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US physician practices for diagnosing familial hypercholesterolemia: data from the CASCADE-FH registry

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Abstract

Background—In the US familial hypercholesterolemia (FH), patients are underidentified, despite an estimated prevalence of 1:200 to 1:500. Criteria to identify FH patients include Simon Broome, Dutch Lipid Clinic Network (DLCN), or Make Early Diagnosis to Prevent Early Deaths (MEDPED). The use of these criteria in US clinical practices remains unclear.

Objective—To characterize the FH diagnostic criteria applied by US lipid specialists participating in the FH Foundation's CASCADE FH (CAscade SCreening for Awareness and DEtection of Familial Hypercholesterolemia) patient registry.

Methods—We performed an observational, cross-sectional analysis of diagnostic criteria chosen for each adult patient, both overall and by baseline patient characteristics, at 15 clinical sites that

had contributed data to the registry as of September 8, 2015. A sample of 1867 FH adults was analyzed. The median age at FH diagnosis was 50 years, and the median pretreatment low-density lipoprotein cholesterol (LDL-C) value was 238 mg/dL. The main outcome was the diagnostic criteria chosen. Diagnostic criteria were divided into five nonexclusive categories: “clinical diagnosis,” MEDPED, Simon Broome, DLCN, and other.

Results—Most adults enrolled in CASCADE FH (55.0%) received a “clinical diagnosis.” The most commonly used formal criteria was Simon–Broome only (21%), followed by multiple diagnostic criteria (16%), MEDPED only (7%), DLCN only (1%), and other (0.5%), $P < .0001$. Of the patients with only a “clinical diagnosis,” 93% would have met criteria for Simon Broome, DLCN, or MEDPED based on the data available in the registry.

Conclusions—Our findings demonstrate heterogeneity in the application of FH diagnostic criteria in the United States. A nationwide consensus definition may lead to better identification, earlier treatment, and ultimately CHD prevention.

Keywords

Familial hypercholesterolemia; Simon Broome; Dutch lipid clinic network; MEDPED; Hypercholesterolemia

Introduction

Familial hypercholesterolemia (FH) is an autosomal dominant disorder characterized by severe lifelong elevations in low-density lipoprotein cholesterol (LDL-C).¹ Thus far, mutations in at least three genes have been found to cause the disorder: low-density lipoprotein receptor (*LDLR*, Online Mendelian Inheritance in Man [OMIM] # 143890), apolipoprotein B-100 (*APOB*, OMIM # 107730), and proprotein convertase subtilisin-like kexin type 9 (*PCSK9*, OMIM # 603776). Although affected individuals have a 20-fold increased risk of premature atherosclerotic cardiovascular disease,² early diagnosis and treatment with lipid-lowering drugs reduces the risk of coronary heart disease (CHD) to rates comparable to the general population.^{3,4}

Three diagnostic criteria can predict FH-causing mutations with >80% sensitivity or specificity: Simon Broome, Dutch Lipid Clinic Network (DLCN), and the US Make Early Diagnosis to Prevent Early Death (MEDPED).^{5–7} The Simon Broome Familial Hyperlipidemia Register began in 1980 as an effort to identify all FH patients in the United Kingdom, resulting in the creation of the eponymous diagnostic criteria for FH.^{8,9} In the Netherlands, the DLCN criteria were a critical component of a public health strategy to identify patients with FH for genetic testing, early treatment, and CHD prevention.¹⁰ The US MEDPED criteria were created based on the phenotypic presentation of US families living in Utah.⁵

Consistent application of FH diagnostic criteria improves the identification of index cases. For example, in the Netherlands, the consistent application of DLCN criteria resulted in identification of 71% of estimated cases.¹¹

Unfortunately, in the United States, <10% of cases are identified^{12,13}—despite an estimated prevalence of 1:200 to 1:500^{11,14,15}—and little data are available on the use of FH diagnostic criteria in contemporary US practices. To address these issues, the FH Foundation, a nonprofit research, and advocacy organization, established the US CAscade SCreening for Awareness and DEtection of Familial Hypercholesterolemia (CASCADE-FH) Registry.¹³ CASCADE-FH became active in September 2013 and currently has data on FH patients treated at specialty lipid clinics throughout the country.

We queried CASCADE-FH to characterize how US lipid specialists diagnose FH, specifically, which of the established criteria—Simon Broome, DLCN, or MEDPED—are most commonly used.

Methods

As previously described, the FH Foundation (<http://www.fhfoundation.org>) established the CASCADE-FH registry in September 2013 as a national, multicenter initiative to identify patients with FH in the United States, track their treatments, and measure clinical and patient-reported outcomes over time. To be included in CASCADE-FH, all patients must have had at least one office visit at a participating lipid clinic within the past 5 years with FH diagnosed based on existing clinical or genetic diagnostic methods. Briefly, diagnostic criteria included—but were not limited to—Simon Broome, Dutch Lipid Clinic Network, and MEDPED. No single diagnostic method was required, largely because no consensus diagnostic criteria exist in the US. Patients with either heterozygous or homozygous FH were eligible to enroll. Exclusion criteria included known medical conditions other than FH resulting in hyperlipidemia (e.g., untreated hypothyroidism, nephrotic syndrome, cholestasis, hypopituitarism).

For the current analysis, we queried data from CASCADE-FH patients enrolled from March 2014 to September 2015 (n = 2187) for the specific criteria used to diagnose each patient. We then excluded any patients with missing data for diagnostic method (n = 72 excluded) and age (n = 6 excluded) as well as those with age <18 years (n = 242 excluded) because the DLCN does not apply to pediatric populations.

Fifteen clinical sites contributed data to the registry as of September 8, 2015 (see Supplementary Material for the list). Institutional review boards at each site reviewed and approved the protocol. Signed informed consent was required for all prospectively enrolled patients, and a waiver was approved for retrospective data abstraction. Clinical and laboratory data obtained locally for routine clinical care were abstracted from patient medical records and entered by trained research staff.

Diagnostic methods

The three formal FH diagnostic methods, as entered by each clinical site, used were MEDPED, Simon Broome, and DLCN. Details on each formal diagnostic method are provided in the Supplementary Material. Clinical sites could also chose to report using a “clinical diagnosis” of FH. Patients with a clinical diagnosis were diagnosed according to the provider's clinical judgment, either in isolation or in conjunction with one of these three

formal methods, based on past medical and family history, physical examination findings (e.g., tendon xanthomas), and laboratory data. Diagnostic methods were not mutually exclusive.

Statistical methods

Characteristics of the study population are presented as frequencies and percentages for categorical variables and medians with interquartile ranges for continuous variables. Differences in baseline characteristics by diagnostic method were assessed using the Kruskal–Wallis tests for continuous characteristics and chi-squared tests for categorical characteristics. Owing to the ambiguity of the “other” grouping and the overlapping nature of the “multiple methods” grouping, these groups were not included in the statistical comparison of diagnostic methods. The distribution of baseline characteristics was similarly compared for patients receiving a diagnosis by any formal method vs those with only a clinical diagnosis. Among those patients with a clinical FH diagnosis, we assessed the proportion of patients who met criteria for possible, probable, and definite FH using formal diagnostic tools as defined in the Supplementary Material. Finally, we compared the proportions of patients diagnosed by formal diagnostic methods vs clinical diagnoses only for each enrolling clinic using chi-square tests. Sites which did not use a formal diagnosis method for any enrolled patients were excluded from the statistical comparison.

All data analysis was performed using SAS, v 9.2 (SAS Institute, Cary, NC). $P < .05$ was considered to be statistically significant for all analyses.

Results

Data were analyzed for 1867 patients who met inclusion/exclusion criteria for this analysis. Demographics, clinical, and lipid/lipoprotein characteristics are shown in Table 1. The median age at enrollment was 56 years, and the median age at the time of FH diagnosis was 50 years; 60% were female, 75% were white, and the median BMI was 28 kg/m². Genetic testing was reported in 3.9% ($n = 73$).

With regard to FH phenotypic characteristics, 31% had prior coronary artery disease, 19% had tendon xanthomas, and 41% had a family history of premature myocardial infarction. A family history of FH was present in 22%. Median untreated and treated LDL-C levels were 238 and 145 mg/dL, respectively.

Diagnostic methods used in CASCADE-FH

The most common diagnostic criteria used was clinical diagnosis (only) (55%, $n = 1027$, Figure 1A). Simon Broome was used exclusively in 21% ($n = 390$), MEDPED in 7% ($n = 125$), and DLCN in 1% ($n = 18$). Multiple methods were used in 298 (16%) of cases. The most common combination of multiple methods was Simon Broome plus a clinical diagnosis (Figure 1B).

When examining the total number of the times each diagnostic method was used—including when used in combination with another method (Supplemental Fig. 1)—clinical diagnosis (n

= 1215, 53%) remained the most popular diagnostic criteria. DLCN was used in a total of 153 patients (7%), MEDPED 274 patients (12%), and Simon Broome 643 patients (28%).

Clinical diagnosis vs “formal” criteria

To identify differences between clinically diagnosed patients vs formally diagnosed patients and to confirm clinically diagnosed patients had phenotypic features of FH, we compared clinically diagnosed patients to those diagnosed with either DLCN, Simon Broome, and MEDPED. For this analysis, DLCN, Simon Broome, and MEDPED (when not in combination with clinical diagnosis) were combined into one “formal diagnosis” group ($n = 831$) and were compared to those who were “clinically diagnosed” ($n = 1027$).

Compared with patients who received a formal diagnosis, those receiving a clinical diagnosis were younger (formal diagnosis 55 vs clinical diagnosis 48 years, $P < .0001$, Table 1), diagnosed at earlier ages (48 vs 51 years, $P < .0001$), more commonly male (36% vs 42%, $P < .0080$), and more commonly white (66 vs 81%, $P < .001$).

Coronary artery disease was more common in patients with clinical diagnosis only (21% vs 38%, $P < .0001$), whereas tendon xanthomas were more prominent in the formal diagnosis group (31% vs 9%, $P < .0001$). Family histories of myocardial infarction (49% vs 35%, $P < .0001$) and FH (26% vs 18%, $P < .0001$) were significantly higher in the formal diagnosis group as compared to the clinical diagnosis only group.

Patients identified using clinical diagnosis method (exclusively) had significantly lower median untreated total cholesterol and LDL-C levels (untreated total cholesterol, 340 vs 312 mg/dL, $P < .0001$; LDL-C, 252 mg/dl vs 224 mg/dl, $P < .0001$). Both groups had similar rates of statin treatment (73% vs 73%, $P = .95$), although clinically diagnosed patients more frequently received additional lipid-lowering drugs (83% vs 91%, $P < .0001$) and had lower post-treatment LDL-C (150 vs 140 mg/dL, $P < .0001$).

We identified several differences in clinical characteristics based on specific diagnostic criteria used (Supplementary Tables 1 and 2).

Do clinically diagnosed patients meet criteria for the formal diagnostic criteria?

We sought to understand whether the clinical diagnosis group would have met criteria for DLCN, Simon Broome, or MEDPED using clinical data collected elsewhere as part of the CASCADE-FH registry data capture. Of 1027 patients with a clinical diagnosis, 660 had available pretreatment lipids, 93% of whom met criteria for any of the formal diagnostic methods (Table 2).

MEDPED criteria were met in 37%, whereas Simon Broome probable was met in 61%, Simon Broome definite in 3%, DLCN possible in 53%, DLCN probable in 15%, and DLCN definite in 20%.

Discussion

We identified heterogeneity in the use of diagnostic criteria for FH among lipid specialty clinics participating in a contemporary, US-based registry. Although we identified several differences between formally diagnosed and clinically diagnosed patient cohorts, all groups had severe elevations in LDL-C and a significant burden of coronary artery disease. Over 90% of the clinically diagnosed patients met criteria for Simon Broome, MEDPED, or DLCN—suggesting that lipid specialists in the United States are able to accurately identify FH despite the lack of consensus diagnostic criteria. Our findings suggest, for lipid specialists, the use of formal criteria in place of a clinical diagnosis is not crucial. Rather, the gap in FH identification may be related to a lack of screening efforts in the United States.

Of note, our findings do not advocate for clinical diagnosis to be used by all practitioners. Our data are limited to sites with physicians experienced in treating complex lipid disorders. As such, for most practitioners, the use of unvalidated clinical criteria for the detection of FH is not recommended.

Few similar investigations of nationwide health care provider practices have been undertaken for FH. Comparing our findings with other investigations is difficult. Most prior publications regarding FH patients come from countries that have nationalized health care systems or socialized medicine, offering opportunities to standardize medical practice.^{10,16,17}

For example, in the Netherlands, the DLCN criteria were a critical component of the National Genetic Cascade Screening Programme, a public health strategy to identify FH patients for genetic testing, early treatment, and CHD prevention.¹⁰ The consistent application of these criteria resulted in identification of 71% of estimated cases.¹¹ The Simon Broome Register Group program in the United Kingdom used a similar approach with its own standard criteria, resulting in an estimated identification rate over 10 times greater than that calculated for the United States.^{9,11}

Because genetic testing is lacking in the United States and family history can be difficult to elicit (e.g., due to fractured families that may live in different areas throughout the United States), a need exists for straightforward FH diagnostic criteria that would be easy to apply in the United States. The presence of ICD-10 codes for FH would facilitate recognition of FH in the community, might improve cascade screening and allow tracking of FH outcomes via large databases. Towards these goals, the American Heart Association scientific statement on FH proposes clinical and genetic definitions of FH linked to proposed ICD-10 codes.¹⁸

The lack of consensus in the United States regarding FH diagnostic criteria may create several problematic issues. First, practitioners—other than lipid specialists involved with CASCADE-FH—in the United States may experience confusion when identifying FH patients as no one set of criteria is currently recommended nor included in standard medical training. Second, absence of a consensus further poses an obstacle to cascade screening, a cost-effective identification strategy recommended by several organizations including the National Lipid Association, the Centers for Disease Control, the UK National Institute for

Health and Care Excellence, and the World Health Organization.^{1,19–21} Third, standardized diagnostic criteria offer a tool for active case-finding programs for FH, such as electronic health record querying, as recently recommended in a consensus scientific statement from the American Heart Association.¹⁸ Fourth, payers will continue to have variable policies regarding medications indicated specifically for FH, such as PCSK9 inhibitors, mipomersen, and lomitapide.^{22–26}

We identified several differences between patients diagnosed with formal criteria vs clinical diagnosis. These differences may be influenced by varying population characteristics and provider practices at different sites. Also, these analyses were not the main outcome of this study; as such, they should be regarded as hypothesis-generating.

Multiple diagnostic criteria were chosen for a significant number of patients in CASCADE-FH. The use of mobile phone apps and websites now allows practitioners to quickly determine whether patients meet one or more of the formal criteria.²⁷

Recently, data from exome sequencing have suggested that only 2% of patients with LDL-C > 190 mg/dL have detectable mutations in FH genes.²⁸ Several issues with this study likely led to a much lower FH prevalence compared to other estimates: missense mutations were only included if predicted to be deleterious by all five algorithms used or if labeled as pathogenic/likely pathogenic in ClinVar; exome sequencing misses *LDLR* copy number variations; the investigators had to impute pre-treatment LDL-C levels for those on lipid-lowering drugs. Still their findings imply a higher CHD risk in mutation-positive individuals compared to LDL-C-matched mutation-negative individuals, suggesting a prognostic benefit for genetic screening.

Several limitations to this analysis deserve consideration. First, our study is a retrospective, cross-sectional analysis. Because CASCADE-FH will include prospective data collection, longitudinal assessment may provide a clearer understanding of outcomes associated with each set of diagnostic criteria. Second, the data reflects practices at specialty lipid centers, mostly academic centers, and may not reflect practice in primary care. Third, genetic confirmation of FH was not systematically performed as in other national programs such as the Simon Broome Register Group, and “clinical diagnosis” was not clearly defined. Fourth, CASCADE-FH does not distinguish index cases from cases identified by family screening efforts.

In conclusion, we identified variable practices in diagnostic criteria used for FH among lipid specialists in the United States. Although lipid specialists seem readily capable of identifying FH patients regardless of the criteria used, widespread screening efforts would benefit from consensus diagnostic criteria. The use of uniform criteria—such as those proposed by the AHA scientific statement¹⁸—would lead to better identification of FH patients who can be treated with lipid-lowering agents, ultimately preventing CHD events.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Diagnostic criteria used to diagnose familial hypercholesterolemia in the CASCADE-FH US database. (A) % diagnosed with each criteria. (B) Among patients diagnosed using “multiple diagnostic methods,” breakdown of actual criteria used. DLCN, Dutch Lipid Clinic Network; MEDPED, Make Early Diagnosis, Prevent Early Death.

Table 1
Demographics and clinical characteristics of familial hypercholesterolemia (FH) Patients
in the CASCADE-FH Registry

Characteristic	Total cohort (n = 1867)	Formal diagnosis* (n = 831)	Clinical diagnosis (n = 1027)	P value [†]
Age at enrollment	56 (44–66)	55 (42–63)	58 (46–67)	<.0001
Age at diagnosis of FH	50 (34–60)	48 (31–59)	51 (36–62)	.0001
BMI, kg/m ²	28 (24–31)	27 (24–32)	28 (25–31)	.5282
% Female	60%	64%	57%	.0080
Race/Ethnicity %				<.0001
White	75%	66%	81%	
African American	10%	17%	5%	
Hispanic	5%	9%	2%	
Other	10%	8%	11%	
Phenotypic features (%)				
Premature CAD	19%	21%	38%	<.0001
Tendon Xanthomas	31%	31%	9%	<.0001
Family history of premature MI	41%	49%	35%	<.0001
Family history of FH	22%	26%	18%	<.0001
Untreated lipids (mg/dL)				
Total cholesterol	328 (296–390)	340 (305–400)	312 (288–367)	<.0001
LDL-C	238 (211–292)	252 (220–311)	224 (201–264)	<.0001
Treated lipids (mg/dL)				
Total cholesterol	220 (158–259)	233 (191–293)	222 (177–273)	<.0001
LDL-C	145 (106–197)	150 (113–211)	140 (99–189)	<.0001
Triglycerides	116 (82–170)	109 (79–158)	124 (54–175)	.0003
HDL-C	52 (42–63)	52 (42–64)	51 (41–63)	.1160

CASCADE-FH, CAscade SCreening for Awareness and DEtection of Familial Hypercholesterolemia; BMI, body mass Index; LDL-C, low-density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; MI, myocardial infarction; CAD, coronary artery disease.

Results are presented as median [interquartile range] unless indicated otherwise.

* Formal Diagnosis includes patients diagnosed with DLCN (Dutch Lipid Clinic Network), MEDPED (Make Early Diagnosis, Prevent Early Death), or Simon Broome criteria.

[†] Formal diagnosis vs Clinical diagnosis.

Table 2
Clinically diagnosed patients that meet formal criteria

Diagnostic method	Subjects with pretreatment lipids values (n = 660)
	n (%)
MEDPED	245 (37.12)
Simon Broome	
Probable	401 (60.76)
Definite	20 (3.03)
DLCN	
Possible	351 (53.18)
Probable	101 (15.30)
Definite	130 (19.70)
Any diagnosis method *	611 (92.58)

DLCN, Dutch Lipid Clinic Network; MEDPED, Make Early Diagnosis, Prevent Early Death.

* MEDPED, Simon Broome, or DLCN.