Attainment of LDL-Cholesterol Treatment Goals in Patients With Familial Hypercholesterolemia
5-Year SAFEHEART Registry Follow-Up

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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.

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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.

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
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-CLp(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-CLp(a) goals (LDL-CLp(a) <100 mg/dl in patients without ASCVD and LDL-CLp(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
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 207 (8.3%), current smoking in 725 (26.3%), type 2 diabetes mellitus in 97 (4.5%), and corneal arcus in 916 (33.3%). Median body mass index was 25.9 kg/m² (IQR: 22.9 to 29.1) and waist circumference 87.0 cm (IQR: 76.0 to 97.0). Median TC was 237.0 mg/dl (IQR: 23.0 to 29.1) and fibrinogen level 287 (257.0 to 318.0) mg/dl.

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Table 1 shows the use of different LLT regimens at entry and follow-up. A significant increase in the use of high-intensity statins at follow-up (from 12.5% at inclusion to 35.4% at follow-up; p < 0.001). The prescription of rosuvastatin increased 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 21 (0.83%) patients at inclusion and 106 (4.88%) at follow-up. Previous ASCVD was present in 132 (4.8%) patients, hypertension in 207 (8.3%), current smoking in 725 (26.3%), type 2 diabetes mellitus in 97 (4.5%), and corneal arcus in 916 (33.3%). Median body mass index was 25.9 kg/m² (IQR: 22.9 to 29.1) and waist circumference 87.0 cm (IQR: 76.0 to 97.0). Median TC was 237.0 mg/dl (IQR: 23.0 to 29.1) and fibrinogen level 287 (257.0 to 318.0) mg/dl.

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Table 3 shows the use of different LLT regimens at entry and follow-up. A significant increase in the use of high-intensity statins at follow-up (from 12.5% at inclusion to 35.4% at follow-up; p < 0.001). The prescription of rosuvastatin increased 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 21 (0.83%) patients at inclusion and 106 (4.88%) at follow-up. Previous ASCVD was present in 132 (4.8%) patients, hypertension in 207 (8.3%), current smoking in 725 (26.3%), type 2 diabetes mellitus in 97 (4.5%), and corneal arcus in 916 (33.3%). Median body mass index was 25.9 kg/m² (IQR: 22.9 to 29.1) and waist circumference 87.0 cm (IQR: 76.0 to 97.0). Median TC was 237.0 mg/dl (IQR: 23.0 to 29.1) and fibrinogen level 287 (257.0 to 318.0) mg/dl.
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 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 [−]).

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 LDL-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.

### Table 3: LLT and LDL-C Goal Achievement (Cohort)

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

Values are n (%). A negative sign indicates not present; a plus sign indicates present.

LLT = lipid lowering therapy; other abbreviations as in Table 1.

### 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 [−]).
**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.

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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.

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.