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Longitudinal low density lipoprotein cholesterol goal achievement and cardiovascular outcomes among adult patients with familial hypercholesterolemia: The CASCADE FH registry

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HIGHLIGHTS

- Adults with familial hypercholesterolemia in lipid specialty clinics achieve further LDL-C lowering in specialty care but less than half get to LDL-c < 100 mg/dl.
- Atherosclerotic event rates remain high, including among those with prior atherosclerotic vascular disease and average LDL-c < 100 mg/dl.

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ABSTRACT

Background and aims: There are limited data from the US on outcomes of patients in specialty care for familial hypercholesterolemia (FH).

Methods: CASCADE FH Registry data were analyzed to assess longitudinal changes in medication usage, in low density lipoprotein cholesterol (LDL-C) levels, and the rate of major adverse cardiovascular events (MACE (myocardial infarction, coronary revascularization, stroke or transient ischemic attack) in adults with FH followed in US specialty clinics.

Results: The cohort consisted of 1900 individuals (61% women, 87% Caucasian), with mean age of 56 ± 15 years, 37% prevalence of ASCVD at enrollment, mean pretreatment LDL-C 249 ± 68 mg/dl, mean enrollment

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LDL-C 145 mg/dl and 93% taking lipid lowering therapy. Over follow up of 20 ± 11 months, lipid lowering therapy use increased (mean decrease in LDL-C of 32 mg/dl ($p < 0.001$)). Only 48% of participants achieved LDL-C < 100 mg/dl and 22% achieved LDL-C < 70 mg/dl; ASCVD at enrollment was associated with greater likelihood of goal achievement. MACE event rates were almost 6 times higher among patients with prior ASCVD compared to those without (4.6 *vs* 0.8/100 patient years). Also associated with incident MACE were markers of FH severity and conventional ASCVD risk factors.

Conclusions: With care in FH specialized clinics, LDL-C decreased, but LDL-C persisted > 100 mg/dl in 52% of patients. High ASCVD event rates suggest that adults with FH warrant designation as having an ASCVD risk equivalent. Earlier and more aggressive therapy of FH is needed to prevent ASCVD events.

1. Introduction

Familial hypercholesterolemia (FH) is an autosomal dominant genetic condition that is associated with severe hypercholesterolemia and up to 10–20 fold increased risk of cardiovascular events [1]. FH has an estimated prevalence of approximately 1:220 in the United States and is most often caused by mutations in genes for low density lipoprotein receptor (*LDLR*), and less frequently *APOB* and *PCSK9* [1]. As a consequence of lifelong exposure to severely elevated LDL-cholesterol (LDL-C), untreated patients with heterozygous FH may experience acute coronary syndromes as early as the third decade of life, with a mean age of myocardial infarction of about 50 years in men and 60–65 years in women [2,3]. Unfortunately, it is estimated that more that 90% of patients with FH in the United States and many other countries are unaware of having the condition [4]. Moreover, among patients known to have FH, the diagnosis is often established fairly late in life, frequently after the occurrence of an initial cardiac event [5,6]. Even after establishing a diagnosis of FH, a large proportion of patients with FH continue to have uncontrolled hypercholesterolemia, often necessitating a multi-drug LDL-C lowering regimen in combination with statin therapy [7].

The FH Foundation is a patient-led nonprofit organization that is devoted to increasing awareness of FH, facilitating more widespread and earlier diagnosis of FH, and promoting access to medical treatment. The FH Foundation created the CAscade SCreening for Awareness and DEtection (CASCADE) FH Registry in 2013, which is a national multi-institution initiative to increase FH awareness, characterize trends in treatment, monitor clinical and patient-reported outcomes over time and is the largest cohort of individuals with FH in the United States [8,9]. The results of previous cross-sectional analyses of data from the CASCADE FH Registry demonstrated that the mean age of diagnosis of FH was 47 years, with a median on-treatment LDL-C concentration of 141 mg/dl. Moreover, 36% of patients already had ASCVD with a median age of first cardiac event of 47 years in men and 55 years in women [5]. Despite awareness that FH patients are at very high risk of ASCVD, these data demonstrated that the important goals of early diagnosis and optimal LDL-C lowering have not yet been achieved.

We hypothesized that LDL-C goal achievement among patients in the registry would improve over time in response to increasing use of LDL-C lowering medications. In addition, new LDL-C lowering treatment options have become available during the last 5 years, most notably alirocumab and evolocumab, which are monoclonal antibodies that block the action of proprotein convertase subtilisin kexin type 9 (PCSK9) and were approved by the FDA in 2015 [7]. The primary purpose of the current study was to assess longitudinal trends in LDL-C treatment and goal achievement among adult patients with heterozygous FH in the CASCADE FH registry [5]. The secondary purpose was to assess prospective occurrence of ASCVD events and its correlates within this high-risk population receiving contemporary care at specialized lipid clinics.

2. Patients and methods

2.1. Study design

2.1.1. Cohort description

The CASCADE FH study population for this analysis consisted of a total of 4956 patients enrolled as of August 3, 2018 who were recruited from 35 lipid specialty clinics from across the United States [8]. Each site's activities were approved by the local Institutional Review Board and all participants provided signed informed consent. All enrolled patients had a diagnosis of FH that was established on the basis of clinical (including but not limited to Simon Broome, Dutch Lipid Clinic Network, MEDPED) or genetic diagnostic criteria determined by the local site physician [7,8]. Exclusion criteria included any cause of secondary hypercholesterolemia, such as untreated hypothyroidism, nephrotic syndrome, cholestatic liver disease, and other conditions as previously described [7]. After excluding patients younger than 18 years (n = 567), those with a diagnosis of homozygous FH (n = 77), those for whom follow-up data were unavailable (n = 2367), those who were taking lomitapide or mipomersen (drugs approved only for homozygous FH) (n = 32) and those with missing ASCVD status at baseline (n = 13), the study population for this analysis consisted of 1900 adult patients who had at least one follow-up visit ≥ 6 months from enrollment with data available for analysis. The Registry has grown over the years so that at the close of 2018, there were 5479 patients enrolled at 40 sites (5 pediatric). Of these, most of the 2367 with unavailable data (n = 1895) were enrolled retrospectively through chart review and thus have only one visit. The remainder do not have a follow up data. This study focusses on only on adults with prospective data.

Clinical and laboratory data were abstracted from medical records by trained research staff at each medical center and entered into a centralized electronic data base. LDL-C data for LDL apheresis patients were time-averaged. Demographic data, medical history data, laboratory values, medication use, and outcomes were collected per registry protocol. ASCVD and incident MACE were defined as myocardial infarction, coronary revascularization, stroke, or TIA. Patient follow-up visits were scheduled in accordance with the patient's routine medical care and were not prespecified by the protocol. Follow-up data were collected by local site staff reviewing existing medical records at 6-month intervals.

The multiplication factors for converting units of mg/dl to mmol/L for cholesterol (total cholesterol, LDL-C, and HDL-C) and triglycerides are 38.67 and 88.57, respectively, The multiplication factor for converting lipoprotein(a) units of mg/dl to nmol/L is approximately 2.4, but the range is 1.85–2.85 for large and small apo(a) size, respectively.

2.1.2. Statistical analysis

Categorical variables were quantified as frequencies and percentages and statistically analyzed by Chi-square testing. Continuous variables were quantified as means and standard deviations, or median and interquartile range for nonparametric data, and statistically analyzed by Student's t-tests or Wilcoxon rank sum tests. The enrollment (baseline) LDL-C concentration was defined as the measurement that was available at the time of enrollment in the CASCADE FH Registry, regardless of treatment status. The peak untreated LDL-C concentration was the highest value obtained prior to initiation of treatment with lifestyle and pharmacological intervention. In some cases, results obtained during a drug holiday were reported as the untreated measurement. Given the large number of comparisons, p values < 0.005 were

considered significant and values between 0.05 and 0.005 were considered trends.

LDL-C goal achievement was defined on the basis of LDL-C < 100 mg/dl and < 70 mg/dl. Additionally, comparisons were made between participants who achieved a greater than 50% reduction in LDL-C versus less than 50% reduction compared to the enrollment concentration. LDL-C goal achievement was also analyzed in relation to follow-up time and use of high intensity statins, ezetimibe, niacin, bile acid sequestrants, PCSK9 inhibitors, number of LDL-C-lowering medications, and LDL apheresis, all at enrollment and follow-up. Statin intolerance and hypothyroidism at enrollment and follow-up were also included as covariates.

3. Results

3.1. Patient characteristics

Demographic data for the 1900 patients in this analysis are shown in Table 1, stratified by ASCVD status at enrollment. The mean age at enrollment was 56.1 ± 14.8 years with a mean follow-up duration of 20.2 ± 10.8 months. The cohort was 87.3% Caucasian and 60.8% female. The mean age at diagnosis of FH was 50.0 ± 18.0 and the mean pre-treatment LDL-C concentration was 248.9 ± 68.3 mg/dl. The mean LDL-C concentration at enrollment was 145.3 ± 67.5 mg/dl, with 28.4% having an LDL-C concentration < 100 mg/dl and 10.6% with LDL-C concentration < 70 mg/dl. ASCVD was present in 37.1% of subjects at enrollment. Those with prior ASCVD were more likely to be older, male, or a past or current smoker; they also had higher prevalence of hypertension, diabetes, aortic stenosis, peripheral artery disease, and physical findings of FH (all $p < 0.0001$).

With regard to lipids at enrollment, there was a trend for higher pre-treatment LDL-C levels in subjects with ASCVD. However, those with ASCVD enrolled with lower LDL- C concentrations, reflecting a higher intensity of LDL-C lowering regimens. The rates of LDL-C goal achievement at enrollment were low, but the rates were higher among patients with ASCVD compared to those without ASCVD ($p < 0.0001$ for each threshold). Prior ASCVD was associated with lower HDL-C but not with lipoprotein(a) levels. However, lipoprotein(a) levels were unavailable for nearly two-thirds of patients.

3.2. Longitudinal LDL-C goal achievement

Longitudinal changes in LDL-C were analyzed in 1621 patients who had baseline and follow-up LDL-C values suitable for analysis. Absolute LDL-C values decreased by a mean of 31.7 ± 67.5 mg/dl from 144.0 ± 66 to 112.3 ± 58.7 mg/dl (−11.8%, ($p < 0.001$)) (Fig. 1A), but there was substantial inter-individual variation in the change in LDL-C (Fig. 1B). Importantly, the proportion of patients with LDL-C > 200 mg/dl decreased by about 60% (Fig. 1A).

During follow-up, 779 (48.1%) patients achieved an LDL-C < 100 mg/dl and 352 (21.7%) achieved an LDL-C < 70 mg/dl, comprising increases of 20% and 11% in the proportion of patients achieving these goals compared to enrollment, respectively. Patients with ASCVD at enrollment were more likely to achieve LDL-C < 100 mg/dl and < 70 mg/dl compared to patients without ASCVD at enrollment (219/588, 37.2% *vs* 246/1033, 23.8%, $p < 0.0001$ and

Table 1
Baseline characteristics of the cohort stratified by the presence or absence of known ASCVD at the time of enrollment.

Characteristic	Overall N = 1900	No ASCVD N = 1196	ASCVD N = 704	p[a]
Demographics				
Age at enrollment, yrs (s.d.)	56.1 (14.8)	52.9 (15.8)	61.5 (10.9)	< 0.0001
Follow-up time, months (s.d.)	20.2 (10.8)	19.9 (10.8)	20.8 (10.7)	0.06
Sex				< 0.0001
Male, nr (%)	744 (39.2)	394 (32.9)	350 (49.7)	
Female, n (%)	1156 (60.8)	802 (67.1)	354 (50.3)	
Race/ethnicity				0.02
Hispanic, n (%)	45 (2.4)	31 (2.6)	14 (2.0)	
White, n (%)	1659 (87.3)	1022 (85.5)	637 (90.5%)	
Black, n (%)	88 (4.6)	62 (5.2)	26 (3.7)	
Asian, n (%)	43 (2.3)	30 (2.5)	13 (1.8)	
Other, n (%)	65 (3.4)	51 (4.3)	14 (2.0)	
Past medical history, number (%)				
Smoking (past or present)	682 (36.0)	358 (30.0)	324 (46.2)	< 0.0001
Peripheral artery disease, number (%)	63 (5.9)	19 (2.9)	44 (10.9)	< 0.0001
Hypertension, n (%)	887 (46.8)	432 (36.2)	455 (64.8)	< 0.0001
Diabetes, n (%)	269 (14.2)	120 (10.1)	149 (21.3)	< 0.0001
Aortic valve stenosis, number (%)	59 (3.1)	19 (1.6)	40 (5.8)	< 0.0001
Highest pre-treatment LDL-C				
LDL-C, mg/dL (s.d.)	248.9 (68.3)	245.3 (62.1)	255.3 (78.0)	0.014
Enrollment lipids				
LDL-C, mg/dL (s.d.)	145.3 (67.5)	151.7 (65.2)	134.4 (70.0)	< 0.0001
LDL-C < 70 mg/dL, n(%) (%)	197 (10.6)	79 (6.7)	118 (17.2)	< 0.0001
LDL-C < 100 mg/dL, n(%) (%)	530 (28.4)	281 (23.8)	249 (36.2)	< 0.0001
HDL-C, mg/dL (s.d.)	54.2 (17.4)	56.2 (17.8)	51.0 (16.2)	< 0.0001
Triglycerides, mg/dL (s.d.)	145.0 (93.7)	143.5 (91.5)	147.6 (97.3)	0.37
Total cholesterol, mg/dL (s.d.)	225.2 (74.5)	233.4 (71.0)	211.4 (78.2)	< 0.0001
Lipoprotein (a), mg/dL, median (IQR) (n = 732)	28.0 (10.0, 83.5)	28.0 (9.0, 83.0)	29.0 (10.0, 84.0)	0.50
Physical findings				
BMI, kg/m^2 (s.d.)	29.5 (10.0)	29.2 (11.9)	29.9 (5.8)	0.068
Systolic BP, mmHg (s.d.)	127.8 (17.0)	127.2 (16.7)	128.7 (17.6)	0.06
Diastolic BP, mmHg (s.d.)	76 (68, 82)	76 (69, 82)	75 (68, 82)	0.06
Corneal arcus, n (%)	331 (23.7)	193 (21.0)	138 (29.0)	0.0008
Tendon xanthomas, n (%)	404 (27.6)	223 (23.3)	181 (35.7)	< 0.0001
Xanthelasmas, n (%)	95 (6.9)	60 (6.6)	35 (7.4)	0.61

[a] p-values for continuous variables were derived from comparison of means by t-testing. p value for lipoprotein(a) is from Wilcoxon rank-sum testing comparing medians. Categorical and proportional data were compared by Chi-square testing.

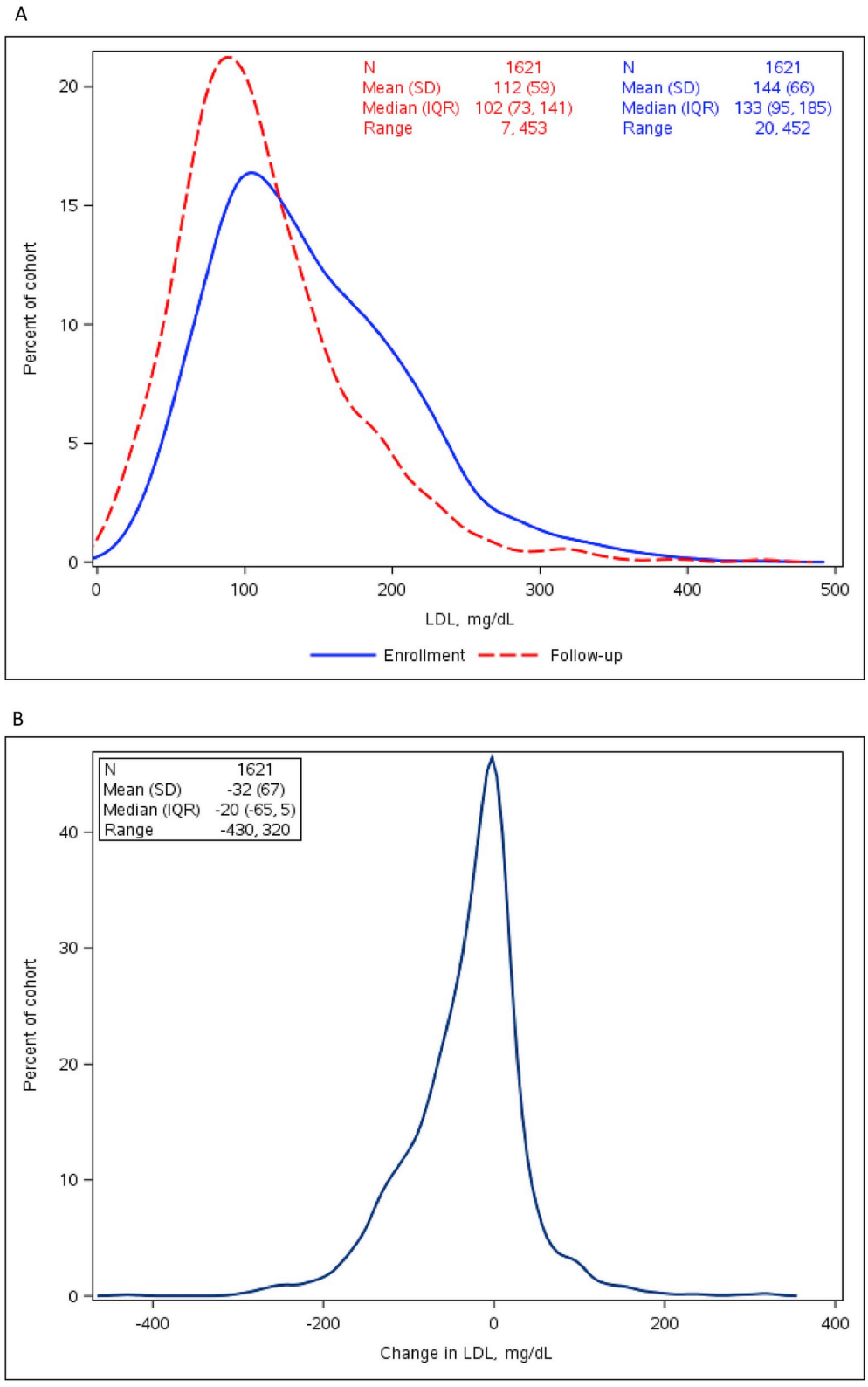

Fig. 1. (A) LDL-C distribution at enrollment (solid blue line) and follow-up (red dashed line) among patients in the FH registry (n = 1621 with baseline and follow-up data). The red dashed line is shifted to the right showing LDL-C reduction over time in the cohort. (B) Distribution of change in LDL-C concentration between enrollment and follow-up, demonstrating a wide standard deviation of LDL-C change. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

108/588, 18.4% *vs* 67/1033, 6.5%, $p < 0.0001$, respectively). High intensity statin use, number of lipid-lowering medications used at enrollment, PCSK9 inhibitor use, and treatment with LDL apheresis were associated with higher likelihood of LDL-C goal achievement. Treatment with ezetimibe, niacin and bile acid sequestrants at enrollment were associated with increased LDL-C goal achievement at enrollment, but not at follow-up.

A total of 318 patients (19.6%) achieved ≥ 50% reduction in LDL-C

after enrollment. Significant characteristics ($p < 0.005$) of patients who achieved ≥ 50% LDL-C lowering were the presence of ASCVD at enrollment, absence of lipid lowering therapy at enrollment (corresponding to a higher entry LDL-C concentration), and/or aortic stenosis, with a trend for smoking. Women were less likely to achieve LDL-C goals compared to men. Patients who achieved ≥50% reduction in LDL-C took more lipid lowering therapies during follow-up compared to those with < 50% reduction, but there were no specific medications or therapies that accounted for this LDL-C outcome.

3.3. Lipid-lowering medication use

At enrollment 92.8% of patients were taking lipid-lowering therapy, but only 73.7% were taking a statin. The most common reasons for not taking a statin were reported as intolerance/allergy (77%) or patient preference (10%). Details about lipid-lowering drug use and goal achievement at enrollment and follow-up are shown in Table 2 (the cohort presented is limited to those taking statins). Those taking higher intensity statins had lower achieved LDL-c levels at enrollment compared to those not taking a stain or on lower intensity statins, and this trend persisted at the end of study after additional medications were added. A histogram comparing the number of lipid lowering medications at enrollment and follow-up is presented in Fig. 2. There was a shift toward higher numbers of total lipid lowering medication used, particularly among patients who had ASCVD at enrollment. Ezetimibe was the most commonly added non-statin adjunctive medication, with use increasing from 41.2% to 46.9% ($p = 0.0005$).

PCSK9 inhibitors were being used by 209 patients at enrollment, all of whom entered the registry after FDA approval of this drug class in the summer of 2015. During follow-up, the number of subjects using a PCSK9 inhibitor increased to 563 (29.6%) at study end. Comparing those who added PCSK9 inhibitors after enrollment to those who did not, the magnitude of absolute LDL-C reduction during follow-up was 2.8 fold greater (68.8 ± 73.8 *vs* 24.9 ± 73.8 mg/dl, $p < 0.0001$).

3.4. Incident ASCVD events

A total of 107 incident ASCVD events occurred in 69 (3.6%) out of 1900 patients during follow-up, which corresponds to an annualized event rate of 2.2/100 patient-years (Table 3). Second events occurred in 24 out of 69 patients with incident events during follow-up. Individuals with ASCVD at enrollment were 5.6 times more likely to have incident events compared to those without prior ASCVD (4.6/100 patient-years

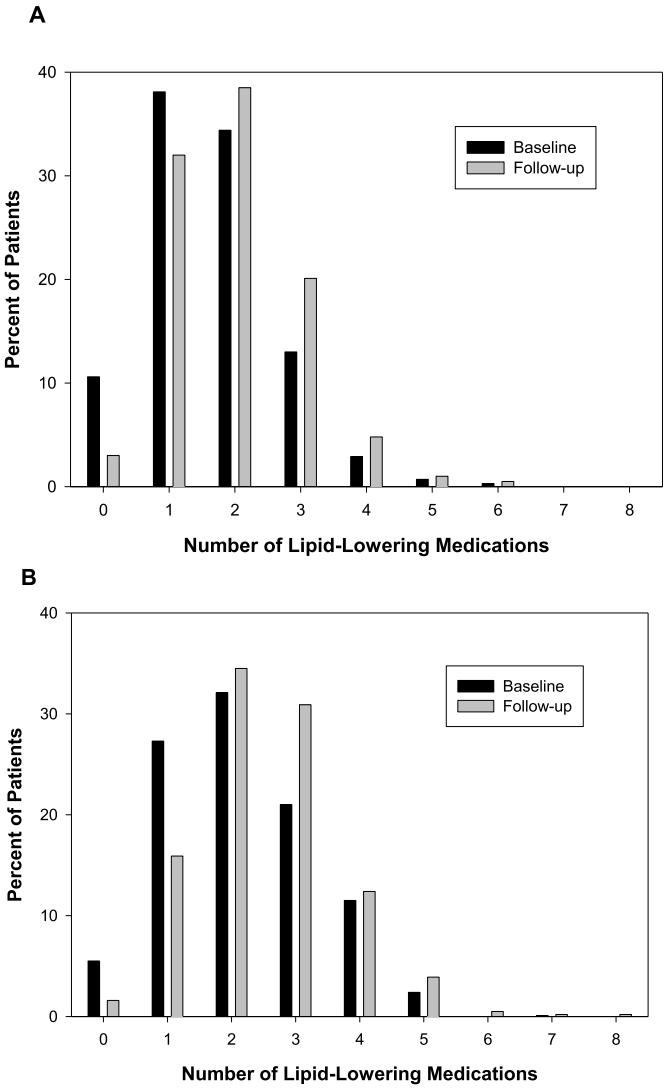

Fig. 2. Increase in lipid lowering agents used during follow up compared to baseline.
(A) Patients without ASCVD at baseline (n = 1196); (B) patients with ASCVD at baseline (n = 704).

Table 2
LDL goal achievement and non-statin drug use stratified by statin intensity.

Characteristic	No statins N = 348	Low/moderate intensity N = 469	High intensity N = 722	*p*
LDL-C concentration				
Enrollment LDL-C, mg/dL mean (s.d.)	170.3 (72.9)	143.6 (64.5)	130.9 (61.0)	< 0.0001
Follow-up LDL-C, mg/dL mean (s.d.)	131.4 (69.3)	111.7 (52.3)	97.9 (48.7)	< 0.0001
Follow-up LDL-C < 100 mg/dL, n (%)	130 (37.4)	217 (46.3)	419 (58.0)	< 0.0001
Follow-up LDL-C < 70 mg/dL, n (%)	63 (18.1)	81 (17.3)	199 (27.6)	< 0.0001
LDL-C decrease, mg/dL, mean (s.d.)	38.8 (73.4)	31.9 (65.3)	33.0 (63.6)	0.29
LDL-C decrease, % (s.d)	10.8 (79.2)	12.0 (48.5)	15.7 (43.3)	0.32
Other lipid lowering therapies at follow-up				
Number of non-statin lipid lowering therapies				< 0.0001
0 n (%)	95 (27.3%)	140 (29.9%)	179 (24.8%)	
1 n (%)	73 (21.0%)	148 (31.6%)	268 (37.1%)	
2 n (%)	120 (34.5%)	134 (28.6%)	182 (25.2%)	
3 n (%)	51 (14.7%)	37 (7.9%)	71 (9.8%)	
4 n (%)	9 (2.6%)	9 (1.9%)	16 (2.2%)	
5 n (%)	0 (0.0%)	1 (0.2%)	5 (0.7%)	
6 n (%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	
Ezetimibe n (%)	120 (34.5)	198 (42.2)	410 (56.8)	< 0.0001
Niacin n (%)	22 (6.3)	34 (7.2)	60 (8.3)	0.49
Bile acid sequestrants n (%)	36 (10.3)	31 (6.6)	41 (5.7)	0.018
PCSK9 inhibitors n (%)	202 (58.0)	110 (23.5)	175 (24.2)	< 0.0001
LDL apheresis n (%)	29 (8.3)	8 (1.7)	9 (1.2)	< 0.0001

Table 3
Occurrence of ASCVD events during a mean follow-up of 20 ± 11 months. Event rates among those with available follow-up (N = 1900)[a].

Outcome	Baseline ASCVD[b]		
	Overall (N = 1900)	No (N = 1196)	Yes (N = 704)
MI	16 (0.50)	2 (0.10)	14 (1.16)
Stroke	9 (0.28)	3 (0.15)	6 (0.49)
TIA	7 (0.22)	4 (0.20)	3 (0.25)
PCI	42 (1.33)	5 (0.25)	37 (3.14)
CABG	13 (0.41)	3 (0.15)	10 (0.82)
Composite of these 5 events	69 (2.21)	16 (0.82)	53 (4.57)
Aortic valve replacement	2 (0.06)	1 (0.05)	1 (0.08)

A total of 107 events occurred in 69 patients out of 1900 after enrollment. The data in this table show the occurrence of first events after enrollment. The occurrence of second events occurred in 24 patients and is not shown in the table.
[a] Cells contain number of events (rate per 100 patient-years).
[b] Baseline ASCVD was defined as a history of myocardial infarction, coronary revascularization, stroke, or TIA prior to enrollment.

vs 0.82/100 patient-years, respectively, $p < 0.0001$). Incident ASCVD events were predominantly coronary artery disease events rather than cerebrovascular events.

Characteristics that were significantly different between those with and without incident ASCVD events during follow up are presented in Table 4. These included older age at diagnosis of FH, older age at

Table 4
Patient characteristics stratified by absence or incidence of ASCVD events during follow-up.

Characteristic	No ASCVD N = 1831	ASCVD N = 69	*p*
Demographics			
Age at enrollment, yrs (s.d.)	55.8 (14.8)	62.3 (12.4)	0.0004
Follow-up time, months(s.d.)	20.1 (10.8)	24.1 (10.2)	0.0021
Sex			0.0026
Male n (%)	705 (38.5)	39 (56.5)	
Female n (%)	1126 (61.5)	30 (43.5)	
Past medical history			
Smoking history n (%)	647 (35.4)	35 (50.7)	0.0093
Peripheral arterial disease n (%)	57 (5.6)	6 (15.4)	0.011
Hypertension n (%)	838 (45.8)	49 (71.0)	< 0.0001
Diabetes n (%)	241 (13.2)	28 (40.6)	< 0.0001
Prior documentation of ASCVD n (%)	651 (35.6%)	53 (76.8%)	< 0.0001
Prior MI n (%)	240 (13.1%)	28 (40.6%)	< 0.0001
Prior TIA n (%)	66 (3.6%)	8 (11.6%)	0.0008
Prior PCI or stent n (%)	325 (17.8%)	34 (49.3%)	< 0.0001
Prior CABG n (%)	224 (12.2%)	26 (37.7%)	< 0.0001
Prior heart failure n (%)	50 (2.8%)	7 (10.1%)	0.0004
Age at diagnosis, yrs (s.d.)	49.7 (18.0)	57.4 (16.2)	0.0007
Highest pre-treatment lipids			
LDL, mg/dL (s.d.)	248.4 (68.3)	260.5 (67.4)	0.20
Enrollment lipids			
LDL, mg/dL(s.d.)	145.4 (67.3)	144.3 (72.3)	0.90
HDL, mg/dL(s.d.)	54.6 (17.4)	45.0 (15.3)	< 0.0001
Triglycerides, mg/dL(s.d.)	143.1 (90.2)	195.5 (153.2)	0.0066
Lp(a), mg/dL, median (Q1, Q3)	28.0 (10.0, 82.8)	42.7 (7.0, 140.0)	0.66
Follow-up lipids			
LDL, mg/dL(s.d.)	112.4 (58.6)	98.8 (59.9)	0.077
HDL, mg/dL(s.d.)	55.5 (29.4)	45.9 (13.0)	< 0.0001
Triglycerides, mg/dL(s.d.)	131.7 (88.5)	157.1 (106.8)	0.075
Physical examination			
BMI, kg/m^2 (s.d.)	29.4 (10.2)	31.2 (6.1)	0.020
Systolic BP mmHg (s.d.)	127.7 (17.0)	129.6 (18.1)	0.37
Diastolic BP mmHg (s.d.)	75.4 (10.5)	75.4 (16.7)	0.99
Corneal arcus	317 (23.5%)	14 (28.0%)	0.47
Tendon xanthomas	387 (27.4%)	17 (33.3%)	0.35
Lipid lowering therapies at enrollment			
Taking any lipid lowering therapy n (%)	1534 (92.6%)	62 (96.9%)	0.20
Number of lipid lowering therapies			0.026
0 n (%)	122 (7.4%)	2 (3.1%)	
1 n (%)	541 (32.7%)	16 (25.0%)	
2 n (%)	579 (35.0%)	27 (42.2%)	
3 n (%)	277 (16.7%)	13 (20.3%)	
4–6 n (%)	136 (8.3%)	6 (9.4%)	
Taking any statin n (%)	1274 (73.8%)	49 (72.1%)	0.75
High intensity statin n (%)	726 (42.0%)	21 (30.9%)	0.067
PCSK9 inhibitors n (%)	204 (18.9%)	5 (11.1%)	0.19
LDL apheresis n (%)	56 (3.2%)	7 (10.3%)	0.0019

enrollment, longer duration of follow up, more likely male, more frequent hypertension, more frequent diabetes, more frequent history of ASCVD, more frequent history of heart failure, lower HDL-C at enrollment, and more likely to be undergoing LDL/lipoprotein apheresis, (all $p < 0.003$). There were trends for smoking, and higher triglycerides at enrollment. The higher frequency of treatment with LDL/lipoprotein apheresis in individuals with incident ASCVD events likely reflects the higher prevalence of prior ASCVD and greater prevalence of other ASCVD risk factors.

4. Discussion

The results of the present analysis of longitudinal data from 1900 adult patients with heterozygous FH in the CASCADE FH Registry confirmed very late diagnosis of FH at age 50 ± 18 years, frequently only after the onset of ASCVD, and low rates of achievement of LDL-C goals during follow-up (only 48% with LDL-C < 100 mg/dl and 22% < 70 mg/dl). Although these rates of LDL-C goal achievement are suboptimal, they are actually much higher than the results from a recent retrospective analysis that showed LDL-C < 100 mg/dl and 70 mg/dl in only 25% and 8% of FH subjects, respectively, over a mean follow-up of 11.1 years in specialty lipid clinics [10]. Results in this study are similar to those reported from other longitudinal registries including the SAFEHEART study [6].

The prevalence of ASCVD was already high at enrollment, affecting 37% of patients, which reflects the 10 to 20-fold increased risk of ASCVD among patients with FH. After enrollment in the registry, intensification of the LDL-C lowering regimen occurred, but only modest further LDL-C lowering was achieved for most participants. Despite this partial treatment success, the pooled incidence of ASCVD events during follow-up was high, particularly among the subgroup with ASCVD at enrollment. Patients with recurrent events had lower LDL-C and were taking more lipid-lowering medications than those with de novo events; this reflects guideline-based intensification of LDL-C lowering treatment for those with prior ASCVD. Patient characteristics at enrollment associated with the occurrence of new ASCVD events were older age at diagnosis of FH, older age at enrollment, male gender, lower HDL-C, and higher prevalence of other traditional ASCVD risk factors (hypertension, diabetes; trends for smoking, higher triglycerides, and higher BMI).

Multiple factors contributed to high rates of failure to achieve LDL-C goals, but the predominant contributor was the severely elevated mean pretreatment LDL-C concentration of 249 ± 68 mg/dl. Although treatment with maximal dose rosuvastatin 40 mg/d is expected to reduce the LDL-C concentration by an average of 60%, this amount of LDL-C lowering may not be fully achievable in some patients with FH, particularly those with more severe defects in LDL receptor function [11]. Moreover, even if a 60% reduction was achieved, this would reduce the LDL-C concentration to an average of 100 mg/dl. Although only 77% of patients were taking a statin at follow-up (due to reported intolerance in non-users), nearly two-thirds were taking 2 or 3 lipid-lowering medications and 10.4% were taking 4–7 medications.

The high rates of statin non-use are greater than the 10% rates of statin intolerance reported in cross-sectional analyses of those being treated for non-specific hyperlipidemia and the < 1.5% rates of statin intolerance observed in randomized placebo-controlled clinical trials [12]. This finding may reflect a referral bias as patients with higher rates of statin intolerance may be more likely to be referred to specialty clinics involved in this study. Higher doses of statins required to achieve LDL goals in subjects with FH may also increase side effects [12]. Other potential barriers to LDL-C goal achievement may include discontinuation of drug therapy due to pill burden fatigue, concerns about cost, and side-effects resulting from use of multi-drug regimens.

Initiation of PCSK9 inhibitors after enrollment resulted in substantial LDL-C lowering. Improved access to PCSK9 inhibitors among patients with FH, especially those with highest ASCVD risk, is likely to substantially improve LDL-C goal achievement [13–15]. The rate of success reported in obtaining PCSK9 inhibitors is low in FH patients [16]. Since 72% of patients in our cohort had LDL-C > 100 mg/dl at enrollment and 37% had extant ASCVD, a large majority of patients are likely to have qualified for treatment with a PCSK9 inhibitor in accordance with FDA-approved indications. Strategies have been reported that resulted in 94–96% success in obtaining authorization for treatment with PCSK9 inhibitors, which might help facilitate increased use of PCSK9 inhibitors among patients with FH who have refractory LDL-C elevation [17–19].

The incidence of ASCVD events in this population was high despite the relatively short follow-up window and the achievement of an LDL-C concentration < 100 mg/dl in 48% of participants. Our findings are consistent with results from other longitudinal studies of patients that demonstrated high rates of recurrent ASCVD events in FH [6,20–23]. If the high rates of incident ASCVD events in our cohort persisted over time, the extrapolated 10-year event rates for our combined endpoint of myocardial infarction, revascularization, stroke, and transient ischemic attack would be 46% among individuals known to have ASCVD and nearly 10% among those without a diagnosis of ASCVD at enrollment. Therefore, it may be appropriate to designate FH as an ASCVD risk equivalent. Such a designation could lead to an LDL-C goal < 70 mg/dl in adult patients with FH and without ASCVD, similar to recommended treatment goals for secondary prevention in patients with ASCVD. The results of previous angiographic studies performed primarily among patients treated with statins compared to placebo demonstrated that the average LDL-C concentration at which progression of plaque accumulation ceases is around 70 mg/dl [24].

The identification of very high rates of incident ASCVD in this population of FH patients also underscores the importance of early diagnosis and early initiation of LDL-C lowering treatment, as well as controlling other ASCVD risk factors. Diagnosis of FH later in life was an important correlate of incident ASCVD events. Results from a recent meta-analysis of LDL-C lowering trials demonstrated that the greatest cardiovascular benefit from LDL-C lowering was achieved among those with the highest baseline LDL-C concentration such as patients with FH [25]. This implies that aggressive LDL-C lowering may produce greater cardiovascular benefit in patients with FH. Current recommendations support initiation of statin therapy in childhood starting at age 8–10 years in patients with FH [26].

There are several limitations to this analysis. Our data are longitudinal, but the results are only observational. Assessments of outcomes were dependent on patient's having follow-up visits with the local registry site. Patients in the registry were selected from specialty clinics and may not be representative of FH patients in the general population. Specialty clinics may provide more aggressive LDL-C lowering therapy. Patients may have been self-selected for more severe illness, more refractory or severe LDL-C elevation, or higher rates of statin intolerance. Information about the nature of statin intolerance or allergy was not available from the database. Recruitment for the FH registry started in 2013, but PCSK9 inhibitors were not clinically available until two years later, so the prevalence of use of PCSK9 inhibitors and potential for impact on outcomes is likely to change over time. Lipoprotein(a) results were unavailable for nearly two-thirds of patients limiting interpretation of the lack of association between lipoprotein (a) and risk, particularly for those with prior ASCVD. Time-averaged values for those on LDL apheresis were not available on all patients.

4.1. Conclusions

These results confirm that FH is a highly atherogenic condition that is associated with substantial morbidity and mortality. Despite the intensive efforts of providers from specialty clinics in this study to lower the LDL-C concentration, success in achieving LDL-C levels < 100 mg/dl and < 70 mg/dl occurred only in the minority of patients, and rarely

occurred with statin monotherapy. Initiation of effective LDL-lowering therapy at a young age is an essential strategy for preventing the first, early onset, ASCVD event. Aggressive LDL-C lowering in secondary prevention is a necessity for preventing recurrent ASCVD events. Despite use of 2 or 3 LDL-C lowering drugs in nearly 2/3 of patients and LDL-C < 100 mg/dl in nearly half of patients, our results demonstrated high event rates in those with and without prior ASCVD. Defining FH as an ASCVD risk equivalent may be warranted on the basis of longitudinal data from this and other international registry data, which may justify an LDL-C goal < 70 mg/dl in most previously untreated adults with FH in a primary prevention setting.

Nevertheless, the opportunity to improve FH care exists now. Studies to determine the optimal LDL-C goal in patients with FH for lifelong ASCVD prevention should be undertaken. New medications, both available and in development, allow for the possibility of more effective lifetime control of LDL-C. Increased awareness, the availability or genetic testing, and screening for FH in childhood and young adulthood should help facilitate earlier initiation of treatment and improved outcomes. Hopefully, results from future registry studies will document improved outcomes.

Conflicts of interest

P. Barton Duell: Institutional Research Grant; Significant; Regeneron, Esperion, Retrophin. Consultant/Advisory Board; Modest; Akcea, Esperion, Regeneron, RegenxBio, Retrophin, Astra Zeneca.

Linda C. Hemphill: Modest: Consulting- Akcea/IONIS, The Medicines Company, Regeneron.

Seth S. Martin: Modest: scientific advisory boards of Amgen, Sanofi, Regeneron, Esperion, Novo Nordisk, Quest Diagnostics, and Akcea Therapeutics, Significant: research support from Apple, Google, iHealth, Nokia, NIH, the Maryland Innovation Initiative, AHA, Aetna Foundation, PJ Schafer Memorial Fund, and David and June Trone Family Foundation. Co-inventor on a pending patent filed by Johns Hopkins University for a system of LDL-C estimation.

Zahid S. Ahmad: Modest Regeneron, American Heart Association research funding; Honorarium for educational talks: Amgen, Akcea; Advisory boards: Aegerion, Akcea, Sanofi.

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Paul Thompson: Significant - Research Support: Sanolfi, Regeneron, Esperion, Amarin and Pfizer; Significant -Consultant/Advisory Board: Amgen, Regeneron, Sanolfi, Esperion, Amarin; Significant - Speaker Honoraria: Amarin, Regeneron, Sanofi, Amgen, Boehringer Significant - Stock Shareholder: Abbvie, Abbott Labs, J&J; General Electric, Serapta, Medtronic.

Daniel J. Rader: Significant: Consultant/Advisory Board: Alnylam, Novartis, Pfizer.

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Trial registration

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Author contributions

The project was led by Dr. Duell who submitted the original ms. proposal to the Publications Committee of the CASCADE FH Registry. Additional drafting and critical review of the ms. supporting Dr. Duell was performed by Drs. Gidding, Knowles, and Kindt, who also provided leadership and administration from the FH Foundation. Statistical support was provided by Dr. O'Brien, Dr. Roe, and Mr. Shrader. Ms. Wilemon and Ms. Ahmed provided patient insight and participated in the development of the Registry. The remaining authors, as did those mentioned above, contributed patients to the Registry, critically reviewed and provided comments for at least three preliminary drafts of the paper, and provided final approval.

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