of premature atherosclerotic cardiovascular disease.

DISCUSSION

We report the characteristics, LLT use, and attainment of LDL-C goals in a longitudinal cohort of molecularly defined FH patients participating in the SAFEHEART registry. This unique national repository of FH information in Spain is based on data obtained from real clinical practice, including primary care. The present study shows that although 71.8% of FH cases are on maximal LLT, an LDL-C treatment target <100 mg/dl was reached by only 11.2% of patients. The presence of T2DM, a defective allele

mutation, ezetimibe use, and the absence of previous ASCVD, were independently associated with LDL-C goal achievement; interestingly, Lp(a) levels were not.

Although an increased LDL-C level and the presence of xanthomas have been considered specific signs for the clinical diagnosis of FH, our results in a well-defined FH population demonstrated that xanthomas are present in <20% of patients (17).

Our longitudinal study showed that LDL-C in FH patients can alter favorably over time with change in LLT and education of physicians. The proportion of patients on maximal LLT increased to 71.8%, mainly owing to increased use of ezetimibe and maximal combination therapy. Data from other cross-sectional studies conducted in 5 hospital lipid clinics and based on a Dutch FH population (54% of them molecularly diagnosed) showed LDL-C levels <100 mg/dl in 21% patients (8). However, another cross-sectional study with genetically defined FH patients, most of them managed in a primary care setting, showed LDL-C levels <100 mg/dl in 12.2% of patients, more similar to our study (18). In a study performed in 5 centers in France (32.2% genetically characterized), only 10.4% reached LDL-C <100 mg/dl levels despite maximal treatment (19). With regard to the type of mutation, in a recent work, 22% of patients with a null mutation and 27.1% patients with a defective mutation had an LDL-C value <130 mg/dl (20). Furthermore, a large, randomized clinical trial in patients at high cardiovascular risk with severe hypercholesterolemia found that patients with FH on dual therapy (atorvastatin 40 mg and ezetimibe 10 mg) were approximately 4 times more likely to achieve an LDL-C level <100 mg/dl compared with those on monotherapy (atorvastatin 40 mg) (17% vs. 4%, respectively) (21). Furthermore, in every study, results may have been modified by numerous variables, such as participant lifestyles and the association of different cardiovascular risk factors, that could have biased the results.

A strong recommendation for the use of high-intensity statins (16) and combined therapy with ezetimibe (9,10) should be established in FH patients, with the use of ezetimibe now being well supported by IMPROVE-IT (IMProved Reduction of Outcomes: Vytorin Efficacy International Trial) (22). Our study emphasized that there continues to be a major treatment gap in care, with plenty of room for improvement in terms of using more high-intensity therapy, including the recently approved proprotein convertase subtilisin/kexin type 9 monoclonal antibodies, although the cost-effectiveness of the latter agents remains to be demonstrated (23). However, our results also show the enormous difficulty these patients have achieving lipid targets despite using the best currently available LLT (17). Moreover, LDL-C goal achievement was similar whether patients were treated by specialists or general practitioners. This underscores that although awareness of FH may be suboptimal in primary care (24), it is possible to support clinicians via a registry and foundation (such as the Spanish Fundación Hipercolesterolemia Familiar) to achieve a level of care for patients with FH that is comparable to specialist care. Registries can optimize the management of FH by enabling the integration of primary and specialist care (12,25), but this needs to be formally demonstrated.

When baseline results were compared with the findings at the final visit, a significant reduction in the proportion of active smokers was found. It may reflect the seriousness with which these patients take their disease and the impact that the messages from their physicians may have in changing lifestyle choices.

STUDY LIMITATIONS. We acknowledge some strengths and limitations of our study. To our knowledge, this is the largest longitudinal study of a molecularly characterized heterozygous FH population that reflects real-life clinical care of patients by both general practitioners and specialists. Nevertheless, there are some limitations, such as the fact that the study uniquely employed national registry data to investigate the goals of therapy in FH. Future studies should explore the relationship between treatment and the incidence of ASCVD in FH, as well the management of children and adolescents, and the patients' perceptions and experiences of care. The present findings emphasized the potential of a well-organized registry in assessing national trends in the care of FH.

CONCLUSIONS

SAFEHEART registry data demonstrated that most FH patients still had high LDL-C levels and failed to achieve recommended LDL-C targets despite the great majority (71.8%) receiving maximal LLT. We were able to demonstrate an increase in LLT intensity and a significant decrease in LDL-C levels during follow-up. The presence of T2DM, a defective allele mutation, ezetimibe use, and the absence of previous ASCVD were independent predictors of LDL-C goal achievement. These results emphasized that FH patients need more intensive LLT. Hence, there is a medical need for new LLT in combination with current therapy to help patients reach lower LDL-C levels and prevent development of premature ASCVD, although the clinical value and

cost-effectiveness of new treatments have yet to be fully demonstrated.

ACKNOWLEDGMENTS The authors thank the Spanish Familial Hypercholesterolemia Foundation for assistance in the recruitment and follow-up of participants, and to the FH families for their valuable contribution and willingness to participate.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Pedro Mata, Fundación Hipercolesterolemia Familiar, C/ General Alvarez de Castro 14, 28010, Madrid, Spain. E-mail: pmata@colesterolfamiliar.org. OR Dr. Leopoldo Pérez de Isla, Hospital Clínico San Carlos, Unidad de Imagen Cardiovascular, C/ Profesor Martín Lagos s/n, 28040, Madrid, Spain. E-mail: leopisla@hotmail.com.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Familial hypercholesterolemia is the most common genetic disorder associated with premature ASCVD. Despite intensive lipid-lowering therapy, many patients with FH have high plasma LDL-C levels. The type of LDL-receptor mutation, use of ezetimibe, diabetes, and overt ASCVD are related to the likelihood of attaining LDL-C treatment goals.

TRANSLATIONAL OUTLOOK: Long-term clinical studies are needed to evaluate the effectiveness and clinical value of combinations of current lipid-lowering strategies and new treatments in patients with FH.

REFERENCES

1. Goldstein JL, Hobbs HH, Brown MS. Familial hypercholesterolemia. In: Scriver CR, Beaudet AL, Sly WS, Valle D, editors. The Metabolic and Molecular Basis of Inherited Disease, Volume II. New York, NY: McGraw-Hill, 2001:2863–913.

2. Scientific Steering Committee on behalf of the Simon Broome Register Group: Mortality in treated heterozygous familial hypercholesterolaemia: implications for clinical management. Atherosclerosis 1999;142:105–12.

3. Neil A, Cooper J, Betteridge J, et al. Reductions in all-cause, cancer, and coronary mortality in statin-treated patients with heterozygous familial hypercholesterolaemia: a prospective registry study. Eur Heart J 2008;29:2625–33.

4. Versmissen J, Oosterveer DM, Yazdanpanah M, et al. Efficacy of statins in familial hypercholesterolaemia: a long term cohort study. BMJ 2008;337:a2423.

5. Alonso R, Mata N, Castillo S, et al. Cardiovascular disease in familial hypercholesterolaemia: influence of low-density lipoprotein receptor mutation type and classic risk factors. Atherosclerosis 2008;200:315–21.

6. Jansen AC, van Wissen S, Defesche J, et al. Phenotypic variability in familial hypercholesterolaemia: an update. Curr Opin Lipidol 2002;13:165–71.

7. Alonso R, Andres E, Mata N, et al. Lipoprotein(a) levels in familial hypercholesterolemia: an important predictor of cardiovascular disease independent of the type of LDL receptor mutation. J Am Coll Cardiol 2014;63:1982–9.

8. Pijlman AH, Huijgen R, Verhagen SN, et al. Evaluation of cholesterol lowering treatment of patients with Familial hypercholesterolemia: a large cross sectional study in the Netherlands. Atherosclerosis 2010;209:189–94.

9. Nordestgaard BG, Chapman MJ, Humphries SE, et al., for the European Atherosclerosis Society Consensus Panel. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease. Eur Heart J 2013;34:3478–90.

10. Watts GF, Gidding S, Wierzbicki AS, et al. Integrated guidance on the care of familial hypercholesterolaemia from the International FH Foundation. Int J Cardiol 2014;171:309–25.

11. Bufalino VJ, Masoudi FA, Stranne SK, et al. The American Heart Association's recommendations for expanding the applications of existing and future clinical registries: a policy statement from the American Heart Association. Circulation 2011;123:2167–79.

12. Hammond E, Watts GF, Rubinstein Y, et al. Role of international registries in enhancing the care of familial hypercholesterolaemia. Int J Evid Based Healthc 2013;11:134–9.

13. Mata N, Alonso R, Badimón L, et al. Clinical characteristics and evaluation of LDL-cholesterol treatment of the Spanish Familial Hypercholesterolemia Longitudinal Cohort Study (SAFEHEART). Lipids Health Dis 2011;10:94.

14. Wierzbicki AS, Humphries SE, Minhas R, Guideline Development Group. Familial hypercholesterolaemia: summary of NICE guidance. BMJ 2008;337:a1095.

15. Alonso R, Defesche JC, Tejedor D, et al. Genetic diagnosis of familial hypercholesterolemia using a DNA-array based platform. Clin Biochem 2009;42:899–903.

16. Stone NJ, Robinson JG, Lichtenstein AH, et al., for the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014;63:2889–934.

17. Alonso R, Mata P, Zambón D, et al. Early diagnosis and treatment of familial hypercholesterolemia: improving patient outcomes. Expert Rev Cardiovasc Ther 2013;11:327–42.

18. Leren TP, Berge KE. Subjects with molecularly defined familial hypercholesterolemia or familial defective apoB-100 are not being adequately treated. PLos ONE 2011;6:e16721.

19. Béliard S, Carreau V, Carrié A, et al. Improvement in LDL-cholesterol levels of patients with familial hypercholesterolemia: can we do better? Analysis of results obtained during the past two decades in 1669 French subjects. Atherosclerosis 2014;234:136–41.

20. Santos PC, Morgan AC, Jannes CE, et al. Presence and type of low density lipoprotein receptor (LDLR) mutation influences the lipid profile and response to lipid-lowering therapy in Brazilian patients with heterozygous familial hypercholesterolemia. Atherosclerosis 2014;233:206–10.

21. Stein E, Stender S, Mata P, et al., for the Ezetimibe Study Group. Achieving lipoprotein goals in patients at high risk with severe hypercholesterolemia: efficacy and safety of ezetimibe co-administered with atorvastatin. Am Heart J 2004;148:447–55.

22. Cannon CP, Blazing MA, Giugliano RP, et al. Ezetimibe added to statin therapy after acute coronary syndromes. N Engl J Med 2015;372:2387–97.

23. Giugliano RP, Sabatine MS. Are PCSK9 inhibitors the next breakthrough in the cardiovascular field? J Am Coll Cardiol 2015;65:2638–51.

24. Bell DA, Garton-Smith J, Vickery A, et al. Familial hypercholesterolaemia in primary care: knowledge and practices among general practitioners in Western Australia. Heart Lung Circ 2014;23:309–13.

25. Vickery AW, Bell D, Garton-Smith J, et al. Optimising the detection and management of familial hypercholesterolaemia: central role of primary care and its integration with specialist services. Heart Lung Circ 2014;23:1158–64.

KEY WORDS cardiovascular disease, LDL-receptor mutations, lipid-lowering therapy, low-density lipoprotein cholesterol

APPENDIX For an expanded list of the SAFEHEART Investigators, please see the online version of this article.