Journal of the American Heart Association

ORIGINAL RESEARCH

Contemporary Homozygous Familial Hypercholesterolemia in the United States: Insights From the CASCADE FH Registry

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BACKGROUND: Homozygous familial hypercholesterolemia (HoFH) is a rare, treatment-resistant disorder characterized by early-onset atherosclerotic and aortic valvular cardiovascular disease if left untreated. Contemporary information on HoFH in the United States is lacking, and the extent of underdiagnosis and undertreatment is uncertain.

METHODS AND RESULTS: Data were analyzed from 67 children and adults with clinically diagnosed HoFH from the CASCADE (Cascade Screening for Awareness and Detection) FH Registry. Genetic diagnosis was confirmed in 43 patients. We used the clinical characteristics of genetically confirmed patients with HoFH to query the Family Heart Database, a US anonymized payer health database, to estimate the number of patients with similar lipid profiles in a "real-world" setting. Untreated low-density lipoprotein cholesterol levels were lower in adults than children (533 versus 776 mg/dL; P=0.001). At enrollment, atherosclerotic cardiovascular disease and supravalvular and aortic valve stenosis were present in 78.4% and 43.8% and 25.5% and 18.8% of adults and children, respectively. At most recent follow-up, despite multiple lipid-lowering treatment, low-density lipoprotein cholesterol goals were achieved in only a minority of adults and children. Query of the Family Heart Database identified 277 individuals with profiles similar to patients with genetically confirmed HoFH. Advanced lipid-lowering treatments were prescribed for 18%; 40% were on no lipid-lowering treatment; atherosclerotic cardiovascular disease was reported in 20%; familial hypercholesterolemia diagnosis was uncommon.

CONCLUSIONS: Only patients with the most severe HoFH phenotypes are diagnosed early. HoFH remains challenging to treat. Results from the Family Heart Database indicate HoFH is systemically underdiagnosed and undertreated. Earlier screening, aggressive lipid-lowering treatments, and guideline implementation are required to reduce disease burden in HoFH.

Key Words: atherosclerotic cardiovascular disease ■ homozygous familial hypercholesterolemia ■ lipid-lowering treatments ■ low-density lipoprotein cholesterol ■ xanthomas

Homozygous familial hypercholesterolemia (HoFH) is a rare inherited condition associated with extremely elevated levels of serum low-density lipoprotein cholesterol (LDL-C) and markedly elevated risk for premature atherosclerotic cardiovascular disease (ASCVD), especially coronary artery disease (CAD) and

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This article was sent to Daniel Edmundowicz, MD, Guest Editor, for review by expert referees, editorial decision, and final disposition.

Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.122.029175

For Sources of Funding and Disclosures, see page 12.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- Data from the CASCADE (Cascade Screening for Awareness and Detection) FH Registry indicate that only individuals with the most severe homozygous familial hypercholesterolemia (HoFH) phenotypes are diagnosed in childhood, missing the opportunity to prevent early atherosclerotic cardiovascular disease with timely initiation of aggressive lipid-lowering treatment (LLT).
- In the largest US description of contemporarily treated patients with HoFH, 68% of adults and 75% of children had not reached goal lipid levels despite being cared for in specialty lipid clinics and the availability of potent LLTs; the use of LLTs with low-density lipoprotein receptor–independent mechanisms has the potential to dramatically improve goal attainment.
- Among 277 people with a phenotype consistent with HoFH identified in the Family Heart Database of >81 million individuals, 20% had atherosclerotic cardiovascular disease, only 19% were on high-intensity statins, 18% were on more advanced LLTs, and 40% were not on lipid-lowering medications. These data provide insights into the possible underdiagnosis and inadequate care of these individuals.

What Are the Clinical Implications?

- Universal lipid screening of children is critical to ensure the timely diagnosis and treatment of every patient with HoFH, irrespective of the phenotypic severity, and is necessary to prevent the high and markedly premature atherosclerotic cardiovascular disease burden of this condition.
- Patients with HoFH must be intensively treated with a combination of multiple LLTs, including advanced, HoFH-specific medications to achieve target low-density lipoprotein cholesterol levels.
- Increased awareness of HoFH is necessary so that patients with a lipid profile consistent with HoFH can be referred to specialty clinics for comprehensive evaluation and initiation of appropriate therapy.

Nonstandard Abbreviations and Acronyms

APOB	apolipoprotein B100
FH	familial hypercholesterolemia
HICC	HoFH International Clinical Collaborators
HoFH	homozygous familial hypercholesterolemia
LDLR	low-density lipoprotein receptor
LDLRAP1	low-density lipoprotein receptor adaptor protein 1
LLT	lipid-lowering treatment
PCSK9	proprotein convertase subtilisin/kexin type 9

aortic stenosis.[1–3] Historically, the mean age of death in untreated patients with HoFH was about 18 years,[4] making an early diagnosis and initiation of appropriate lipid-lowering treatments (LLTs) imperative. HoFH is most frequently caused by biallelic pathogenic variants in the low-density lipoprotein receptor (*LDLR*), but pathogenic variants in other genes in the LDLR pathway, such as apolipoprotein B100 (*APOB*), proprotein convertase subtilisin/kexin 9 (*PCSK9*), and LDLR adapter protein 1 (*LDLRAP1*) causing autosomal recessive hypercholesterolemia, can also result in the HoFH phenotype.[1] Patients with HoFH, especially those with biallelic *LDLR* mutations, are known to respond less vigorously to LLTs, which depend on functioning low-density lipoprotein receptors.[5] On the basis of the estimated prevalence of heterozygous familial hypercholesterolemia (FH) (between ~1:250 and ~1:300),[6–8] the prevalence of HoFH may be ≈1:250 000 to 1:360 000, corresponding to about 1103 to 1332 individuals in the United States.

Historically, HoFH has been diagnosed clinically in patients with untreated LDL-C levels ≥500 mg/dL, xanthomas before the age of 10 years, or both parents with a phenotype consistent with heterozygous FH.[1] However, increased use of genetic diagnosis and large cohort studies have highlighted the broad phenotypic spectrum of genetically diagnosed HoFH with LDL-C levels below the historically used cutoff,[1–3,9–12] prompting a proposal for a less stringent threshold for untreated LDL-C levels.[13]

Results from the HICC (HoFH International Clinical Collaborators) registry, including data on 751 patients with HoFH, confirm that HoFH remains underdiagnosed and undertreated worldwide.[1,3,11] Although characteristics and treatment patterns of cohorts with HoFH from Europe, South Africa, and Japan have been published,[2,10–12,14,15] there is little information on the health status of patients with HoFH in the United States, where awareness of HoFH clinical characteristics, diagnostic and therapeutic guidelines, and access to lipid specialists remain suboptimal.[16]

Here, we present data from a contemporary cohort of patients with HoFH from 20 lipid specialty clinics across the United States participating in the CASCADE (Cascade Screening for Awareness and Detection) FH Registry, highlighting gaps in care and opportunities for improvement in diagnosis and treatment. We also present novel data from the Family Heart Database, a

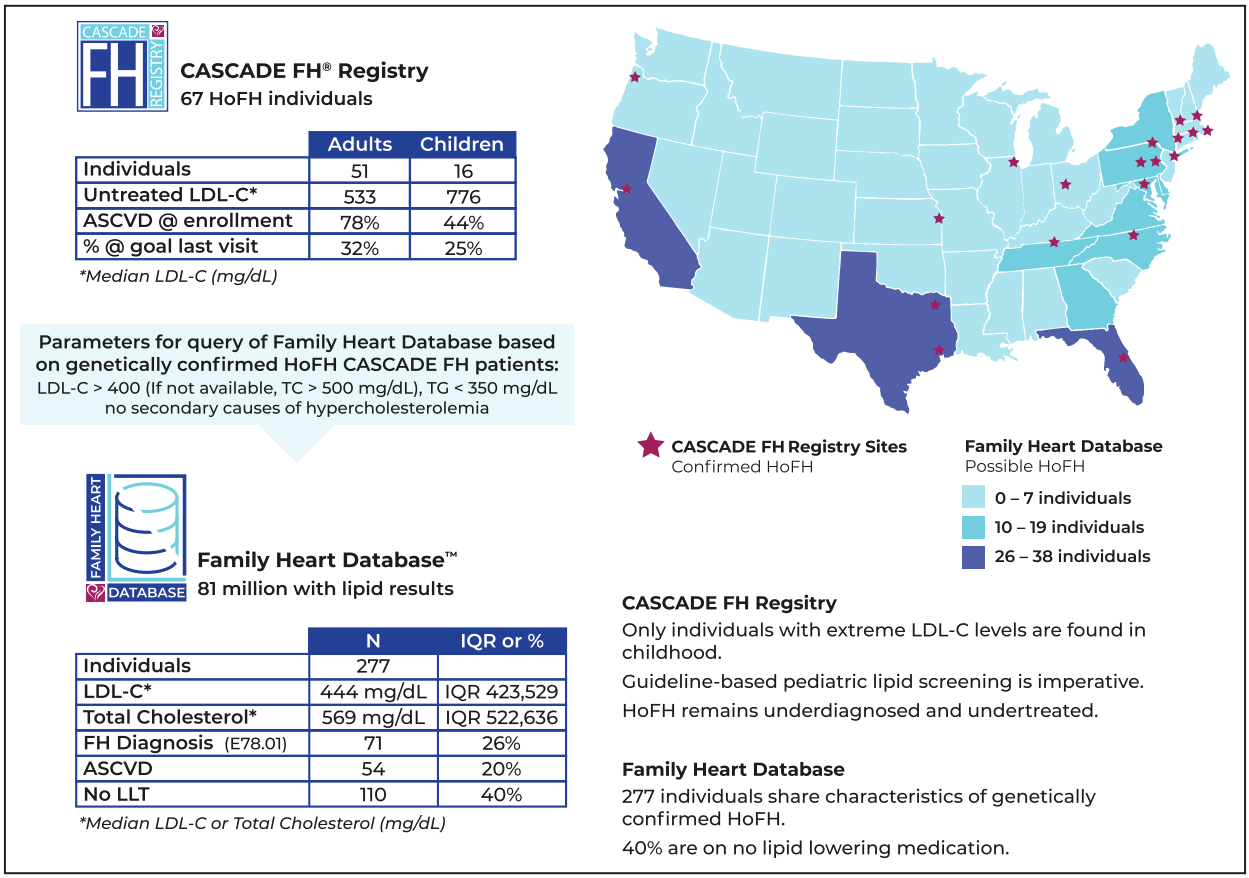

Figure 1. Lipid values and status of individuals with HoFH living in the United States.
ASCVD indicates atherosclerotic cardiovascular disease; CASCADE, Cascade Screening for Awareness and Detection; FH, familial hypercholesterolemia; HoFH, homozygous familial hypercholesterolemia; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering treatement; TC, total cholesterol; and TG, triglycerides.

national database of >81 million individuals with clinical and laboratory data, to provide unique insights into the number, characteristics, and ASCVD burden of individuals across the United States with clinical profiles consistent with genetically diagnosed patients with HoFH within the CASCADE FH Registry (Figure 1).

METHODS

Because of the sensitive nature of the data collected for this study, requests to access the data set from qualified researchers trained in human subject confidentiality protocols may be sent to the Family Heart Foundation at cascade-fh@thefhfoundation.org.

Study Population

This analysis examined patients with HoFH enrolled at sites participating in the CASCADE FH Registry, which was created in 2013 by the Familial Hypercholesterolemia Foundation (renamed the Family Heart Foundation in 2021), a patient-centric research and advocacy organization. The aim of the registry is to describe the characteristics, treatment patterns, and clinical events in patients with FH (both heterozygous and homozygous) in the United States.[17] Details of the registry have been described elsewhere.[17] This study is registered in ClinicalTrials.gov (NCT01960244). Before entering patient data into the CASCADE FH Registry, each site is required to receive institutional review board approval. Signed informed consent was obtained for prospectively enrolled patients, and a waiver of consent was obtained for retrospective patients. Prospectively enrolled children provided assent.

Currently, a total of 4506 patients with FH have been prospectively enrolled in the registry at 40 sites in the United States, 20 of which follow up patients with HoFH. The present analysis focuses on patients with either a clinical or a genetic diagnosis of HoFH. Clinical diagnosis was defined as an untreated LDL-C level ≥400 mg/dL (or an untreated total cholesterol level ≥500 mg/dL if LDL-C is unavailable) and a family history of hypercholesterolemia in both parents or xanthomas[13]; or treated LDL-C level >300 mg/dL.[1] Genetic diagnosis was defined as the presence of biallelic pathogenic or

likely pathogenic variants in *LDLR*, *APOB*, *PCSK9*, or *LDLRAP1* genes[1] or by the presence of 2 variants (one pathogenic or likely pathogenic and the other variant of unknown significance) in patients with untreated LDL-C levels consistent with the historical diagnosis of HoFH (LDL-C >500 mg/dL). Seven individuals with severe FH with total cholesterol and LDL-C levels ranging from 467 to 543 mg/dL and from 368 to 476 mg/dL, respectively, but no clear family history or presence of xanthomas, were carefully reviewed and ultimately excluded from the analysis. Their characteristics are summarized in Data S1 and Table S1.

We extracted CASCADE FH Registry data on patients with HoFH from inception of the registry to April 2020 when study enrollment was paused during the COVID-19 pandemic. We identified 67 individuals with HoFH who had at least 1 office visit at a participating site. Of these, 50 provided consent for prospective follow-up.

Variables

The following variables were considered: lipid panel before treatment, at time of enrollment, and at the most-recent follow-up visit; lipoprotein(a) if available; LDL-C levels at or below guideline thresholds at most recent follow-up in the registry; and family history of hypercholesterolemia and ASCVD, medications, ASCVD events and procedures, and ASCVD risk factors. For this analysis, guideline-based threshold/target LDL-C levels were defined as <100 and <130 mg/dL for adults and children without ASCVD, respectively, and <70 mg/dL in both adults and children with ASCVD.[18,19] High-intensity statin was defined as a daily dose of 40 or 80 mg of atorvastatin or 20 or 40 mg of rosuvastatin,[19] in both adults and children. Cardiovascular outcomes collected included aortic valve disease (supravalvular and aortic valve stenosis and aortic valve replacement), CAD, fatal and nonfatal myocardial infarction, revascularization, including percutaneous coronary intervention, coronary artery bypass grafting, and stroke/transient ischemic attack.

Genetic testing was obtained by individual sites and performed by Clinical Laboratory Improvement Amendments–certified or experienced FH research laboratories. Genetic variants were classified following the consensus guidelines for LDLR variant classification from the Clinical Genome Resource Variant Curation Expert Panel or provided by Chora et al.[20,21] Novel, previously unreported variants were classified as predicted loss of function if they were stop-gain, frameshift, deletion, or splicing variants. Previously unreported missense variants were classified as variants of unknown significance.

Family Heart Database

The Family Heart Database is distinct from the CASCADE FH Registry and includes a combination of anonymized insurance claims with diagnosis codes, procedure codes, and prescription data as well as lipid values from 81 885 302 people in the United States between May 1, 2012, and June 30, 2020. This database provides a significant source of data to address a range of research questions on FH and ASCVD.[22–25]

To evaluate the number of individuals who may have HoFH in a "real-world" setting, we queried the Family Heart Database to identify individuals whose lipid values mirrored those of the individuals from the CASCADE FH Registry with genetically proven HoFH, and we assessed whether they carried a diagnosis of FH as defined by the presence of *International Classification of Diseases, Tenth Revision* (*ICD-10*), code E78.01, introduced in 2016. Appropriate criteria were applied to the algorithm to exclude individuals with secondary hypercholesterolemia (eg, obstructive liver disease, hypothyroidism, and nephrotic syndrome). In addition, unless diagnosed with FH, or on an HoFH medication, we excluded individuals older than the oldest age at diagnosis of the genetically confirmed patients with HoFH (age, 37 years). This was done to exclude those with uncoded secondary cause of hypercholesterolemia. Using our prior approach, paid prescription data were used for extracting information on LLT for identified patients.[23] See Data S2 for a detailed description of the criteria used.

Statistical Analysis

Data from the CASCADE FH Registry were stratified by age (<18 and ≥18 years) at the time of registry enrollment. Continuous variables were summarized as median (IQR), and categorical variables were summarized as frequencies (percentages). Differences in continuous variables were statistically evaluated by Wilcoxon rank-sum test, and differences in categorical variables were evaluated by Fisher exact test. A 1-sided ANOVA was performed to test the relationship between mean post-treatment LDL-C levels and the number of LLTs at both enrollment and latest follow-up visit. Two patients with LDL-C and total cholesterol levels significantly higher at follow-up than enrollment (exceeding Tukey outlier limit) and with known adherence issues were excluded from the analysis. A cube-rooted transformation was applied to the data before this analysis to normalize the distributions. All hypothesis tests were performed at predetermined significance level of α=0.05. All statistical analyses were performed using R (v 3.6.3).

RESULTS

Demographics and Clinical Characteristics

Demographics and clinical characteristics of the cohort of the 67 patients with HoFH at CASCADE FH Registry enrollment are summarized in Figure 1 and

Table 1. Demographics and Clinical Characteristics at Enrollment, Stratified by Age Groups (n=67)

Variable	Adults (n=51)		Children (n=16)		*P* value
	No.	Values	No.	Values	
Demographics					
Age at enrollment, y	50	41.9 (28.8–52.9)	16	9.6 (5.8–11.8)	-
Age at diagnosis, y	51	12.6 (4.1–26.5)	11	2.0 (2.0–3.5)	-
Female sex, n (%)	51	27 (52.9)	16	7 (43.75)	0.6
Race, n (%)	51		16		0.08
White		34 (66.7)		6 (37.5)	
Black		5 (9.8)		2 (12.5)	
Other		12 (23.5)		8 (50.0)	
Ethnicity, n (%)	51		16		
Hispanic		9 (17.6)		6 (37.5)	0.2
Physical findings					
Systolic BP, mm Hg	51	124 (116–135)	15	103 (96–115)	<0.001
Diastolic BP, mm Hg	51	68 (60–76)	15	60 (58–64)	0.05
BMI, kg/m^2	51	27.6 (23.9–30.5)	16	20.4 (15.7–22.5)	<0.001
Lipid levels					
TC, mg/dL	50	312 (219–438)	15	385 (181–736)	0.4
LDL-C, mg/dL	50	235 (147–358)	14	317 (97–603)	0.6
HDL-C, mg/dL	50	38 (30–54)	15	39 (27–42)	0.3
Triglycerides, mg/dL	50	100 (65–163)	15	96 (52–136)	0.3
Cardiovascular risk factors, n (%)					
Tobacco use	51	14 (27.5)	16	0 (0.0)	0.02
Current	51	7 (12.7)	16	0 (0.0)	0.2
Former	51	7 (19.0)	16	0 (0.0)	0.2
Hypertension	51	20 (39.2)	16	0 (0.0)	0.007
Diabetes	51	3 (5.9)	16	0 (0.0)	1
Obesity	51	14 (27.5)	16	0 (0.0)	0.02
Cardiovascular disease					
Aortic valve stenosis, n (%)	51	13 (25.5)	16	3 (18.8)	0.7
CAD, n (%)	51	40 (78.4)	16	7 (43.8)	0.02
Age at onset, y	38	30.5 (21.1–41.0)	6	8.9 (4.5–10.7)	<0.001
MI, n (%)	51	11 (21.6)	16	0 (0.0)	0.05
Age at onset, y	8	28.0 (23.2–40.0)	0	0 (0.0)	-
Procedures/interventions					
Aortic valve replacement, n (%)	51	7 (13.7)	16	0 (0.0)	0.2
Age, y	5	24.0 (16.0–37.0)	-	-	-
CABG, n (%)	51	21 (41.2)	16	2 (12.5)	0.04
Age at onset, y	19	36.0 (26.0–41.0)	2	10.0 (8.0–12.0)	0.04
PCI/stent, n (%)	41	18 (35.3)	16	0 (0.0)	0.004
Age at onset, y	17	28.0 (22.4–41.0)	…	…	…
Liver transplant, n (%)	51	2 (3.9)	16	3 (18.8)	0.08
Age at onset, y	2	17.0 (16.5–17.5)	3	6.0 (5.0–7.0)	0.2
Insurance status, n (%)	51		16		0.6
Commercial		28 (54.9)		6 (37.5)	
Medicare/Medicaid		17 (33.3)		8 (50.0)	
No insurance		1 (1.9)		0 (0)	
Unknown/other		5 (9.8)		2 (12.5)	

Data are expressed as median (interquartile range) or number (percentage). BMI indicates body mass index; BP, blood pressure; CABG, coronary artery bypass grafting; CAD, coronary artery disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; PCI, percutaneous coronary intervention; and TC, total cholesterol.

Table 1, stratified by age at enrollment, with 51 adults and 16 children. The median age at enrollment in the registry was 41.9 (IQR, 28.8–52.9) years for adults and 9.6 (IQR, 5.8–11.8) years for children. The median age at diagnosis was 12.6 (IQR, 4.1–26.5) years in adults and 2.0 (IQR, 2.0–3.5) years in children. Overall, 34 (50.7%) patients were female sex; 40 (59.7%) patients self-identified as White race, 7 (10.4%) patients self-identified as Black race, and 15 (22.4%) patients self-identified as Hispanic ethnicity. However, the racial and ethnic distribution was somewhat different between adults and children, with fewer children self-identified as White race (37.5% versus 66.7%) and more as Hispanic ethnicity (37.5% versus 17.6%) than adults.

Of the adult patients, 14 (27.5%) were reported as former or current smokers, 20 (39.2%) had a diagnosis of hypertension, and 14 (27.5%) patients were obese, with a body mass index ≥30 kg/m^2. No child had any modifiable risk factors.

At enrollment in the CASCADE FH Registry, LDL-C levels (almost all treated) were 235 (147–358) mg/dL in adults and 317 (97–603) mg/dL in children. Overall, 70.1% of the patients with HoFH in the registry had a positive history of ASCVD at enrollment, with differences noted between adults and children. Most adults had significant underlying cardiovascular disease, with 40 (78.4%) having CAD, 13 (25.5%) having aortic valve stenosis, 7 having undergone aortic valve replacement, and 11 (21.6%) having experienced a myocardial infarction. More than a third of the adults had undergone coronary artery bypass grafting (41.2%) or percutaneous coronary intervention (35.3%) at median ages of 36.0 and 28.0 years, respectively; however, among those enrolled as adults, the youngest ages reported for those interventions were 8.0 and 13.0 years, respectively. None of the children had a percutaneous coronary intervention, but 2 had undergone coronary artery bypass grafting at 6 and 14 years. Two children who underwent liver transplant at ages 4 and 8 years were diagnosed with CAD at 2 and 3 years, respectively. At enrollment, 43.8% and 18.8% of the children had evidence of CAD and aortic valve stenosis, respectively, with a median age of diagnosis of CAD being 8.9 years.

Table 2 reports untreated lipid levels and other information aiding the diagnosis of HoFH, stratified by age at enrollment. As expected, untreated levels of LDL-C were extremely elevated in both groups. However, median (IQR) untreated LDL-C levels were significantly lower in adults than children (533 [467–702] versus 776 [704–892] mg/dL; *P*=0.001). Similar results were observed among adults: those diagnosed at an early age had higher untreated LDL-C than those diagnosed later (Figure 2). Furthermore, although most adults and children reported a family history of FH or hypercholesterolemia in at least 1 parent, only 37.5% of children reported a family history of cardiovascular disease, in contrast to the 84.1% of adults. Tendon xanthomas were reported in 56.3% of children (present in 80.4% of adults), and none of the children presented with corneal arcus (identified in 46.8% of adults). Overall, of the 67 patients with HoFH in the CASCADE FH Registry, 76% were initially evaluated on the basis of a family member's FH diagnosis, whereas the remaining 24% were initially evaluated on the basis of physical findings, routine lipid screen, or family or personal history of ASCVD.Illustrative of the clinical severity of HoFH, 6 registry patients have undergone liver transplantation between 4 and 18 years. They are described in detail in Data S3 and Table S2. Because lipid values improved dramatically following transplantation, these patients were excluded from further lipid-related analyses.

Table 2. Untreated Lipid Panel, Family History, and Physical Signs

Variable	Adults (n=51)		Children (n=16)		*P* value
	No.	Values	No.	Values	
Untreated lipid levels					
TC, mg/dL	46	643 (582–800)	16	855 (756–962)	0.005
LDL-C, mg/dL	39	533 (467–702)	16	776 (704–892)	0.001
HDL-C, mg/dL	13	39 (33–43)	8	31 (25–36)	0.08
Triglycerides, mg/dL	12	124 (105–183)	8	164 (130–175)	0.5
Family history, n (%)					
Cardiovascular disease	44	37 (84.1)	16	6 (37.5)	<0.001
FH or hypercholesterolemia	50	49 (98.0)	16	16 (100.0)	1.0
Physical findings, n (%)					
Corneal arcus	47	22 (46.8)	16	0 (0.0)	<0.001
Tendon xanthomas	51	41 (80.4)	16	9 (56.3)	0.1
Genetic diagnosis	29	28 (96.6)	15	15 (100.0)	1

Data are expressed as median (interquartile range) or number (percentage). FH indicates familial hypercholesterolemia; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; and TC, total cholesterol.

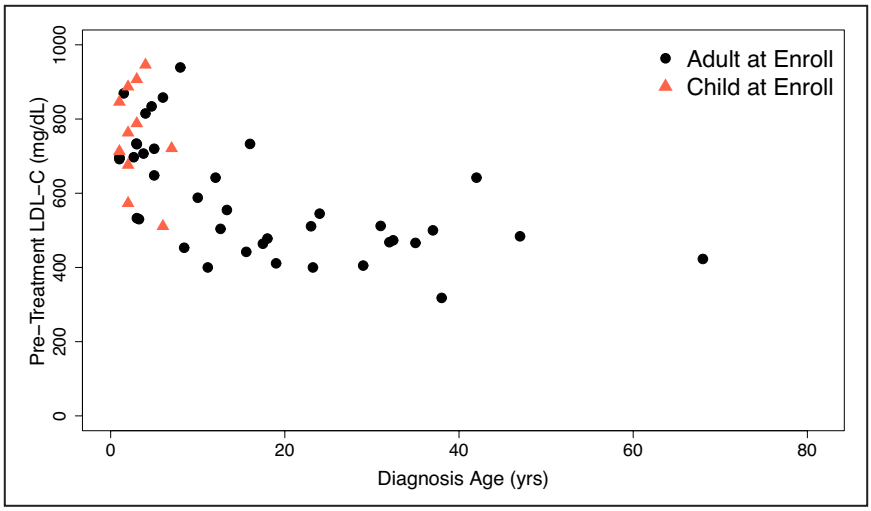

Figure 2. Untreated LDL-C levels and age at diagnosis in patients enrolled in the CASCADE FH Registry as children (red symbols) and as adults (black symbols). CASCADE indicates Cascade Screening for Awareness and Detection; FH, familial hypercholesterolemia; and LDL-C, low-density lipoprotein cholesterol.

LDL-C Levels, LLTs, and LDL-C Goal Attainment

Despite the substantial reduction in LDL-C levels at the time of enrollment (Table 1) compared with untreated levels (Table 2; median reduction of 49.0% [31.8%–64.3%] in adults and 47.5% [18.5%–57.8%] in children), levels remained far above treatment goals in most patients with available data: goal LDL-C levels were achieved at enrollment by 3 (6.3%) adults and 2 (18.2%) children. The number of LLTs at enrollment was significantly different between adults and children (P=0.04). Notably, 40.9% of adults and 69.3% of children were being treated with ≤2 LLTs (Table 3). A total of 38.8% of adults and 30.8% of children were receiving lipoprotein apheresis. Although there was a large variability in individual response to LLTs, lower LDL-C levels were generally associated with a greater number of LLTs (P<0.001; Figure 3A).Follow-up data were available for a subgroup of 39 adults and 8 children with median 3.8 (IQR, 2.5–4.0) years of follow-up. During follow-up, 5 individuals (11%) experienced a total of 7 significant cardiovascular events, including 1 aortic valve replacement (age, 52 years), 4 myocardial infarctions (ages, 46, 53, 58, and 65 years), 1 percutaneous coronary intervention (age, 53 years), and death (age, 51 years).

Table 3. LLTs Used Among Adults and Children With HoFH at the Time of Enrollment

LLT	Adults Enrollment (n=49)	Children Enrollment (n=13)
Statin		
Any statin	41 (83.7)	12 (92.3)
High-intensity statin	36 (73.5)	7 (53.8)
Ezetimibe	32 (65.3)	8 (61.5)
Bile acid sequestrant	9 (18.4)	0 (0.0)
PCSK9 inhibitors	7 (14.3)	0 (0.0)
Lomitapide	12 (24.5)	1 (7.7)
Mipomersen	3 (6.1)	0 (0.0)
Niacin	8 (16.3)	0 (0.0)
Fibrate	1 (2.0)	0 (0.0)
Apheresis	19 (38.8)	4 (30.8)
No. of LLTs		P=0.04
0	4 (8.2)	1 (7.7)
1	9 (18.4)	3 (23.1)
2	7 (14.3)	5 (38.5)
3	12 (24.5)	4 (30.8)
≥4	17 (34.7)	0 (0.0)

Data are given as number (percentage). Patients with liver transplant are excluded. HoFH indicates homozygous familial hypercholesterolemia; LLT, lipid-lowering treatment; and PCSK9, proprotein convertase subtilisin/kexin type 9.

At the most recent follow-up (37 adults and 8 children), adults had median LDL-C levels that were 50.3% and 72.5% lower, and children had median LDL-C levels that were 35.6% and 61.4% lower compared with levels at enrollment and pretreatment, respectively (Figure 3B and Table S3). The substantial decrease in LDL-C following enrollment is attributable to the increased use of LLTs, including the introduction of PCSK9 monoclonal antibody therapy (in adults) and lipoprotein apheresis (in children) (Table 4). At the most recent visit, 82.0% of adults and 87.5% of children were treated with ≥3 LLTs (Table 4). Goal LDL-C levels at the

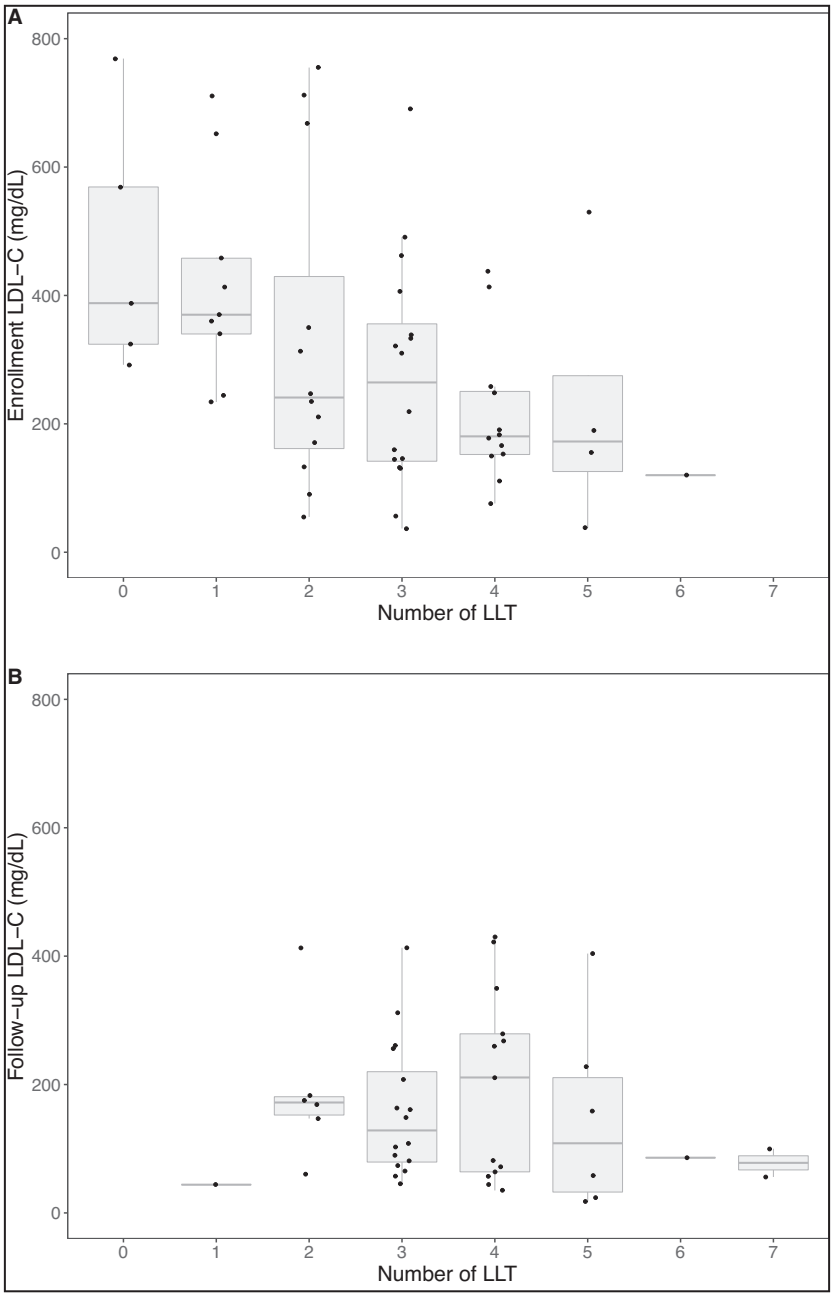

Figure 3. Distribution of treated LDL-C levels by number of LLTs among patients with homozygous familial hypercholesterolemia at time of enrollment in the CASCADE FH Registry (A; n=59) and at the last follow-up visit (B; n=45).
Patients with liver transplants were excluded. CASCADE indicates Cascade Screening for Awareness and Detection; FH, familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; and LLTs, lipid-lowering treatments.

most recent follow-up were achieved by 12 (32.4%) adults and 2 (25.0%) children. Six adults were receiving evinacumab as part of an open-label clinical trial. Their untreated LDL-C levels, as well as those before and during treatment with evinacumab, are shown in Table S4. Modifications to their LLT that included the addition of evinacumab resulted in a mean 50% reduction in LDL-C levels, consistent with the 49% LDL-C lowering reported in placebo-controlled data.[26]

At least 1 lipoprotein(a) measurement was available for 41 of 51 (80%) adults and 8 of 16 (50%) children; however, the relationship of measurement to LLT was not reported. Lipoprotein(a) was noted to be elevated in 14 of 49 (29%) patients, of whom 4 were receiving

Table 4. LLTs Used Among Adults and Children With HoFH at Last Follow-up Visit

LLT	Adults		Children		*P* value	
	Enrollment (n=39)	Follow-up (n=39)	Enrollment (n=8)	Follow-up (n=8)	Enrollment	Follow-up
Statin						
Any	33 (84.6)	35 (89.7)	7 (87.5)	8 (100.0)	1.0	1.0
High intensity	29 (74.4)	28 (71.8)	3 (37.5)	3 (37.5)	0.09	0.1
Ezetimibe	28 (71.8)	32 (82.1)	5 (62.5)	6 (75.0)	0.7	0.6
Bile acid sequestrant	8 (20.5)	8 (20.5)	0 (0.0)	1 (12.5)	0.3	1.0
PCSK9 inhibitors	7 (17.9)	28 (71.8)	0 (0.0)	1 (12.5)	0.3	0.003
Lomitapide	9 (23.1)	9 (23.1)	1 (12.5)	3 (37.5)	0.7	0.4
Mipomersen	3 (7.7)	1 (2.6)	0 (0.0)	0 (0.0)	1.0	1.0
Niacin	8 (20.5)	6 (15.4)	0 (0.0)	0 (0.0)	0.3	0.6
Fibrate	1 (2.6)	1 (2.6)	0 (0.0)	0 (0.0)	1.0	1.0
Evinacumab	0 (0.0)	6 (15.4)	0 (0.0)	0 (0.0)	-	0.6
Apheresis	14 (35.9)	16 (41.0)	2 (25.0)	6 (75.0)	0.7	0.1
No. of LLTs						
0	3 (7.7)	0 (0.0)	1 (12.5)	0 (0.0)	0.04	0.4
1	6 (15.4)	1 (2.6)	1 (12.5)	0 (0.0)		
2	5 (12.8)	6 (15.4)	4 (50.0)	1 (12.5)		
3	9 (23.1)	12 (30.8)	2 (25.0)	5 (62.5)		
≥4	16 (41.0)	20 (51.3)	0 (0.0)	2 (25.0)		

Data are given as number (percentage). Patients with liver transplants are excluded. HoFH indicates homozygous familial hypercholesterolemia; LLT, lipid-lowering treatment; and PCSK9, proprotein convertase subtilisin/kexin type 9.

lipoprotein apheresis. Of the 35 with lipoprotein(a) in the normal range, 20 (57%) were receiving lipoprotein apheresis (see Data S4).

Genetic Variants

In the CASCADE FH Registry, 45 (30 adults and 15 children) of the 67 patients with HoFH were reported to have undergone genetic testing. A genetic diagnosis was confirmed in 43 patients. Specific variant information was reported in the registry for 34 of them who carried either 2 pathogenic or likely pathogenic variants (n=30) or 2 variants (1 of them variant of unknown significance) in the presence of an LDL-C level compatible with the classic clinical diagnosis of HoFH (n=4; pretreatment LDL-C levels ranging between 642 and 939 mg/dL). Among these patients, 30 carried biallelic variants (either identical or not) in the *LDLR* gene; 2 carried variants in *LDLRAP1*; 1 carried a biallelic variant in *APOB*; and 1 carried 1 variant in *LDLR* and 1 in *APOB*. No patients were found to carry gain-of-function *PCSK9* variants. In total, 28 distinct variants were reported, which are summarized in Tables S5 through S7. No pathogenic variants were found in 1 patient, despite having an untreated LDL-C of 504 mg/dL, xanthomas by the age of 12 years, and a family history of hypercholesterolemia and ASCVD in both parents. Positive genetic testing was reported in another patient who had an untreated LDL-C of 511 mg/dL and a family history of FH and ASCVD, but genetic test results were not available to the site investigator.

The broad spectrum of untreated LDL-C levels in patients with genetically confirmed HoFH is shown in Table 5. LDL-C levels ranged from 318 mg/dL in an adult patient homozygous for a well-known *APOB* variant to 1006 mg/dL in a pediatric patient carrying 2 *LDLR* pathogenic variants. The lowest LDL-C level observed in a carrier of biallelic LDLR pathogenic variants was 405 mg/dL. The highest triglyceride level in our genetically diagnosed cohort was 353 mg/dL in a child. The oldest age at diagnosis of these patients was 37 years.

Family Heart Database

As described earlier in Methods, we interrogated the Family Heart Database to determine how many individuals have lipid levels similar to those of genetically confirmed registry patients and, as such, should be evaluated for HoFH.[22]

Considering all inclusion and exclusion criteria (see Data S2), a total of 277 individuals (50% female sex) with severe hypercholesterolemia were identified in the Family Heart Database. Of these, 20% had an *ICD-9 or 10* code consistent with the presence of ASCVD. Concerningly, 40% of the 277 individuals were not on any LLT, and only a small fraction were on combination treatment and/or on PCSK9 inhibitors. Only 13 (5%) were on lomitapide, approved for the treatment

Table 5. Untreated Lipid Levels in Clinical and Genetically Diagnosed Patients With HoFH

	Clinically diagnosed				Genetically diagnosed			
Variable	No.	Adults	No.	Children	No.	Adults	No.	Children
Total cholesterol								
Median (25/75)	19	604 (557–744)	1	792	25	714.0 (593–864)	15	873 (754–963)
Minimum/maximum		471/935		792		358/1023		518/1068
LDL-C								
Median (25/75)	16	471 (420–520)	1	721	22	645.0 (516.5–729)	15	788.0 (695–896)
Minimum/maximum		400/834		721		318/939		405/1006
HDL-C								
Median (25/75)	4	43 (37–44)	0	…	9	37.0 (33–42)	8	31.3 (25–36)
Minimum/maximum		20/45				23/55		22/39
Triglycerides								
Median (25/75)	4	188 (105–302)	0	…	8	123.5 (105–152)	8	164.0 (130–175)
Minimum/maximum		85/420				40/218		71/353

Data are in mg/dL. 25/75 indicates 25th to 75th percentile; HDL-C, high-density lipoprotein cholesterol; HoFH, homozygous familial hypercholesterolemia; and LDL-C, low-density lipoprotein cholesterol.

of HoFH (Table 6). An *ICD-10* code consistent with FH (E78.01), introduced in 2016, was found for only 26% of individuals. Of these individuals, 52 (18.8%) were aged <18 years (Table 6).

DISCUSSION

We report on the clinical characteristics, genetics, and treatment patterns of 67 adults and children with HoFH, enrolled in the CASCADE FH Registry, the largest cohort in the United States to date. Our findings confirm and extend those reported in other cohorts worldwide and highlight the need to refocus on current recommendations for screening, diagnosis, and treatment of HoFH. The results also demonstrate the potential for newer therapies with a mechanism of action that does not depend on the low-density lipoprotein receptor, such as evinacumab, to dramatically lower LDL-C levels. The findings of the Family Heart Database provide further indication that in the "real world" there is a profound need for increased awareness, diagnosis, and aggressive treatment for patients with HoFH in the United States.

One of the most striking results from our study is the significantly higher untreated LDL-C levels found in patients enrolled in the registry as children compared with patients enrolled as adults. Although this is at least in part attributable to a survival bias, it is interesting to note that higher untreated LDL-C levels were also associated with a younger age of diagnosis in the adult group, suggesting that only the most severely affected patients, such as those presenting with physical signs, are diagnosed in childhood, whereas the rest are diagnosed later in life or not at all.

Possible explanations for the missed diagnosis of "less severe" HoFH in children may include the absence of the classic HoFH physical findings; incomplete family history attributable to family dynamics; a lack of clinically evident ASCVD in the parents of children with HoFH because of the parents' young age; and parents being treated for their hypercholesterolemia without a proper diagnosis of FH.[27–29] The American Academy of Pediatrics and the National Heart, Lung, and Blood Institute recommend screening children at the age of 2 years if they come from a family with known FH or premature ASCVD, and universal screening between the ages of 9 and 11 years. Unfortunately, the implementation of these guidelines is suboptimal,[30–33] possibly because of lack of medical professional awareness, conflicting recommendations from the US Preventive Services Task Force,[34] incomplete knowledge of family history on the part of the patients, and resistance to screening children for hyperlipidemia. Delayed diagnosis represents a missed opportunity to initiate lifesaving treatments in a timely manner and to counsel individuals from an early age on the importance of maintaining a healthy lifestyle to reduce the risk of developing hypertension, diabetes, and other modifiable risk factors. Thus, we believe that universal pediatric screening for FH at an early age should become the norm rather than the exception. The proven causal association of LDL-C burden and ASCVD,[35] the higher mortality that has been associated with lack of aggressive LLT in HoFH,[3] and the reductions in cardiovascular disease events that have been reported in a cohort of children with FH followed up for >20 years[36] all support our position that all individuals with HoFH deserve to be identified in early childhood. Notably, 8 genetic metabolic disorders among the 35 congenital diseases in the US national Recommended Uniform Screening

Table 6. Family Heart Database

Variable	Value (n=277)
Female sex, n (%)	139 (50.2)
Age, n (%)	
<18 y	52 (18.8)
19–49 y	180 (65)
50–59 y	18 (6.5)
≥60 y	23 (8.3)
Unknown	4 (1.4)
Maximum LDL-C, median (IQR)	444 (423–509)
Maximum TC, median (IQR)	569 (522–636)
FH positive	71 (25.6)
ASCVD positive	54 (19.5)
FH and ASCVD positive	34 (12.3)
LLT	
No LLT	110 (39.7)
Ezetimibe	3 (1.1)
LI/MI statins	29 (10.5)
HI statins	52 (18.8)
Statins+ezetimibe	32 (11.6)
PCSK9i	38 (13.7)
Lomitapide	13 (4.7)
Apheresis with/without LLT	
Apheresis	2 (0.7)

Data are given as number (percentage) unless otherwise indicated. Number of individuals with lipid profile overlapping with that of genetically confirmed patients with homozygous familial hypercholesterolemia enrolled in the CASCADE FH Registry. ASCVD indicates atherosclerotic cardiovascular disease; CASCADE, Cascade Screening for Awareness and Detection; FH, familial hypercholesterolemia; HI, high intensity; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; LI, low intensity; LLT, lipid-lowering treatment; MI, medium intensity; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitors; and TC, total cholesterol.

Panel for newborns have a prevalence estimate lower than HoFH.[37] On the basis of this consideration and the recent data that suggest the ability to diagnose FH using dried blood from heel sticks in neonates,[38] we believe that pursuing neonatal screening for HoFH is warranted.

Our data strongly suggest that, in the United States, underdiagnosis and undertreatment of HoFH can lead to serious clinical consequences. The frequency of adults and children with ASCVD at enrollment underscores the high-risk status and urgency of early diagnosis. The paucity of patients who reached goal LDL-C highlights the importance of these patients being followed up in specialty clinics. The improvement in LDL-C levels at follow-up likely reflects entry into specialty care, initiation of more aggressive LLT, and the advent of newer LLT. In addition, the feedback and comparative data among the registry sites provided by the Family Heart Foundation, the foundation's guidance on navigating insurance requests for add-on treatment, such as lomitapide, evinacumab, and PCSK9 inhibitors, and evidence-based data on the negative cardiac impact that rejection of PCSK9 inhibitor treatment had on patients[23] all likely played a role in improving LDL-C levels. As topics such as quality of life[39,40] and even pregnancy[41–43] are coming to the forefront of management of HoFH, the Family Heart Foundation and other patient-centric advocacy groups will have invaluable roles in advancing better care for these patients.

Even with additional therapeutic options, at follow-up, many patients remained far above their LDL-C goal. Our results are consistent with various other studies examining phenotypic variability in response to LLTs in patients with HoFH.[2,11,12,14] The availability of new highly effective therapeutic approaches, such as the recently approved evinacumab, provides optimism about the ability to bring these patients to their LDL-C goals.[26] Of the 6 adults who entered an open-label study in which they received evinacumab while enrolled in the CASCADE FH Registry, the observed dramatic 50% LDL-C lowering was consistent with published data[26] and was far greater than the typically modest LDL-C lowering achieved with most LDL-C–lowering medications in patients with HoFH. In addition, the ongoing trials of lomitapide and evinacumab in children as young as 5 years may allow expanded use of more effective treatment starting at an earlier age. In fact, the US Food and Drug Administration has recently approved this expanded use of evinacumab. Likewise, recent data support the use of alirocumab in children, and evolocumab is already approved from the age of 13 years for children with HoFH.[44] We strongly advocate for all patients with HoFH to have access to life-saving LLTs, lipoprotein apheresis, and specialty care, regardless of ability to pay.[3,45]

Recognizing the broad phenotypic spectrum and the wide range of LDL-C levels reported in the literature,[2] we adopted an LDL-C level cutoff of 400 mg/dL for our clinical definition, instead of the historically used cutoff of 500 mg/dL, together with other clinical criteria.[1,13] This approach is supported by the range of untreated LDL-C levels found in patients with genetically confirmed HoFH. We, however, recognize that LDL-C levels below the classic cutoff of 500 mg/dL may overlap with patients with other forms of severe hypercholesterolemia, including heterozygous FH, and that a careful evaluation of other factors beyond LDL-C (family history, presence of xanthomas, and genetics) is needed to confirm the diagnosis.

The 67 patients with HoFH in the CASCADE FH Registry represent only a small fraction of the estimated 1103 to 1330 individuals with HoFH in the United States today.[6–8] And although other centers that are not part of the registry may also be treating patients with HoFH, it is unlikely that more than a small fraction have been diagnosed. To gain insights into the

possible number of unidentified patients with HoFH in the general population, we queried the Family Heart Database and identified 277 individuals with LDL-C or total cholesterol levels similar to those found in the genetically confirmed patients with HoFH in the CASCADE FH Registry who also met our exclusion criteria (see Data S2). The individuals identified all have severe hypercholesterolemia, warranting a thorough medical evaluation. Those found to have FH deserve a comprehensive cardiovascular investigation, risk factor modification, and aggressive lipid lowering. Yet, most of the patients either were on no LLT (40%) or were grossly undertreated. In addition, only 26% had an *ICD-10* diagnosis of FH, which was introduced in 2016, and only 5% were on the HoFH-specific therapy, lomitapide, suggesting that many of these high-risk patients remain undiagnosed. Improved awareness of HoFH, development of strategies for more effective implementation of existing diagnostic and treatment guidelines, and increased referrals to centers specializing in FH may reduce underdiagnosis and undertreatment of patients with HoFH, thereby averting the high burden of ASCVD.

In conclusion, data from the CASCADE FH Registry confirm that HoFH is a severe disorder with a clinical presentation more variable than once believed. Our data also suggest that individuals with higher LDL-C and a more severe clinical phenotype may be more likely to be diagnosed early in life, leaving many individuals with HoFH with the missed opportunity of earlier diagnosis and intervention before development of ASCVD. Even those who are diagnosed often fail to achieve optimal LDL-C levels despite multiple therapies. Access to recently approved LLT for HoFH provides the realistic possibility of reaching LDL-C targets in these difficult-to-treat patients. Thus, the growing availability of novel and more effective LDL-C–lowering treatments for both adults and children managed by experienced specialists is expected to improve LDL-C goal achievement and attenuation of ASCVD. The data from the Family Heart Database highlight the fact that most individuals with lipid profiles consistent with HoFH remain grossly undertreated and that only 26% of these patients carried an FH diagnosis.

Increased awareness of this condition, together with universal pediatric screening for FH, as recommended by the American Academy of Pediatrics and National Heart, Lung, and Blood Institute, as well as the creation of a strong national referral system, is crucial for the timely identification and treatment of all patients with HoFH. In this context, we believe that pursuing neonatal screening should be considered.[37] Such screening is likely to allow identification not only of children with HoFH but also their parents, who may be unaware of their own heterozygous FH diagnosis.

ARTICLE INFORMATION

Received January 29, 2023; accepted April 6, 2023.

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Sources of Funding

Dr Martin is supported by grants/contracts from the American Heart Association (20SFRN35380046, 20SFRN35490003, 878924, and 882415), Patient-Centered Outcomes Research Institute (PCORI) (ME-2019C1-15328), National Institutes of Health (NIH) (R01AG071032 and P01 HL108800), the David and June Trone Family Foundation, Pollin Digital Health Innovation Fund, and Sandra and Larry Small; Dr Knowles is supported by the NIH through grants P30 DK116074 (to the Stanford Diabetes Research Center), R01 DK116750, R01 DK120565, and R01 DK106236; and by a grant from the Bilateral Science Foundation. Dr Linton is supported by NIH grants P01HL116263, HL148137, HL159487, and HL146134.

Disclosures

Dr Cuchel reports institutional support for the conduction of clinical trials from Regeneron Pharmaceuticals and Regenxbio; and consulting fees from Amryt Pharma; Dr Duell has received institutional grants and/or served as a consultant for Akcea, Amryt, Esperion, Ionis, Kaneka, Regeneron, and Regenxbio. Outside of this work, Dr Martin reports consulting fees from Amgen, AstraZeneca, BMS, Dalcor, Esperion, iHealth, Kaneka, Novartis, Novo Nordisk, Sanofi, and 89bio. Dr Martin was listed as a coinventor on a patent application filed by Johns Hopkins University for the Martin/Hopkins method of low-density lipoprotein cholesterol, and that patent application has since been abandoned to enable global use without intellectual property restrictions. Dr Linton has received research support from Amgen, Regeneron, Ionis, Merck, REGENXBIO, Sanofi and Novartis; and has served as a consultant for Esperion, Alexion Pharmaceuticals, and REGENXBIO. Dr McGowan has served as a consultant for Novartis and lectured on pediatric lipid screening for Abbott. Dr Ballantyne reports grant/research support to institution from Akcea, Amgen, Arrowhead, Esperion, Ionis, Merck, Novartis, Novo Nordisk, Regeneron, National Institutes of Health, American Heart Association, and American Diabetes Association; and reports consulting for 89Bio, Alnylam Pharmaceuticals, Althera, Amarin, Amgen, Arrowhead, Astra

Zeneca, Esperion, Genentech, Gilead, Illumina, Matinas BioPharma Inc, Merck, New Amsterdam, Novartis, Novo Nordisk, Pfizer, Regeneron, and Sanofi-Synthelabo. Dr Rader is on Scientific Advisory Boards for Alnylam, Novartis, Pfizer, and Verve and is the Chief Scientific Advisor for the Family Heart Foundation. The remaining authors have no disclosures to report.

Supplemental Material

Data S1–S4
Table S1–S7
Reference [46]

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SUPPLEMENTAL MATERIAL

Appendix

List of CASCADE FH® sites and personnel

SITE	INVESTIGATOR	RESEARCH TEAM
Massachusetts General Hospital	Linda Hemphill, MD	Dianne Brennan, Amy Jewell, Shriie Ganesh
Baylor College of Medicine	Christie Ballantyne, MD	TerryTechmanski, Mini Grace Varughese, MD, Xiaoming Jia, MD, Aliza Hussain, MD, Ali Agha, MD, Matthew Deshotels, MD
The Rogosin Institute	Lisa Hudgins, MD	Nelson Chen, Betty Jane Sloan
The University of Kansas Medical Center	Patrick Moriarty, MD	Julie-Ann Dutton, Mark McClellan
University of Pennsylvania	Marina Cuchel, MD,PhD	Daniel J. Rader, MD, Archna Bajaj, MD, Daniel Soffer, MD, Douglas Jacoby, MD, Paull C. Lee, Benjamin Thieu
Oregon Health & Science University	P. Barton Duell, MD	Jill Rose, Tina Kaufman, Jonathon Purnell, MD, Michael Shapiro, MD
Vanderbilt Medical Center	MacRae Linton, MD	Barbara Carranza Leon, MD, Jennifer Kelley, MD, Beth Meader,ANP, Sherry Bowman, Anca Ifrim
Duke University Medical Center	John Guyton, MD	Shubi Khan
Preventive Cardiology Inc	Seth Baum, MD	Johanna Lore, Ashlee Mattone Murray
UT Southwestern Medical Center	Zahid Ahmad, MD	Chandna Vasandani, PhD
Lancaster General Hospital - Research Institute	Rolf Andersen, MD	Rebekah Nevin, Kate Clipman
NYU Langone Center	James Underberg, MD	Eugenia Gianos, MD, Vanessa Milne Hurta
The Ohio State University Medical Center	John Larry, MD	Matthew Jindra
Children's Hospital Corporation, dba Boston Children's Hospital	Sarah DeFerranti, MD	Jacob Hartz, MD, Heather Harker Ryan
Johns Hopkins University	Seth Martin, MD	Kathleen Byrne, ANP, Emily Brown
University of California, San Francisco	John Kane, MD	Eveline Stock, MD, Mary Malloy, MD, Dorothy Wallder
Thomas Jefferson University	David J. Whellan, MD	Melissa McCarey
Ann and Robert Lurie Children's Hospital of Chicago	Irwin Benuck, MD	Kathleen Van'T Hof
Nemours Cardiac Center	Samuel Gidding, MD (formerly at Nemours Cardiac Center)	Kristi Fitzgerald, Frances Zappalla, DO, J.Alitio Canas, MD, Matthew Benson, MD, Carol Prospero
Hartford Hospital	Paul Thompson, MD	Antonio Fernandez, MD, Karen Knight, William Roman

Data S1. Severe FH

Seven severe FH individuals with TC and LDL-Cs ranging from 467-543 mg/dL and 368-476 mg/dL, respectively, and no known secondary causes of hypercholesterolemia (e.g. untreated hypothyroidism, nephrotic syndrome, and cholestasis) were considered to possibly have HoFH. Their cases were carefully reviewed and ultimately excluded from the analysis. While there was considerable overlap between their lipid levels and those of genetically confirmed HoFH, these patients either did not have physical findings, family history, or personal history to meet the criteria for a diagnosis of HoFH. Their characteristics are summarized in **Table S1**. Two of these subjects underwent genetic testing. One of them was found to be heterozygous for a known *LDLR* pathogenic variant, but no other pathogenic variant was found; this finding combined with the absence of CAD history in the family and hypercholesterolemia only identified later in life in the father precluded the diagnosis of HoFH. The second patient was found to carry 3 *LDLR* variants: a benign variant (p.Ala391Thr), a pathogenic variant (p.Cys75Ser) and a VUS (p.Cys116Ser). With an untreated LDL-C level of 368 mg/dL and a poorly defined family history, the diagnosis of HoFH could not be made.

Data S2. Family Heart Database Query.

The Family Heart Database was queried in order to identify individuals who may have HoFH in the "real world". The following criteria were utilized for our query:

1. Maximum recorded LDL-C levels greater than or equal to 400 mg/dL, OR, if LDL-C results was not available, maximum recorded TC levels greater than or equal to 500 mg/dL. These cutoffs were selected as an approximation of the lowest LDL-C and TC levels observed in a HoFH patient of the CASCADE-FH registry carrying two pathogenic *LDLR* variants.
2. Maximum recorded triglyceride levels lower than or equal 350 mg/dL, the highest triglyceride level observed in observed in a HoFH patient of the CASCADE-FH registry carrying two pathogenic *LDLR* variants.
3. Exclusion of individuals with 1) ICD codes indicating a diagnosis for diabetes, hypothyroidism, hypertriglyceridemia, nephrotic syndrome, primary biliary cirrhosis, or sclerosing cholangitis or 2) no recorded diagnosis code at any timepoint. These criteria were used to exclude patients with known secondary causes of dyslipidemia.
4. Exclusion of individuals older than 37 years, unless:
    a. Records indicated treatment at any time with lomitapide, a LLT approved only for HoFH
    b. Records included a diagnosis of FH (as indicated by the presence of the specific ICD10 diagnosis code, E78.0) in the context of the lipid criteria listed above.

The age cutoff criterium was based on the oldest age at diagnosis of the genetically confirmed HoFH patients and was adopted as an arbitrary filter to exclude those individuals with uncoded

secondary cause of hypercholesterolemia. The rationale for this choice lay on the assumption that by that age most of these patients are either identified and treated or are deceased.

Information on lipid lowering treatment was extracted from the database using paid prescription data, as previously reported.[1] The lipid-lowering treatments for these patients were classified as follows. Every patient was represented only once in the analysis, using the most effective therapy recorded and grouped based on potency of LDL-C therapy: no LLT > ezetimibe >low or moderate intensity statin > high intensity statin > statin + ezetimibe > PCSK9 inhibitors > HoFH medications. Using our prior approach for determining the "statin + ezetimibe" category, we considered medications that include both in one pill (Vytorin, Liptruzet) and any paid prescription for a statin that was within 30 days of a paid prescription for ezetimibe. Finally, we also extracted the presence of lipoprotein apheresis treatment.

Data S3. Liver transplant.

Illustrative of the severity of HoFH, six individuals (5 children and one 18-year-old) in the registry have undergone liver transplantation (one underwent a combined liver/renal transplant), with five of them receiving their transplant before enrollment in the registry. At the time of transplantation, these individuals were aged 4, 6, 8, 15, 17, and 18 years. Because their lipid values improved dramatically with transplantation (see **Table S2**), we have excluded them from the main lipid analysis but discuss their cases below. Some of these cases have been previously described.[46] Overall, the lipid profiles of all 6 patients responded extremely well to liver transplantation. Only one patient experienced a serious adverse event linked to nonadherence with immunosuppression therapy, which resolved.

Patient LT1: This Hispanic female was retrospectively enrolled in the registry at age 19. She was diagnosed at the age of 5 on the basis of lipid levels, xanthomas, known high cholesterol in both parents, and eventually, genetic testing. Her LDL-C was still unacceptably high despite 30% reduction while on statin, ezetimibe. An echocardiogram, stress test and chest magnetic resonance angiography (MRA) at ages 8 and 9 were negative. However, a chest computed tomography angiography (CCTA) at age 11 showed mild calcified stenosis of the LM ostium (with motion artifact) and large amount of calcified plaque in the aortic root. At age 12, she began biweekly lipoprotein apheresis. At age 13, a CCTA followed by coronary angiography showed >70% occlusion of the RCA and nearly complete occlusion of the LM ostia that was treated with percutaneous coronary intervention (PCI with stent). She also had mild aortic stenosis and insufficiency as well as soft plaque in the aortic root. A carotid ultrasound was normal. At age 15, she underwent a liver transplant. Complications included hospitalizations for

acute liver rejection due to noncompliance with immunosuppressants and acute pyelonephritis with septic shock. At age 17, a CT angiogram showed a patent coronary stent and <50% occlusion of the RCA.

Patient LT2: This Hispanic female enrolled in the registry at age 14. She was diagnosed at age 2 after the appearance of xanthomas; the diagnosis was confirmed with genetic testing. She had a family history of both HeFH and premature CAD. Her initial cardiac evaluation at age 3 showed mild aortic insufficiency and diffuse intimal thickening with some mild, nonobstructive plaque in the LAD, LM by intravascular ultrasound (IVUS), not seen on the angiogram (RCA not evaluated because of spasm). This regressed after 1.5 years of statin, ezetimibe and biweekly lipoprotein apheresis. However, 5 years later, there were new aortic plaques adjacent to the right and left coronary ostium as well as in the iliac artery, and her xanthomas were quickly enlarging. At age 8, she underwent a liver transplant. Post-transplant complications included bile duct obstruction and pancreatitis 8 weeks after surgery. CCTA at age 15 showed minimal CAD and unchanged mild aortic insufficiency.

Patient LT3: This Asian male enrolled in the registry at age 23. He was diagnosed at the age of 1 after the sudden death of his brother, who also had HoFH. Genetic testing confirmed the presence of two identical known *LDLR* variants and the diagnosis of HoFH. At age 4, he was treated with statin with minimal response, then portacaval shunt surgery followed by biweekly lipoprotein apheresis. His aortic valve remained disease-free, and his first coronary catheterization at age 10 was normal. At age 14, however, he developed severe nephrotic syndrome and progressive renal failure, poorly controlled hypertension, and severe

hypothyroidism. His LDL-C increased into the 600s despite statin, ezetimibe and lipoprotein apheresis. Coronary angiography showed narrowing of the proximal RCA and multiple plaques in the first diagonal off the LAD that progressed by age 18 to severe ostial/proximal stenosis of the RCA, 60% stenosis of the mid LAD and 60% stenosis of the 1st septal perforator. An echocardiogram showed mild aortic and annular sclerosis and ventricular hypertrophy. He underwent a combined renal/liver transplantation without surgical complications or signs of rejection. Repeat catheterization showed regression of disease in the main coronaries evident at 1.5 years and 4.5 years after transplant. However, at 4.5 years, a new asymptomatic 30% to 49% stenosis of the minor ramus artery was detected. An exercise stress test was negative. His highest pre-treatment and most recent post-transplant lab values were obtained in 2017 (age 26) while on ezetimibe 10 mg per day and simvastatin 20 mg per day can be seen below. He continues on tacrolimus and antihypertensives and levothyroxine and has developed Stage 3 renal failure. At age 30, he is asymptomatic for CVD and is a 4th year medical student.

Patient LT4: This Asian male was retrospectively enrolled in the registry at age 9. He was diagnosed at the age of 2 based high LDL-C, xanthomas, parents with HeFH and the presence of two identical known *LDLR* variants. He did not have aortic valve disease, but CCTA showed mild focal narrowing of the RCA and moderate plaque in the thoracic aorta. He had minimal response to lipid-lowering medications and did not have adequate venous access for lipoprotein apheresis. His parents elected to have liver transplantation. At the age of 4 he underwent a liver transplant. Coronary CTA at age 7 showed no plaque in the RCA and LAD; he also had mild+ aortic insufficiency.

Patient LT5: This Hispanic male enrolled in the registry at age 9. He was diagnosed at age 4 due to elevated LDL-C, xanthomas, family history of HeFH and premature CAD and the presence of two identical known *LDLR* variants. He had little response to statin therapy. At age 5 he was found to have mild aortic stenosis. At age 6, he underwent 2 vessel coronary artery bypass procedure. He was subsequently treated with lipid apheresis which was aborted due to recurrent clotting of his intravenous lines. Ultimately, at age 6 he underwent a liver transplantation. Post-transplant, statin was discontinued. At age 8, an allograph aortic valve conduit was successfully placed without complications.

Patient LT6 This Hispanic female enrolled in the registry at age 17. She was diagnosed clinically at the age of one due to elevated LDL-C, xanthomas, and a family history of both HeFH and premature CAD. She had a minimal response to atorvastatin, ezetimibe and bile acid sequestrants. She began biweekly lipoprotein apheresis at age 5. Her first catheterization at age 6 showed mild plaque in the proximal LM artery and aortic calcification adjacent to the RCA ostium. IVUS showed additional plaque in the LCX. An echocardiogram showed mild Aortic. Insufficiency (AI). This progressed to mild Aortic Stenosis (AS) with continued AI one year later. A repeat catheterization at age 8 showed normal coronaries (narrowed RCA ostium felt due to vasospasm), but IVUS showed mild plaque in the LAD and LCX. A CCTA at age 10 done because of intermittent chest pain showed mild plaque in the proximal LAD and RCA, possible obstructive plaque in the RCA ostium and diffuse aortic plaque at the sinuses of Valsalva, ascending and thoracic aorta. An echo showed progression to moderate calcified AS and AI with mild LVH. A carotid ultrasound at age 13 showed moderate plaque in both internal and common carotid arteries. At age 14, CCTAs showed normal coronaries but with motion artifact. At age

17, the echocardiogram showed severe AS and moderate AI, and she developed SOB on exertion. Cath showed 50% stenosis of the proximal RCA. She underwent a Ross procedure to replace her aortic valve with her pulmonary artery valve. She was unable to adhere to the very low-fat diet required to tolerate lomitapide. One year later at age 18, she underwent liver transplantation complicated only by transient T wave inversions shortly after surgery. However, 1 year after surgery, she was noncompliant with tacrolimus and had an episode of acute liver rejection. During steroid immunosuppression, she developed insulin-requiring diabetes that has persisted after the discontinuation of steroids. She is a college student.

Data S4. Lipoprotein(a) levels.

At least one lipoprotein (a) result was available for 49/67 (73%) of HoFH patients in the CASCADE FH Registry including 41 (80%) of adults and 8 (50%) of children, however the relationship to LLT was not reported. Of the 49 patients with an available Lp(a), 36 (73%) and 9 (18%) had a history of ASCVD and aortic stenosis respectively at the time of registry enrollment. During prospective follow-up, 5 individuals experienced 7 ASCVD events with one being fatal.

An elevated Lp(a), defined as > 50 mg/dL or >125 nmol/L, was noted in 14/49 (29%) of patients. Of those with an elevated Lp(a), all (100%) had ASCVD at the time of registry enrollment and 1(7%) had known aortic stenosis, but none of them experienced an ASCVD event during the prospective follow-up period. Four were receiving lipoprotein apheresis.

Of the 35 with an Lp(a) in the normal range, 20 (57%) were receiving lipoprotein apheresis. Given that lipoprotein apheresis is known to acutely lower Lp(a) and that time of testing in relation to apheresis was not collected in the registry, it is possible that we are underestimating the percentage of individuals with elevated Lp(a).

Table S1. Untreated TC and LDL-C and other characteristics of Severe FH patients.

	TC	LDL-C	FamFH+	FamCVD+	Tendon xanthomas	genetics	
SevFH1	467	368			N	Y	p.A391T (B) p.C116S (VUS) p.C75S (LP/P)
SevFH2	499	409	S	N	Y	N	
SevFH3	543	476	UNK	UNK	Y	N	
SevFH4	503	402	M, S	M	UNK	N	
SevFH5	500	412	M, S	M, S, MGM	Y	N	
SevFH6	512	419	M	M	N	UNK	
SevFH7	529	420	F	N	N	Y	c.313+2T>C

SevFH, severe familial hypercholesterolemia; TC, total cholesterol; LDL-C, low density lipoprotein cholesterol; FamFH+, family history positive for familial hypercholesterolemia; Fam CVD+, family history positive for cardiovascular disease; F, Father; M, mother; MGM, maternal grandmother; N, negative; S, sibling; UNK, Unknown; B, benign; VUS, variant of unknown significance; LP/P, likely pathogenic/pathogenic

Table S2. Laboratory results of patients that underwent liver transplant.

	Patient 1		Patient 2		Patient 3		Patient 4		Patient 5		Patient 6	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Lipid panel (mg/dl)												
TC	758	147	674	171	864	195	967	134	1019	160	866	110
LDL-C	720	87	573	110	697	132	887	82	946	67	692	53
TG		30		50		65		50	171	53		155
HDL-C		54		50		50		42	38	82		26
Lp(a)		19				37		18			62	14
Transaminases (IU/L)												
AST		23		8		22		38		37		19
ALT		28		16		28		21		47		26

Pre, before liver transplant; Post, after liver transplant; TC, total cholesterol; LDL-C, low density lipoprotein cholesterol; TG, triglycerides; HDL-C, high density lipoprotein cholesterol; Lp(a), lipoprotein (a); AST, aspartate aminotransferase; ALT, alanine aminotransferase

Table S3. Lipid Levels Among Adults and Children with Homozygous FH: Data (mg/dl) are expressed as median (IQR) and min/max range. Patients that underwent liver transplant and 2 patients with evidence of non-compliance are not included.

	Adult				Children			
	n	**Enrollment**	**Follow-up**	**% Reduction**	**n**	**Enrollment**	**Follow-up**	**% Reduction**
TC	36	274 (215/414) 75/772	186 (126/256) 63/521	38 (-8/59) -92/80	7	464 (397/772) 281/845	326 (147/400) 103/480	32 (-0.4/74) -16/88
LDL-C	36	187 (146/345) 38/711	127 (59/213) 18/422	50 (-11/71) -105/93	7	406 (342/712) 211/769	256 (112/337) 65/430	36 (3/77) -21/92
HDL-C	33	37 (29/52) 17/74	44 (32/56) 17/75	-4.5 (-36/8) -88/53	7	39 (27/47) 23/55	37 (23/41) 20/57	19 (-32/35) -70/51
TG	34	98 (60/157) 34/315	74 (55/129) 23/291	19 (-25/34) -228/91	7	96 (73/143) 27.0/204.0	65 (44/109) 19/176	-19 (-28/45) -141/91
	n	**Pre-Treatment**	**Follow-up**	**% Reduction**	**n**	**Pre-Treatment**	**Follow-up**	**% Reduction**
TC	31	604 (579/800) 358/983	192 (127/249) 63/521	70 (61/78) 29/92	7	792 (754/855) 581/961	326 (147/400) 103/480	56 (47/82) 38/88
LDL-C	27	511 (459/673) 318/939	147 (71/196) 18.0/422	73 (62/86) 36/96	7	721 (695/776) 511/907	256 (112/337) 65/430	61 (51/86) 42/91
HDL-C	9	34 (32/43) 20/55	38 (32/58) 17/62	-13 (-43/24) -190/47	2	35 (32/37) 30/39	32 (29/36) 25/39	3 (-14/20) -30/20
TG	9	116 (85/124) 50/420	75 (66/78) 46/191	33 (17/37) -125/84	2	212 (142/283) 71/353	62 (40/83) 19/104	25 (-11/60) -46/95

TC, total cholesterol; LDL-C, low density lipoprotein cholesterol; TG, triglycerides; HDL-C, high density lipoprotein cholesterol.

Table S4. LDL-C levels and LLT of HoFH patient treated with Evinacumab at last follow-up visit. LDL-C levels are reported in mg/dL.

	Untreated	Before evinacumab		During evinacumab (15mg/kg/mo)		
Pt #	LDL-C	LDL-C	LLT	LDL-C	% Change	LLT
E-1	707	304	R 40mg/day, EZ 10mg/day, L 5 mg /2x/wk A q week	211	31%	R 40mg/day, EZ 10mg/day, A q week
E-2	530	260	Ator 80mg/day, EZ 10mg/day, Evol 420mg/mo, A q 2 week	82	68%	Ator 80mg/day, EZ 10mg/day, A q 2 week,
E-3	869	839	R 40mg/day, EZ 10mg/day, A q 2 week	404	52%	R 40mg/day, EZ 10mg/day, Evol 420mg/mo, PE q mo
E-4	642	102	Ator 5 mg qod, EZ 10mg/day, Evol 140 mg q2wk, A q 2 wk	58	43%	Ator 5 mg qod, EZ 10mg/day, Evol 140 mg q2wk, A q 2 wk,
E-5	400	195	R 40mg/day, EZ 10mg/day, A q 2 week, Evol 140 mg q2wk, L 5 mg/day, Fen 135 mg/day	100	49%	R 40mg/day, EZ 10mg/day, A q 2 week, Evol 140 mg q2 wk, L 5 mg/day, Fen 135 mg/day
E-6	n/a	189	Ator 80mg/day, EZ 10mg/day, Evol 140mg/2wk, A q 2 week, N 2000 mg/day	86	54%	Ator 80mg/day, EZ 10mg/day, Evol 140mg/2wk, A q 2 week, N 2000 mg/day
Median (IQR)	642 (530/707)	228 (191/293)		93 (83/183)	51% (45,54%)	

LDL-C, low density lipoprotein cholesterol; LLT, lipid lowering treatment; IQR, interquartile range; R, rosuvastatin; EZ, ezetimibe; L,lomitapide; A, apheresis; Ator, atorvastatin; Evol, evolocumab; PE, plasma exchange; Fen, fenofibrate; N, niacin. LDL-C levels are reported as untreated, at the last visit before starting evinacumab and at last follow-up while treated with evinacumab. For patients undergoing apheresis, LDL-C levels reported are pre-apheresis.

Table S5. Molecular Characterization of Variants Found in True Homozygotes

Nucleotide change	Protein Effect	Variant Classification*	Functionality	N
LDLR				
c.304C>T	p.Gln102Ter	P	Null	1
c.590G>A	p.Cys197Tyr	LP	Predicted Defective	3
c.2043C>A	p.Cys681Ter	P	Null	3
c.249delTinsGG	p.Ile83fs	P	Predicted Null	2
c.1055G>A	p.Cys352Tyr	LP	Predicted Defective	1
c.191-512_940+631del	-	P	Predicted Null	1
c.530C>T	p.Ser177Leu	P	Null	2
c.1090T>C	p.Cys364Arg	LP	Predicted Defective	1
c.654_656del	p.Gly219del	P	Null	1
LDLRAP1				
Homozygous deletion of exons 5-9 of LDLRAP1 gene	-	P	Predicted Null	1
c.460-1G>A (intron 4)	-	P	Predicted Null	1
APOB				
c.10580G>A	p.(Arg3527Gln)	P	Defective	1

* Variant Classification for *LDLR* according to ClinGen FH VCEP Guidelines (DOI 10.1016/j.gim.2021.09.012), for *APOB* and *LDLRAP1* according to the ClinGen general guidelines (DOI 10.1038/gim.2015.30). LP, likely pathogenic; P, pathogenic.

Table S6. Molecular Characterization of – Variants found in compound heterozygotes.

Nucleotide change 1	Protein Effect	Variant Class*	Functionality	Nucleotide change 2	Protein Effect	Variant Class*	Functionality	N
LDLR								
c.590G>A	p.Cys197Tyr	LP	Pred Def	c.1016T>C	p.Leu339Pro	VUS	NA	1
c.1A>T	p.Met1Leu	P	Null	c.418G>A	p.Glu140Lys	P	Def	1
c.261_262delinsAG	p.Trp87Ter	P	Pred Null	c.1056_1060+3del	-	LP	Pred Def/Null	1
c.302A>G	p.Glu101Gly	VUS	Pred Def	c.1216C>A	p.Arg406Arg	LP	Def/Null	1
c.1382del	p.Gly461fs	P	Pred Null	c.1238C>T	p.Thr413Met	LP	Pred Def	1
c.1878del	p.Ala627fs	P	Pred Null	c.314-?_940+?del	-	P	Def/Null	1
c.1118_1121dup	p.Tyr375fs	P	Null	c.2113G>C	p.Ala705Pro	VUS	NA	1
c.501C>A	p.Cys167Ter	P	Pred Null	c. 798T>A	p.Asp266Glu	P	Def	1
c.680_681del	p.Asp227fs	P	Pred Null	c.2389+1G>T	p.Ala771Ile796del	P	Def/Null	1
c.269A>C	p.Asp90Ala	LP	Pred Def	c.2390-?_2583+?del	-	P	Pred Null	1
c.681C>G	p.Asp227Glu	P	Def	c.1775G>A	p.Gly592Glu	P	Def	1

c.301G>A	p.Glu101Lys	P	Def	c.1898G>A	p.Arg633His	LP	Pred Def	1
c.1775G>A	p.Gly592Glu	P	Def	c.519C>G	p.Cys173Trp	LP	Pred Def	1
c.682G>T	p.Glu228Ter	P	Null	c.191-?_1845+?dup	-	P	Pred Null	1
c.337G>T	p.Glu113Ter	P	Pred Null	c.1246C>T	p.Arg416Trp	P	Def	1

* Variant Classification for *LDLR* according to ClinGen FH VCEP Guidelines (DOI 10.1016/j.gim.2021.09.012). Def, defective; Pred, predicted; LP, likely pathogenic; P, pathogenic; VUS, variant of unknown significance.

Table S7. Molecular Characterization of – variants found in double heterozygotes.

LDLR	Protein Effect	Variant Class	Functionality	APOB	Protein Effect	Variant Class	Functionality	N
c.314-?_940+?del	-	P	Def/Null	c.7976C>T	p.Pro2659Leu	VUS	NA	1

* Variant Classification for *LDLR* according to ClinGen FH VCEP Guidelines (DOI 10.1016/j.gim.2021.09.012), for *APOB* according to the ClinGen general guidelines (DOI 10.1038/gim.2015.30). P, pathogenic; VUS, variant of unknown significance