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Clinical Research Article

Homozygous Familial Hypercholesterolemia in Spain: Data From Registry of the Spanish Atherosclerosis Society

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Abstract

Context: Homozygous familial hypercholesterolemia (HoFH) is a rare disease characterized by the presence of 2 pathogenic variants in the *LDLR*, *APOB*, *PCSK9*, or *LDLRAP1* genes, which cause very high levels of LDL-cholesterol and premature atherosclerotic cardiovascular disease (ASCVD).

Objective: To analyze the current situation regarding diagnosis, cardiovascular disease, lipid-lowering treatment, and degree of control of lipids in patients with HoFH in the National Dyslipidemia Registry of the Spanish Atherosclerosis Society.

Methods: Subjects with HoFH, confirmed by the presence of 2 pathogenic variants in the genes mentioned above, included in the registry from 2013 to June 2023 with an updated review were analyzed.

Results: Of 71 included subjects with HoFH, 40.8% were women, aged 52 [24-62] years, 57 adults and 13 children. The median follow-up was 7 [4-13] years. Age of diagnosis was 14 [2-26] years, with 10% of ASCVD at diagnosis and 27% of current ASCVD at 40.6 (13.4) years of age; 38% were on PCSK9 inhibitors, 9 patients on lomitapide, 9 on LDL apheresis, and 1 patient on evinacumab. Subjects with more than 4 therapies achieved >80% reduction in LDLc. In the last visit, the median LDLc was 139.3 [89.4-204.2] mg/dL. ASCVD was strongly associated with male sex and family history of ASCVD, relative risk 5.26 (1.53-18.10) and 2.53 (1.03-6.26), $P < .05$, respectively. Only 18% and 10% meet the recommended LDLc goal in primary and secondary prevention respectively.

Conclusion: The current situation of HoFH in Spain is better than expected, with marked reductions in LDLc levels with new treatments. In this population, recommended LDLc goals are difficult to achieve despite maximum lipid-lowering therapy. ASCVD has been reduced and delayed by 2 decades.

Key Words: homozygous familial hypercholesterolemia, genetic diagnosis, atherosclerotic cardiovascular disease, LDL-cholesterol, therapies

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; FH, familial hypercholesterolemia; HDLc, high-density lipoprotein cholesterol; HoFH, homozygous familial hypercholesterolemia; IQR, interquartile range; LDLc, low-density lipoprotein cholesterol; LLT, lipid-lowering treatment; PCSK9i, proprotein convertase subtilisin/kexin 9 inhibitor; SEA, Spanish Atherosclerosis Society.

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Homozygous familial hypercholesterolemia (HoFH) or biallelic familial hypercholesterolemia (FH) comprises the presence of 2 pathogenic variants in genes involved in low-density lipoprotein (LDL) cholesterol (LDLc) removal from blood: LDL receptor (*LDLR*), apolipoprotein B (*APOB*) and proprotein convertase subtilisin/kexin type 9 (*PCSK9*) with autosomal semi-dominant inheritance, and in LDL receptor adaptor protein 1 (*LDLRAP1*) with autosomal recessive inheritance (1). Affected subjects present extremely high levels of LDLc from birth, leading to very premature cardiovascular disease and extravascular deposits in the form of extensive xanthomas. HoFH is a rare disease, potentially fatal without early treatment, with the onset of cardiovascular events before the age of 20 years and cardiovascular mortality before the age of 30 years without treatment (2). Currently, it is estimated that one in 250 000 to 360 000 individuals is affected, and very few, probably less than 5%, are identified (3).

Even with an early diagnosis, the prognosis of these patients has been very poor because the HoFH response to traditional lipid-lowering treatments, including statins and ezetimibe, is minimal (4). In most cases, the only effective treatment was LDL apheresis. Recently, proprotein convertase subtilisin/kexin 9 inhibitors (PCSK9i) have produced moderate reductions in LDLc but only in those subjects with some residual activity in the LDL receptor (5). New lipid-lowering drugs that have an action independent of the LDL receptor, such as evinacumab and lomitapide, have been a breakthrough for these patients as they are associated with marked reductions in LDLc and a substantial decrease in the frequency of apheresis, in some cases even allowing it to be discontinued (6).

A recent report of a large worldwide cohort of HoFH highlighted the global situation, revealing late diagnosis, cardiovascular disease at diagnosis in almost 10% of patients, significant differences in management according to country income, with higher and earlier cardiovascular mortality in low-income countries, and inequalities in access to novel therapies and referral units (7). For this reason, the recently published European Guidelines call for action in different countries, advocating for registries and multidisciplinary management (3).

In 2016, we conducted an exhaustive search to estimate the prevalence of HoFH in Spain (8). In that study, 97 individuals with HoFH were identified, with an estimated prevalence of 1:450,000, which was higher than expected. There was a strong relationship between genotype and phenotype, with carriers of null allele having the highest LDLc levels and prevalence of premature cardiovascular disease (8). Most of the identified HoFH cases were included in the Dyslipidemia Registry of the Spanish Atherosclerosis Society (SEA) and have been followed since then. The present study updates the clinical characteristics, current management, achievement of LDLc objectives, and the impact of new therapies in real clinical practice in a large cohort of patients with HoFH included in the registry.

Methods

This study is an observational, retrospective, multicenter analysis that includes the patients with a genetic diagnosis of HoFH included in the Dyslipidemia Registry of the SEA as of June 15, 2023. This is an online registry where more than 50 certified lipid clinics in Spain enter cases of various types of primary hyperlipidemia (9). The registry was approved by a central ethics committee (Comité Ético de Investigación Clínica de Aragón, CEICA), and participants receive and sign an informed consent form. All data included in the registry are anonymous.

Genetic testing was performed in all cases with a clinical suspicion of HoFH. The latter was based on an LDLc level > 400 mg/dL without treatment or > 300 mg/dL under intensive lipid-lowering treatment, excluding causes of secondary hyperlipidemia, or LDLc > 190 mg/dL and tendinous xanthomas before the age of 10 years.

The genetic inclusion criteria were: 2 pathogenic variants in the same gene (monogenic, biallelic FH), including *LDLR*, *APOB*, *or PCSK9* genes with the same variant (formerly true homozygous) or with different variants (formerly compound heterozygous); or 2 pathogenic variants in different genes (digenic biallelic FH, formerly double heterozygous), including *LDLR*, *APOB*, *or PCSK9* genes. Subjects with 2 pathogenic variants in homozygosity or compound heterozygosity in *LDLRAP1* were also included.

To differentiate whether the 2 variants were on the same allele (cis) or on different alleles (trans) various methods were used: family segregation in first-degree relatives; haplotypes were examined using common *LDLR* variants and a pairwise list of *LDLR* variants: c.(829G>A; c.12G>A) p.(Trp4*; Glu 277Lys); c.(1061-8T>C;274C>G)26; c.(313 + 1G>C; c.274C >G) p.(NA; Gln92Glu); and c.(2397_2405delCGTCTT CCT;1690A>C) (p.Val800_Leu802del; Asn564His), which have previously been shown to appear in combination on the same allele in the Spanish population (8). Genetic diagnosis was reported following the HGVS nomenclature (10). The pathogenicity of the FH mutations was assigned according to what was established in the guideline from the American College of Medical Genetics and Genomics (11) and the ClinGen Familial Hypercholesterolemia Expert Panel (12).

Clinical Data

The clinical data recorded for each patient were: sex, vital status, age at most recent visit, age at diagnosis, presence of atherosclerotic cardiovascular disease (ASCVD) in first-degree relatives, presence and type of personal ASCVD, and age at the time of the first ASCVD event and recurrent ASCVD events, aortic stenosis, and presence of subclinical atherosclerosis. Cardiovascular risk factors including hypertension, diabetes, smoking, dietary habits, and physical exercise, as well as physical examination including height, weight, blood pressure, waist circumference, and presence of tendon or skin xanthomas were also recorded. Lipid-lowering treatment information included initiation of therapy, use of statins, ezetimibe, resins, PCSK9i (alirocumab and evolocumab), lomitapide, evinacumab, all doses, and apheresis and its frequency. Lipid levels: untreated and current levels of cholesterol, LDLc, high-density lipoprotein cholesterol (HDLc), triglycerides, and lipoprotein(a).

Statistical Analysis

Statistical analyses were performed with SPSS 27.0 software (IBM, SPSS, Inc, Chicago, IL,). Data are expressed as mean ± SD for numerical variables that followed a normal distribution or as median and interquartile range [IQR] for other numerical variables. Qualitative variables are expressed as number and percentage. Comparisons between groups were performed using Student *t* tests or Mann-Whitney U tests.

Differences were considered significant when the 2-tailed *P* value was < .05.

Comparisons of survival times free from ASCVD were assessed using the Kaplan-Meier estimates and the groups were compared by log-rank tests. The association between survival times free from ASCVD and HoFH groups was calculated using proportional hazards Cox regression. A multivariable Cox regression model was generated and included the covariables showed in Table 1. Afterwards, we fitted the new model keeping all the variables that showed $P < .2$.

Results

Of the 78 subjects who fulfilled the genetic diagnosis of HoFH, 7 were excluded due to lack of follow-up information. Of the remaining 71 patients, 57 had biallelic monogenic semi-dominant hypercholesterolemia: 22 with the same 2 pathogenic variants in the *LDLR* gene and 3 with 2 pathogenic variants in *APOB*; 32 with 2 different pathogenic variants, one in each copy of the *LDLR* gene, and 12 had 2 null variants; 10 had biallelic digenic semi-dominant hypercholesterolemia: *LDLR* + *PCSK9* 6 subjects, *LDLR* + *APOB* 3 subjects, and *APOB* + *PCSK9* 1 subject. Monogenic biallelic recessive hypercholesterolemia or autosomal recessive hypercholesterolemia (2 pathogenic variants in *LDLRAP1* gene) was present in 4 subjects (Fig. 1). The pathogenic variants of HoFH are shown in Supplementary Table 1 (13).

Table 1. Clinical characteristics and lipid profile without lipid-lowering treatment at recruitment

Age at diagnosis, years (range)	14 [2-26]
Familial ASCVD, N (%)	29 (40.8)
Personal ASCVD at diagnosis, N (%)	7 (9.7)
Current ASCVD, N (%)	20 (28.2)
- Coronary heart disease	17 (85)
- Cerebrovascular disease	3 (15)
Age of ASCVD diagnosis, years	40.6 (13.4)
Aortic stenosis, N (%)	6 (8.5)
Hypertension, N (%)	17 (23.9)
Diabetes, N (%)	6 (8.5)
Tobacco consumption, N (%)	
Never	52 (73.2)
Current	8 (11.3)
Former	11 (15.5)
Body mass index, kg/m^2	25.1 (7)
Waist circumference, cm	89 (20.4)
SBP/DBP, mmHg	121.8 (15.8)/71.4 (10.9)
Tendon xanthomas, N (%)	26 (37)
Total cholesterol, mg/dL	528 mg/dL [416-713]
LDL-cholesterol, mg/dL	444 [337-658]
HDL-cholesterol, mg/dL	45 [39-54]
Triglycerides, mg/dL	107 [80-174]
Lipoprotein(a), mg/dL	29.3 [10.5-65]

Mean (SD) for numerical variables that followed a normal distribution or as median and interquartile range (IQR) or number (%) for qualitative variables. N denotes number of subjects.
Abbreviations: ASCVD, arteriosclerotic cardiovascular disease; DBP, diastolic blood pressure; HDL, low-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein; SBP, systolic blood pressure.

The clinical and biochemical characteristics of the participants with HoFH are described in Table 1. Twenty-nine (40.8%) were women, aged 52 [24-62] years, 57 adults and 13 children (< 18 years), with an overall median 54.5 [42-66] years in adults and 9 [7-16] years in children. The median age of the 12 subjects with null-null allele mutations was 21 [11.5-25] years and 53 [36-65] years for the rest in the last visit. The median follow-up was 7 years [4-13].

Clinical characteristics and lipid values without lipid-lowering treatment (LLT) according to the genetic diagnosis are shown in Tables 2 and 3.

Regarding LLT, age of statin initiation was 25 [5.5-44] years and 96% of the subjects were on statins, 81.2% on ezetimibe, 38% on PCSK9i, 9 patients on lomitapide (13%), 9 patients (13%) on LDL apheresis, and 1 patient on evinacumab.

In the last visit, the median [IQR] LDLc of the entire cohort was 139.3 [89.4-204.2] mg/dL. In adults, the mean (SD) LDLc was 133.2 (68.7) mg/dL and, in children, 228.7 (75.9) mg/dL. In subjects with ASCVD the mean LDLc was 105.2 (57) mg/dL.

LLT and the last lipid values according to the genetic diagnosis are reported in Tables 3 and 4. The percentage of LDLc reduction was higher with more LLT (Fig. 2). Patients with LLT including lomitapide had a last visit mean (SD) LDLc of 139 (92) mg/dL, with a mean dose of lomitapide of 32 mg/day. Three patients had discontinued LDL apheresis and the rest had reduced its frequency.

According to the European Guidelines, 13 patients (18%) without ASCVD met the goal of LDLc lower than 70 mg/dL. Of the 20 patients with ASCVD only 2 achieved the goal of LDLc lower than 55 mg/dL, and 8 less than 70 mg/dL. In children, only 1 patient had current LDLc below 115 mg/dL.

In the survival analyses, subjects with biallelic monogenic FH with same variants had significantly shorter survival time free of ASCVD events than those with the other genotypes (Fig. 3). In the Cox regression analysis, male sex and the family history of ASCVD were the 2 independent risk factors for ASCVD events. Baseline LDLc, HDLc, body mass index, tobacco or the presence of null-null allele variant were not independent predictors of ASCVD event (Table 5).

Discussion

This study shows the clinical characteristics, genetic background, current lipid-lowering treatment, LDLc goals and

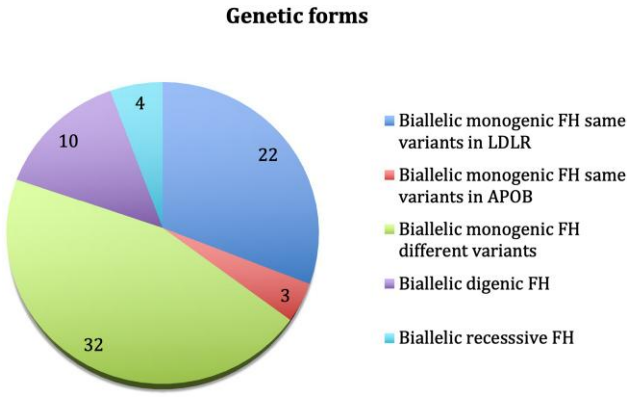

Figure 1. Genetic diagnosis of HoFH subjects.
Abbreviation: FH, Familial hypercholesterolemia (number of patients).

Table 2. Clinical characteristic according to genetic diagnosis

	Biallelic monogenic FH same variants *LDLR*	Biallelic monogenic FH same variants *APOB*	Biallelic monogenic FH different variants *LDLR*	Biallelic digenic FH	Biallelic recessive FH
N	22	3	32	10	4
Gender female, N (%)	7 (32)	2 (67)	13 (40.6)	3 (30)	100
Current age, years	39.4 (20.4)	62 [56-64]	43.7 (25.8)	63.4 (12)	23.5 [17-48]
Age of diagnosis, years	18 [4-26]	25 [24-38.5]	4 [1-23]	47 [34-60]	2 [1-3]
ASCVD, N (%)	11 (50)	0	5 (15.2)	4 (40)	0
ASCVD at diagnosis, N (%)	3 (13.6)	0	1 (3 (3)	3 (30)	0
ASCVD, age	33.7 (16.9)		47 (8)	45 (2.4)	
CHD, N (%)	9 (90)		3 (60)	3 (80)	
Aortic stenosis, N (%)	3 (14)	0	1 (3)	2 (20)	0
Hypertension, N (%)	6 (27.3)	0	5 (15.6)	6 (60)	0
Diabetes, N (%)	2 (9.1)	1 (33.3)	3 (9.1)	0	0
Tobacco consumption, N (%)	Current: 2 (9.1) Former: 3 (13.6)	No	Current: 6 (19) Former: 5 (16)	Current: 0 Former: 3 (30)	0
BMI, kg/m^2	24.4 (6.5)	28.4 [27.4-33]	23.6 (6.4)	30.8 (7.4)	20.8 (3.1)
Tendon xanthomas, N (%)	12 (54.5)	No	10 (31.3)	2 (20)	2 (50)

Abbreviations: *APOB,* apolipoprotein B gene; ASCVD, Arteriosclerotic cardiovascular disease; BMI, body max index; CHD, coronary heart disease; FH, familial hypercholesterolemia; *LDLR,* Low-density lipoprotein receptor gene.

ASCVD-free survival time of a large genetically defined HoFH cohort included in the Dyslipidemia Registry of the SEA a highly representative cohort of HoFH in Spain (8).

Several important points can be derived from this work. First, there is great heterogeneity within the diagnosis of HoFH as previously described, with a high correlation between genotype and phenotype (8). Consistent with findings from other cohorts of HoFH (14, 15), LDLc levels and prevalence of ASCVD are much higher in monogenic semidominant biallelic hypercholesterolemia with the same variants, especially in null allele carriers, with mean baseline LDLc levels of 929 mg/dL and 50% with ASCVD at 33.7 years. This was similar in the Italian cohort of 125 HoFH patients, in whom null allele carriers had the worse phenotype with a cardiovascular event much earlier than the others (16). Biallelic monogenic FH with different variants or digenic FH showed lower baseline LDLc than biallelic monogenic FH with same variants or biallelic recessive FH, but over 400 mg/dL, confirming the recommendation to suspect this disease when LDLc is above this cutoff (3). Biallelic monogenic FH for *APOB* pathogenic variants have a less severe phenotype, and this is consistent with previous findings (17). This great clinical and genetic heterogeneity supports the fact that clinical diagnosis based on a certain LDLc concentration is only one criterion of suspicion. The traditional clinical picture of HoFH possibly does not correspond to more than 50% of cases with a genetic diagnosis and the traditional description represents only the tip of a more complex iceberg. This explains the differences in the prevalence of the disease reported in recent years (3). We have gone from thinking about a disease that affected one in every million inhabitants to a disease that is 3 times more common since we are genetically diagnosing cases with more benign phenotypes. In fact, it would probably make more sense to classify HoFH into 2 groups according to genotype/phenotype than to keep them together as a single, heterogeneous entity.

Second, despite the improvement in LDLc levels, ASCVD continues to be a major problem in this population, of very high prevalence and very early onset that determines its prognosis (7). Almost 10% had ASCVD at diagnosis, but there is great heterogeneity and most of the ASCVD is concentrated in those subjects, especially men, with monogenic semidominant biallelic hypercholesterolemia with the same variants or in subjects with late diagnosis, many of them with initiation of treatment at advanced ages. In fact, in this cohort, the age of diagnosis is too late, 14 [2-26] years, similar to that reported by the world registry (12 years) (7), and age of initiation statin use was also too late, 25 [5.5-44] years. This makes early diagnosis and treatment of all HoFH genotypes inexcusable.

Furthermore, reinforcing early diagnosis of this disease in childhood is a very important point to highlight, because there are currently therapies with data available in the pediatric population, such as alirocumab, lomitapide, and evinacumab, associated with reductions in LDLc similar to the adult HoFH population and good safety data (18-20). Early initiation of treatment will result in lower cumulative LDLc exposure and therefore longer event-free survival (4).

In this study, male sex and family history of ASCVD were strongly associated with the presence of cardiovascular events, confirming the findings of previous reports (21), although baseline LDLc or the presence of null variants was not. This fact could be explained by the difference in the age of carriers of 2 null alleles compared to those with defective alleles (21 vs 53 years), who despite having the least favorable genotype, have not had time to develop ASCVD. However, the genetic type of HoFH did influence ASCVD, true homozygous having the lowest event-free survival. Despite this, ASCVD prevalence is decreasing and being delayed in this population. The mean age of onset ASCVD was 40.6 (13,4) years in all HoFH subjects and 33.7 (16.9) years in biallelic monogenic FH with same variants, almost 2 decades later than previous records (22) and this could be explained by the use of new

Table 3. Lipid levels according to genetic diagnosis

	Biallelic monogenic FH same variants *LDLR* *Null 8/Defective 14*	**Biallelic monogenic FH same variants *APOB***	**Biallelic monogenic FH different variants *LDLR***	**Biallelic digenic FH**	**Biallelic recessive FH**
Lipid levels at diagnosis					
Total cholesterol, mg/dL	720 [481-879,3] Null allele 966 [758-1147,8] Def. allele 516.5 [451.8-794]	389.5 (70.6)	489.5 [418-678]	396 [288.5-564]	626.7 [566-908]
LDL-C, mg/dL	701,5[408,8-850,3] Null allele 929.3 [735.6-1071.7] Def. allele 425.2 [367.5-717]	300.8 (48.15)	424.4 [340.4-570.9]	335.5 [222.7-451.3]	570 [496-911]
HDL-C, mg/dL	39.5 [35-50.5]	46.3 (8.6)	49 (10,6)	39.9 (14.2)	44.2 (8)
Triglycerides, mg/dL	103 [83-183,8]	131.4 (66.4)	127.5 (57.4)	132.5 (79.8)	100.3 (26)
Lp(a), mg/dL	26.5 [4.8-71.3]	40.9 (22.7)	32 [10-70.5]	27.3 [17-111.5]	28.5 [19.3-31.2]
Lipid levels at the last visit of the follow-up					
Total cholesterol, mg/dL	209.4 (82.9) Null allele 265 (91.2) Def. allele 175.2 (57.3)	155 [144-180.5]	242.1 (70)	158,5 (46.3)	279 [106-356]
LDLc, mg/dL	149.4 (81.7) Null allele 219.5 (75.7) Def. allele 106.3 (50)	91 [78-121.8]	173.3 (72)	83.7 (43.5)	199.4 [35-289.2]
HDLc, mg/dL	41.7 (14.6)	45 [43-48]	51.3 (13.5)	50.9 (17.3)	50 [34.8-51.8]
Triglycerides, mg/dL	91.2 (68.5)	63.5 [63.5-90]	92 (38.3)	119.3 (51.6)	99.5 [26-155.8]

Abbreviations: *APOB*, apolipoprotein B gene; FH, familial hypercholesterolemia; Def., defective; HDL-C, High-density lipoprotein cholesterol; LDL-C, Low-density lipoprotein cholesterol; *LDLR*, low-density lipoprotein receptor gene; Lp(a), lipoprotein(a).

Table 4. Lipid-lowering treatment at the last visit of the follow-up

	Biallelic monogenic FH same variants *LDLR*	**Biallelic monogenic FH same variants *APOB***	**Biallelic monogenic FH different variants *LDLR***	**Biallelic digenic FH**	**Biallelic recessive FH**
Statins, N (%)	21 (95.4)	3 (100)	31 (97)	9 (90)	4 (100)
Ezetimibe, N (%)	19 (86.4)	3 (100)	24 (77.4)	6 (60)	4 (100)
PCSK9i, N (%)	7 (32)	2 (67)	9 (28.1)	8 (80)	1 (25)
Lomitapide, N (%) Evinacumab, N	8 (36.4) 1	0	0	0	1
Apheresis, N (%)	6 (27.3)	0	2 (6.3)	0	1 (25)

Abbreviations: *APOB*, apolipoprotein B gene; FH, familial hypercholesterolemia; *LDLR*, low-density lipoprotein receptor gene; PCSK9i, PCKS9 inhibitors.

LLT and apheresis. LDL apheresis has been demonstrated to reduce ASCVD events in this population (23), and the use of new therapies, such as lomitapide or evinacumab, have been demonstrated to prevent ASCVD compared with a previous, retrospective cohort with a 4-year follow-up (24).

Third, with variable phenotypes, it is reasonable to find variable treatment regimens, but they may be too heterogeneous. There are no clear criteria in prescribing drugs. It seems reasonable that treatment should be started with a potent statin + ezetimibe as the first step in 100% of patients, to continue in most cases with PCSK9i if objectives are not achieved, followed by an LDL receptor (LDLr)-independent therapy and finally LDL apheresis, as recommended by the latest published guidelines (3). However, the prescription pattern does not seem to follow these recommendations and the number of subjects outside the objectives and without maximum pharmacological treatment is still very high. It is evident that in this population achieving the goals set by the guidelines is complicated, but with all the available therapies those severe cases that are being treated with receptor-independent therapies such as lomitapide or evinacumab, present LDLc levels around 139-147 mg/dL with reductions greater than 80%. Therefore, undertreatment with this type of therapy is also observed in this cohort, like other cohorts (7). On the contrary, LDL apheresis should be reserved for exceptional cases, mostly people homozygous for null alleles, after previous treatments, and that seems to be the approach followed by the units from the SEA (25).

The mean LDLc levels in this registry are considerably lower than in previous registries (21, 22) and this is possibly due to the therapeutic options currently available. Almost 40% were treated with PCSK9i, especially those carrying defective

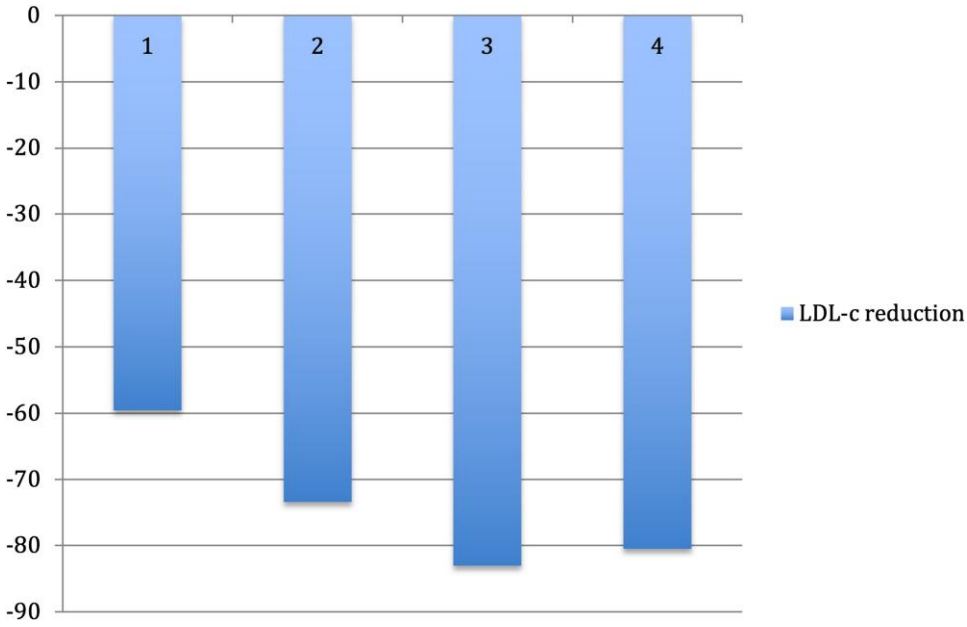

Figure 2. LDLc reduction depending on the number and type of LLT. Groups: 1) Statins and ezetimibe, N = 30. 2) Statins + -ezetimibe and PCSK9i, N = 26. 3) Any LLT plus lomitapide or evinacumab, N = 10. 4) Any LLT plus apheresis, N = 9. Two patients had missing data on LLT.

Abbreviations: LDL-c, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy.

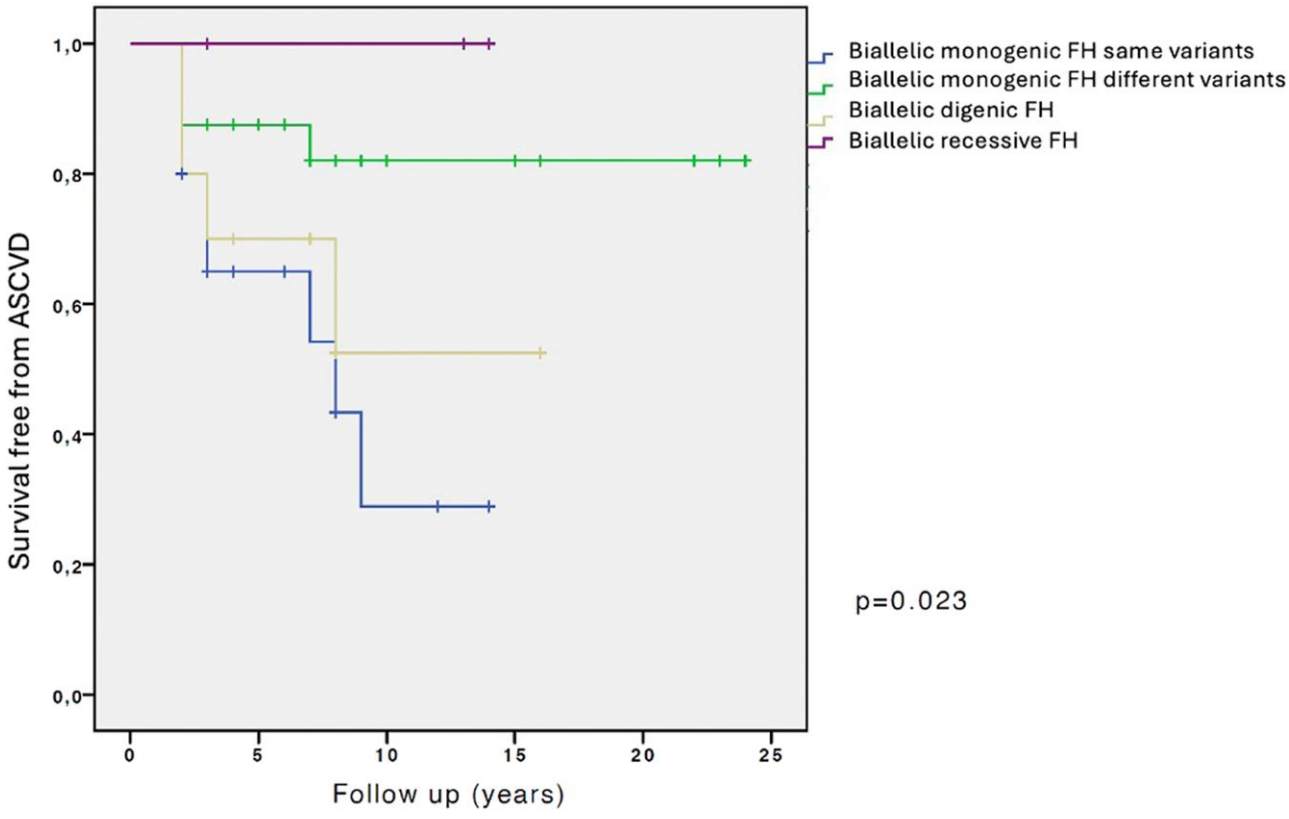

Figure 3. Survival time free from major adverse cardiovascular events stratified by type of genetic diagnosis. The primary outcome in the survival analyses was major adverse cardiovascular events (MACE), defined as a composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG). The statistical test for comparison between groups was a log-rank test.

Abbreviations: ASCVD, atherosclerosis cardiovascular disease; FH, familial hypercholesterolemia; HR, hazard ratio.

alleles. LDLc reductions associated with statins and ezetimibe were 73%; if the effect of statins and ezetimibe is subtracted this would be a reduction of approximately 16% to 24%, similar to the reductions in clinical trials (5, 26). Ten patients were treated with drugs with a mechanism of action independent of the LDLr, 9 with lomitapide and 1 with evinacumab,

Table 5. Prospective multivariable Cox regression analysis of predictive factors for a cardiovascular event

	HR (95% CI)
Family history of cardiovascular disease	2.53 (1.03-6.26), $P = .09$
Male sex	5.26 (1.53-18.10), $P = .043$

Variables introduced in the model: age, sex, smoking, family history of cardiovascular disease, body mass index, low-density lipoprotein cholesterol without lipid-lowering treatment (LLT), high-density lipoprotein cholesterol, and presence of null-null allele variant; the statistically significant variables remained.
Abbreviation: HR, hazard ratio.

achieving reductions with respect to baseline of 83%. These data agree with the results of clinical trials (20, 27), real world data (28-30) and data from the global registry, of those who had 5 treatments (7). Due to the use of these therapies, the number of patients with LDL apheresis is low, in fact in this cohort 3 patients discontinued apheresis, and the rest were able to space it out, which means an improvement in the quality of life of these patients (31). Early initiation of apheresis has been associated with fewer cardiovascular events and continues to be a mainstay in the treatment of severe cases (32). In this cohort there are no cases of liver transplantation, an option that is increasingly out of use as it is associated with major complications (33).

Guideline recommendations of LDLc goals are below 70 mg/dL without ASCVD and below 55 mg/dL with ASCVD, also in HoFH, but the mean LDLc during follow-up was 139.3 [89.4-204.2] mg/dL, and 105.2 (57) mg/dL in subjects with ASCVD. Less than 20% met this target in primary prevention and only 2 patients with ASCVD were below 55 mg/dL, this was similar to recent registries (34). Currently there are difficult objectives to meet due to the severity of the disease, despite using all available LLT. With the use of therapies with LDLr-independent action or even a combination of both (lomitapide and evinacumab), very low levels of LDLc can be achieved (35). Nevertheless, the LDLc level achieved in this cohort represents a significant improvement with reductions of almost 90% in LDLc, mainly in patients treated with new drugs.

This study has several strengths, the large number of patients with HoFH included and that the data belong to a very robust registry involving more than 50 lipid units in the country. In addition, extensive clinical and outcome data have been collected on these patients.

We also acknowledge several limitations in this study such as the fact that not all HoFH patients in Spain are included and the relatively short duration of follow-up. The former can be explained by the fact that HoFH is a very rare disease and this is a single-nation study. Furthermore, although this study reports results which are representative, since the registry contains most HoFH cases in Spain, some, especially HoFH with mild phenotypes, may have been missed.

Conclusion

The current situation of HoFH in Spain is better than expected and previously described, with acceptable LDLc levels and very marked reductions with the use of new drugs. In this population, LDLc recommended goals are difficult to achieve despite maximum lipid-lowering therapy. There has also been an improvement and a delay of almost 2 decades in the onset of cardiovascular disease. Earlier diagnosis and treatment should further improve the prognosis of HoFH.

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Author Contributions

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Data Availability

Some or all datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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