Improved Longitudinal LDL-C Goal Achievement Among Familial Hypercholesterolemia Patients in the CASCADE FH™ Patient Registry

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Background

- Familial hypercholesterolemia (FH) is a common inherited disorder affecting approximately 1 in every 250 individuals.
- FH is associated with 10-20 fold increased risk of CHD and requires aggressive LDL-C lowering, ideally initiated at a young age.
- First-line therapy for patients with FH consists of statins, but non-statins are often required to reduce LDL-C to goal levels (i.e., <100 mg/dL in primary prevention).
- Initial data from the CASCADE-FH Patient Registry demonstrated that LDL-C goal achievement was suboptimal among patients with FH.[1]
- We hypothesized that LDL-C goal achievement has improved over time, particularly after availability of anti-PCSK9 drugs.
- To test this hypothesis, we analyzed longitudinal data from the FH Foundation CASCADE-FH Registry.

CASCADE FH™ Patient Registry

In 2013, the FH Foundation® (a patient-centered research and advocacy organization) created the **CAscade SCreening for Awareness and DEtection (CASCADE) FH Registry,** a national initiative to increase FH awareness, characterize trends in treatment, and monitor clinical and patient-reported outcomes over time.

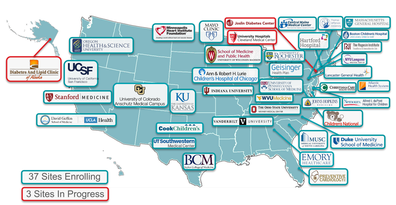


Figure 1: Enrolling clinical sites and sites in progress

Methods

Study Population

- All adult patients (age ≥18 yrs) with a diagnosis of heterozygous FH and at least one follow up visit within 6-12 months after the baseline enrollment visit were included in the analysis. FH was diagnosed by local site providers on the basis of clinical or genetic diagnostic methods.

Methods (continued)

- Exclusion criteria included any secondary cause of hypercholesterolemia (e.g. hypothyroidism, nephrotic syndrome, and cholestasis), a diagnosis of homozygous FH, absence of follow-up visits or missing baseline data, and age < 18 years.
- From March 2014 to August 2017, 4335 individuals were enrolled in CASCADE-FH Patient Registry at 37 sites throughout the US.
- Among the 4335 subjects in the registry, 2355 were excluded because no follow-up data were available, 482 were excluded because they were <18 years old, and 52 were excluded because they had a clinical diagnosis of homozygous FH. The remaining 1432 subjects were included in this analysis.
- Clinical and laboratory information was abstracted from the registry database in a systematic fashion by trained research staff.

Outcomes and Variables

Outcomes included:

1. Achieved LDL-C of <100 mg/dL
2. Achieved LDL-C of <70 mg/dL
3. Achieved LDL-C reduction of 50%
4. LDL-C goal attainment in relation to intensity of statin therapy
5. LDL-C goal attainment in relation to treatment with non-statin LDL-C lowering medications.
6. CHD event rates

Statistical Analysis

- Baseline characteristics are presented as frequency and percentage for categorical variables and mean (standard deviation) for continuous variables.
- Characteristics are compared using the Chi-square test for categorical variables and Student's T-test or ANOVA for continuous variables.
- Event rates are calculated as the number of events per 100 patient-years follow-up.

Results

- Mean entry age was 56.7±14.6 Yr.
- Mean follow-up was 14.7 ± 7.5 months with 1.5±0.7 visits.
- LDL-C at entry to the registry was 143±66 mg/dL
- CHD was present in 38% at entry.
- LDL-C was lower at last follow-up vs entry (115±59 mg/dL, P <0.0001).
- Among the subgroup of statin non-users (26.5 % at entry vs 20.4% at follow up), statin intolerance was reported in 76% at entry and 66% at follow-up.
- PCSK9 mAb use was 5% at entry and 20% at follow up.

Results (continued)

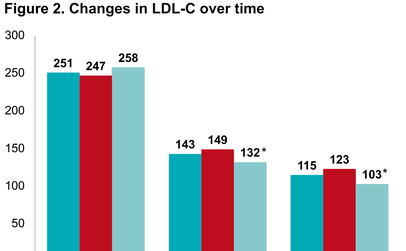
Table 1. Patient characteristics

Baseline Characteristic	No CHD events at entry N=876	With CHD events at entry N=545	P
Age at enrollment (mean)	53.5 (15.8)	61.6 (10.7)	<0.0001
Sex			
Male	286 (32.6%)	273 (50.1%)	<0.0001
Female	590 (67.4%)	271 (49.9%)	<0.0001
Follow-up time in months (mean)	14.6 (7.3)	15.1 (7.8)	<0.0001
Race/ethnicity			
Hispanic	22 (2.5%)	11 (2.0%)	
White	748 (85.4%)	492 (90.3%)	
Black	47 (5.4%)	21 (3.9%)	
Asian	20 (2.3%)	9 (1.7%)	
Other	39 (4.5%)	12 (2.2%)	
Past Medical History			
Smoking	270 (30.8%)	250 (45.9%)	<0.0001
Hypertension	323 (36.9%)	362 (66.4%)	<0.0001
Diabetes	85 (9.7%)	123 (22.6%)	<0.0001
BMI	28.6 (6.1)	30.0 (5.7)	<0.0001
Family History of early CVD	455 (51.9%)	332 (60.9%)	<0.0001

Table 2. Lipid values at baseline compared with follow-up

At entry	Highest pre-treatment LDL-C (mean)	Enrollment lipid level (mean)		Follow-up lipid level (mean)	
		LDL-C (mg/dL)	Total Cholesterol (mg/dL)	LDL-C (mg/dL)	Total Cholesterol (mg/dL)
no CHD present (N=876)	247.2 (61.2)	149.1 (62.5)	231.3 (68.1)	122.8 (54.8)	205.1 (60.4)
CHD present (N=545)	258.4 (81.8)	132.3 (68.7)	208.1 (77.3)	102.9 (64.5)	179.3 (70.7)
P-Value		<0.0001	<0.0001	<0.0001	<0.0001

Figure 2. Changes in LDL-C over time



** Significantly lower compared to group without CHD at entry*

Results (continued)

Table 3. LDL-C goal attainment in relation to statin intensity (N=1212)

Characteristic mean (sd) / %	Overall N=1212	No Statins N=270	Low/moderate intensity N=366	High intensity N=576	P
Enrollment LDL-C, mg/dL	142.2 (65.1)	170.1 (70.6)	141.3 (60.6)	129.7 (61.1)	0.06
Follow-up LDL-C, mg/dL	112.5 (56.8)	132.5 (70.2)	114.8 (51.0)	101.6 (50.2)	<0.0001
Follow-up LDL-C, <70 mg/dL (%)	252 (20.8%)	48 (17.8%)	60 (16.4%)	144 (25.0%)	0.003
Follow-up LDL-C <100 mg/dL (%)	566 (46.7%)	98 (36.3%)	160 (43.7%)	308 (53.5%)	<0.0001
LDL-C change, mg/dL	-29.7 (62.4)	-37.6 (70.5)	-26.5 (57.2)	-28.1 (61.3)	0.003
LDL-C change, (%)	-12.5 (44.3%)	-13.8 (53.8%)	-10.8 (40.3%)	-12.9 (41.8%)	0.04
LDL-C decrease ≥50 (%)	215 (17.7%)	62 (23.0%)	49 (13.4%)	104 (18.1%)	0.007

P-value is for relationship between LDL-C parameters and statin intensity. 72.4% of subjects were taking at least 1 non-statin medication and 40.4% were taking 2 or more non-statin medications.

Table 4. LDL-C Goal attainment in relation to PCSK9 inhibitor use (N=1105)

Characteristic Units are Mean (SD)	Overall N=1105	No N=858	Yes N=247	P
Enrollment LDL-C, mg/dL	144.0 (63.9)	137.8 (61.4)	165.4 (67.6)	0.001
Follow-up LDL-C, mg/dL	114.5 (56.1)	117.3 (50.3)	105.0 (72.2)	<0.0001
Follow-up LDL-C <70 mg/dL	205 (18.6%)	109 (12.7%)	96 (38.9%)	<0.0001
Follow-up LDL-C <100 mg/dL	492 (44.5)	352 (41.0%)	140 (56.7%)	<0.0001
LDL-C change, mg/dL	-29.4 (62.0)	-20.5 (55.1)	-60.4 (73.5)	<0.0001
LDL-C change, %	-12.6 (43.5%)	- 6.8 (38.6%)	-32.4 (52.9%)	<0.0001
LDL-C decrease ≥50%	188 (17.0%)	77 (9.0%)	111 (44.9%)	<0.0001

Table 5. Cardiac event rates during follow-up (N=1432)

Cardiac Event	n (rate per 100 patient-years)
Myocardial infarction (MI)	13 (0.75)
Stroke	7 (0.40)
Transient Ischemic attack (TIA)	3 (0.17)
Percutaneous coronary intervention (PCI)	27 (1.56)
Coronary artery bypass surgery (CABG)	6 (0.34)
Aortic valve replacement (AVR)	2 (0.11)
TOTAL NUMBER OF INDIVIDUALS WITH EVENTS	**44 (2.56)**

Annualized cardiac event rate is 2.56 per 100 patient years excluding AVR. **The annualized event rate among subjects without CHD at baseline was 0.95, whereas the rate was 5.15 among subjects with CHD at baseline.**

Summary

- LDL-C goal achievement has improved in association with increased intensity of drug therapy (including partial availability of anti-PCSK9 mAbs) after a mean follow-up of 14.7 months, but treatment success is still suboptimal with LDL-C ≥ 100 mg/dL in the majority of subjects (53%).
- Barriers to LDL-C goal achievement include statin intolerance, as reflected by 26% of subjects not taking a statin at enrollment and 20% still not taking a statin at follow-up.
- Additional barriers to LDL-C goal achievement may include inadequate access to more potent adjunctive non-statin therapies such as anti-PCSK9 mAb (8.5% taking anti-PCSK9 mAb at enrollment and 20% at follow-up, despite LDL-C ≥ 100 mg/dL in 53% and ≥ 70 mg/dL in 79% at follow-up).
- Cardiac event rates were high during the relatively short follow-up of 1.23 years, with an overall annualized event rate of 2.56 per 100 patient-years (0.95 in primary prevention and 5.15 in secondary prevention).

Limitations

- The nearly 4400 patients in the registry represent only about 0.3% of the estimated total number of FH patients in the United States.
- The number of patients with follow-up data in this analysis comprises only 37% of the adult patients with heterozygous FH in the registry, so the current sample size is small.
- The follow-up time of 14.7 months is relatively short. Greater improvement in LDL-C goal achievement may be observed during longer follow-up.

Conclusions

- LDL-C goal achievement has improved over time, but is still suboptimal among FH patients participating in CASCADE FH Registry.
- Statin intolerance and lack of access to non-statin medications may be barriers that contribute to suboptimal LDL-C.
- The CASCADE-FH Registry will continue to collect longitudinal follow-up data to further assess the improvements in LDL-C goal achievement over time.
- The high prospective rates of CHD events in the CASCADE-FH Registry population underscore the tremendous importance of aggressive LDL-C lowering in patients with FH, even in primary prevention.

Reference:
1) deGoma EM, *et al* Treatment gaps in adults with heterozygous familial hypercholesterolemia in the United States: Data from the CASCADE-FH Registry. Circ Cardiovasc Genet 2016; 9:240–249

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