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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.

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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

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