Prevalence of clinical familial hypercholesterolaemia among patients with high cholesterol levels

Morten Hostrup Martinsen[1], Berit Storgaard Hedegaard[1], Ib Christian Klausen[1] & Martin Bødtker Mortensen[2]

ABSTRACT

INTRODUCTION: Familial hypercholesterolaemia (FH) can be diagnosed using clinical criteria or by direct mutation identification. The prevalence of clinical FH in Danish lipid clinics remains unknown. The objective of this study was to explore the prevalence of clinical FH in patients admitted on suspicion of FH with plasma low-density lipoprotein cholesterol (LDL-C) concentration ≥ 5.0 mmol/l.

METHODS: We reviewed the medical records of 653 patients consecutively (from 1 January 2013 to 1 May 2017) referred to the lipid clinic at Viborg Regional Hospital, Denmark. Patients with LDL-C concentration > 4.9 mmol/l were selected. Clinical FH was assessed using the Dutch Lipid Clinic Network (DLCN) and Simon Broom criteria.

RESULTS: Using DLCN, 315 patients (median 82% (95% confidence interval (CI): 78-86%)) had possible FH, 33 patients (median 9% (95% CI: 6-11%)) had probable FH and 36 patients (median 9% (95% CI: 6-12%)) had definite FH. Thus, a total of 69 patients (median 18% (95% CI: 14-22%)) had probable/definite FH. Using the Simon Broome criteria, 284 (median 74% (95% CI: 70-78%)) patients did not have FH, 67 patients (median 17% (95% CI: 14-21%)) had possible FH and 33 patients (median 9% (95% CI; 6-11%)) had definite FH, resulting in a total of 100 (median 26% (95% CI: 22-30%)) patients having possible/definite FH. The concordance between DLCN and Simon Broome FH was high among patients with definite FH (> 90%), but low among patients with probable or possible FH.

CONCLUSIONS: Clinical FH was common among patients with LDL-C concentration ≥ 5.0 mmol/l referred to a Danish lipid clinic. However, the concordance between the DLCN and the Simon Broome criteria was low in a specialised clinical setting.

FUNDING: The study was supported by a SANOFI grant.

TRIAL REGISTRATION: not relevant.

Familial hypercholesterolaemia (FH) is an autosomal dominant hereditary disease resulting in high levels of plasma low-density lipoprotein cholesterol (LDL-C) [1]. Patients with heterozygous FH have an increased risk of developing premature cardiovascular disease (CVD) before the age of 50 years in men and 60 years of age in women [2, 3]. The clinical diagnosis of FH requires no positive gene test, and a negative gene test does not rule out FH. The clinical criteria commonly used are the Dutch Lipid Clinic Network (DLCN) and the Simon Broome criteria [4, 5]. These criteria define the probability of FH by combining family history of CVD, patient history of CVD, physical examination, untreated LDL-C levels and gene testing [3].

Three mutations may give rise to the majority of genetic FH: mutation in the LDL receptor gene (*LDLR*), in the apolipoprotein B gene (*APOB*) and in genes coding for proprotein convertase subtilisin/kexin type 9 (*PCSK9*) [6].

The prevalence of heterozygous FH has been reported to vary from 1:200 to 1:500 [7]. In Denmark, the estimated prevalence of mutation-causative FH may be 1:217 [8]. A diagnosis of FH is important as lipid-lowering treatment (LLT), primarily statins, may significantly decrease the risk of CVD [5, 9].

In Denmark, FH is often diagnosed and treated in specialised lipid clinics. The prevalence of clinical FH among consecutively referred patients with LDL-C concentration > 4.9 mmol/l to a large lipid clinic is, however, largely unknown.

METHODS

Study population

The medical records of 653 patients referred for evaluation at the Lipid Clinic, Viborg Regional Hospital, Denmark, from 1 January 2013 to 1 May 2017 were examined. Patients were referred from the primary and secondary sector due to either biochemical or clinical suspicion of lipid disorders or because of a family member being diagnosed with FH.

The highest documented and untreated levels of plasma total cholesterol, LDL-C and triglyceride level were obtained through biochemistry history. Furthermore, cholesterol and triglyceride levels at the time of referral were also noted. Ischaemic heart disease (IHD) was confirmed by examining the medical records and included myocardial infarction (MI) and coronary artery bypass grafting (CAGB), percutaneous coronary intervention (PCI) or angina pectoris with documented coronary atherosclerosis evaluated by coronary angio-

ORIGINAL ARTICLE

1) Department of Cardiology, Viborg Regional Hospital
2) Department of Cardiology, Aarhus University Hospital, Denmark

Dan Med J 2019;66(11)5574

TABLE 1 / The Dutch Lipid Clinic Network criteria and the Simon Broome criteria of clinical familial hypercholesterolaemia.

Criteria	Score
Dutch Lipid Clinic Network	
Family history:	
1st-degree relative with premature coronary and/or vascular disease: men aged ⟨ 55 yrs, women aged ⟨ 60 yrs	1
Or	
1st-degree relative with known LDL-C concentration ⟩ the 95th percentile for age and gender	2
1st-degree relative with tendinous xanthomata and/or arcus cornealis	
Or	
Children aged ⟨ 18 yrs with LDL-C concentration ⟩ the 95th percentile for age and gender	
Clinical history:	
Patients with premature coronary artery disease: men aged ⟨ 55 yrs, women aged ⟨ 60 yrs	2
Patients with premature cerebral or peripheral vascular disease: men aged ⟨ 55 yrs, women aged ⟨ 60 yrs	1
Physical examination:	
Tendon xanthoma	6
Arcus cornealis, aged ⟨ 45 yrs	4
LDL-C concentration, mmol/l:	
≥ 8.5	8
6.5-8.4	5
5.0-6.4	3
4.0-4.9	1
FH gene mutation:	
LDLR, *APOB* or *PCSK9* mutation	8
Probable FH	6-8
Possible FH	3-5
Unlikely FH	⟨ 3
Simon Broome	
Definite FH:	–
Adult: total-cholesterol concentration ⟩ 7.5 mmol/l or LDL-C concentration ⟩ 4.9 mmol/l	
Child aged ⟨ 16 yrs: total-cholesterol concentration ⟩ 6.7 mmol/l or LDL-C concentration ⟩ 4.0 mmol/l	
And	
Physical finding of tendon xanthomas or tendon xanthomas in 1st- or 2nd-degree relative	
Or	
DNA evidence of an *LDLR*, *APOB* or *PCSK9* mutation	
Possible FH:	–
Adult: Total-cholesterol concentration ⟩ 7.5 mmol/l or LDL-cholesterol concentration ⟩ 4.9 mmol/l	
Child aged ⟨ 16 yrs: total-cholesterol concentration ⟩ 6.7 mmol/l or LDL-C concentration ⟩ 4.0 mmol/l	
And	
Family history of MI at age ≤ 60 yrs in 1st-degree relative	
Family history of MI at age ≤ 50 yrs in 2nd-degree relative	
Or	
Total cholesterol concentration ⟩ 7.5 mmol/l in adult 1st- or 2nd-degree relative	
Total cholesterol concentration ⟩ 6.7 mmol/l in child, brother or sister aged ⟨ 16 yrs	

APOB = gene coding for apolipoprotein B; FH = familial hypercholesterolaemia; LDL-C = low-density lipoprotein cholesterol; *LDLR* = LDL receptor gene; MI = myocardial infarction; *PCSK9* = gene coding for proprotein convertase subtilisin/kexin type 9.

grams. A medical history of cerebral vascular disease (ischaemic stroke) and peripheral vascular disease (PAD) were also noted. PAD included prior peripheral revascularisation and patients clinically diagnosed with intermittent claudication. Information on CVD (acute myocardial infarction (AMI), coronary artery bypass grafting, PCI or ischaemic stroke) among first- and second-degree relatives was investigated by examining information of family history. At the first consultation, patients were examined for tendon xanthomas and arcus cornealis. Results from a test for FH gene mutations were also obtained from the patient records.

The study was approved by the Danish Data Protection Agency (Ref: 1-16-02-696-16) and the Danish Patient Safety Authority.

Clinical familial hypercholesterolaemia diagnosis

Clinical FH was assessed using the DLCN and the Simon Broome criteria (**Table 1**). For DLCN, it was not possible to evaluate plasma LDL-C levels in first-degree relatives, first-degree relatives with tendon xanthoma and/or arcus cornealis or plasma LDL-C levels of children <18 years. Furthermore, only premature CVD was known among first-degree relatives. Probable or definite FH was considered together as having clinical FH by DLCN criteria and thus grouped under a single FH diagnosis – probable/definite FH.

For the Simon Broome criteria, data on tendon xanthomas in first- and second-degree relatives, mutations in *PCSK9* and total cholesterol levels among relatives were not known. Patients with either possible or definite FH were regarded as having clinical FH determined by the Simon Broome criteria and grouped under the diagnosis possible/definite FH.

Statistical analysis

Data analyses were performed using STATA, version IC/15 (StataCorp LLC, TX, US). Descriptive statistics were stratified according to DLCN and Simon Broome FH status. All continuous data were described as medians with interquartile ranges. Continuous variables were tested for significance using the Wilcoxon-rank sum (Mann-Whitney) test and categorical data using the two-sample test of proportions.

Trial registration: not relevant.

RESULTS

A total of 384 patients with a recorded LDL-C concentration ≥ 5.0 mmol/l were referred during the study period for evaluation at the lipid clinic, Viborg Regional Hospital (**Table 2**), all of which were scored according to the DLCN and the Simon Broome criteria. Patient age at referral ranged from nine years to 80 years of age.

Clinical diagnosis with the Dutch Lipid Clinic Network and the Simon Broome criteria

Using the DLCN criteria, none had unlikely FH, 315 patients (median 82% (95% confidence interval (CI):

TABLE 2 / Patient characteristics.

	Women (n = 214)	Men (n = 170)	All (N = 384)
Gender, %	55.7	44.3	-
Age, yrs, median (± IQR)	60 (± 16)	50 (± 16)	55 (± 18)
Smoker, %	17.5	17.4	17.4
Systolic BP, mmHg, median (± IQR)	138.5 (± 26)	139 (± 24)	139 (± 25)
Concentration at the time of referral, mmol/l, median (± IQR)			
Total-cholesterol	6.3 (± 2.3)	6.0 (± 2.15)	6.2 (± 2.3)
LDL-cholesterol	4.2 (± 2.1)	4.2 (± 2.2)	4.2 (± 2.1)
Triglycerides	1.4 (± 1.1)	1.6 (± 1.3)	1.5 (± 1.2)
Highest concentration recorded, mmol/l, median (± IQR)			
Total-cholesterol	8.1 (± 1.3)	8.0 (± 1.2)	8.0 (± 1.2)
LDL-cholesterol	5.8 (± 1.1)	5.8 (± 1.1)	5.8 (± 1.1)
HDL-cholesterol	1.5 (± 0.6)	1.2 (± 0.4)	1.4 (± 0.6)
Triglycerides	2.3 (± 1.8)	3.0 (± 2.0)	2.6 (± 2.0)
Health background, %			
Diabetes	11.2	7.6	9.6
Prior AMI	4.2	6.5	5.2
CAD, no prior AMI	8.9	15.9	12.0
Prior stroke	4.2	4.1	4.2
Prior PAD	2.3	2.9	2.6
Any CVD	18.7	25.9	21.9
BP medication at referral	32.1	23.1	28.1
Statin at referral	44.8	48.5	46.5

AMI = acute myocardial infarction; BP = blood pressure; CAD = coronary artery disease; CVD = cardiovascular disease; HDL = high-density lipoprotein; IQR = interquartile range; LDL = low-density lipoprotein; PAD = peripheral artery disease.

78-86%)) had possible FH, 33 patients (median 9% (95% CI: 6-11%)) had probable FH and 36 patients (median 9% (95% CI: 6-12%)) had definite FH. This equals a total of 69 patients (median 18% (95% CI: 14-22%)) with probable/definite FH (**Table 3**).

Using the Simon Broome criteria, 284 patients (median 74% (95% CI: 70-78%)) did not have FH, 67 patients (median 17% (95% CI: 14-21%)) had possible FH and 33 patients (median 9% (95% CI: 6-11%)) had definite FH. This yielded a total of 100 patients (median 26% (95% CI: 22-30%)) with possible/definite FH by these criteria (Table 3).

Looking at the concordance between the DLCN and Simon Broome criteria stratified across subgroups (**Figure 1**), 33 patients had definite DLCN FH and Simon Broome FH, i.e. 92%. Sixteen had both probable DLCN and possible Simon Broome FH, i.e. 19%, and 265 patients had possible DLCN FH and not Simon Broome FH, i.e. 79%.

Patient characteristics

Using the DLCN criteria, we found that patients with probable/definite FH were younger than patients with possible FH (51 versus 57 years, $p = 0.002$); they had higher plasma LDL-C concentration at referral as well as highest LDL-C concentration ever recorded (referral: 4.1 mmol/l versus 4.6 mmol/l; highest: 5.7 mmol/l versus 6.7 mmol/l) and they had a higher rate of IHD without a previous MI (8.3% versus 29.0%). Likewise, any prior CVD was more common for probable/definite FH patients than for possible FH (18.4% versus 37.7%), $p < 0.001$). No difference in the prevalence of PAD or stroke was observed between the two groups. Statin treatment at referral was higher for probable/definite FH patients than for those classified as unlikely FH (43.8% versus 58.8%).

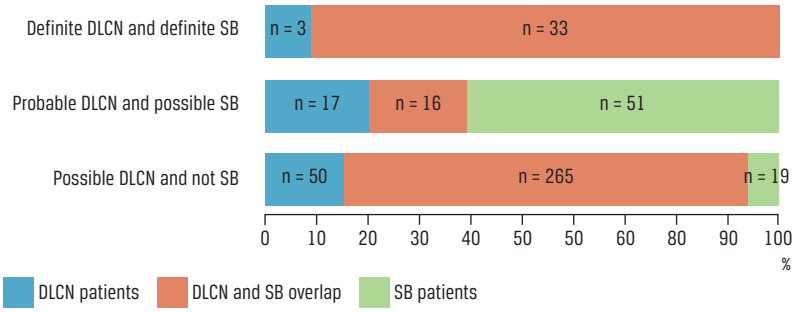
Using the Simon Broome criteria, we found no difference in total cholesterol or LDL-C when comparing patients without FH with patients with possible/definite FH. Possible/definite FH patients showed a higher rate of prior non-MI IHD (22% versus 8.5%, $p < 0.001$) and statin use at referral (56.6 versus 42.9%, $p = 0.002$). No differences were seen in relation to age, smoking status, previous MI, stroke or PAD (Table 3). Statin treatment at referral was higher for possible/definite FH patients than for patients without FH (42.9% versus 56.6%).

TABLE 3 / Characteristics stratified according to familial hypercholesterolaemia diagnosis.

	Dutch Lipid Clinic Network			Simon Broome		
	possible FH	probable/ definite FH	p-value	not FH	possible/ definite FH finite FH	p-value
Patients, n (%)	315 (82)	69 (18)	-	284 (74)	100 (26)	-
Age, yrs, median (± IQR)	57 (± 19)	51 (± 14)	0.002	57 (± 19)	52.5 (± 15)	0.051
Smoker, %	15.1	28.4	0.09	17.1	18.4	0.77
Systolic BP, mmHg, median (± IQR)	140 (± 25)	138 (± 32)	0.49	140 (± 24)	135 (± 29)	0.67
Concentration at the time of referral, mmol/l, median (± IQR)						
Total-cholesterol	6.1 (± 2.1)	6.55 (± 2.8)	0.035	6.2 (± 2.2)	5.95 (± 2.55)	0.29
LDL-cholesterol	4.1 (± 2.2)	4.6 (± 2.5)	0.005	4.2 (± 2.1)	4.1 (± 2.1)	0.37
HDL-cholesterol	1.4 (± 0.5)	1.3 (± 0.5)	0.004	1.4 (± 0.5)	1.3 (± 0.5)	0.14
Triglycerides	1.5 (± 1)	1.5 (1.8)	0.68	1.5 (± 1.1)	1.6 (± 1.4)	0.54
Highest concentration recorded, mmol/l, median (± IQR)						
Total-cholesterol	7.9 (± 1)	8.9 (± 2.1)	⟨ 0.001	8 (± 1.2)	8.2 (± 1.4)	0.057
LDL-cholesterol	5.7 (± 0.9)	6.7 (± 2.15)	⟨ 0.001	5.8 (± 1.1)	5.8 (± 1.2)	0.21
Triglycerides	2.6 (± 2)	2.6 (± 2.1)	0.84	2.6 (± 2.2)	2.8 (± 2.2)	0.60
Health background, %						
Diabetes	9.2	11.6	0.54	10.2	8.0	0.52
Prior AMI	4.8	7.2	0.4	4.9	6.0	0.68
CAD, no prior AMI	8.3	29.0	⟨ 0.001	8.5	22.0	⟨ 0.001
Prior stroke	4.1	4.3	0.93	4.9	2.0	0.21
Prior PAD	2.5	2.9	0.87	2.1	4.0	0.31
Any CVD	18.4	37.7	⟨ 0.001	19.0	30.0	0.02
BP medication at referral	28.1	27.9	0.98	28.0	28.3	0.96
Statin at referral	43.8	58.8	0.02	42.9	56.6	0.02

AMI = acute myocardial infarction; BP = blood pressure; CAD = coronary artery disease; CVD = cardiovascular disease; FH = familial hypercholesterolaemia; HDL = high-density lipoprotein; IQR = interquartile range; LDL = low-density lipoprotein; PAD = peripheral artery disease.

FIGURE 1 / Concordance between Simon Broome (SB) and Dutch Lipid Clinic Network (DLCN) subgroups.



DISCUSSION

Of the 653 patients reviewed, 59% (n = 384) had LDL-C concentration ≥ 5.0 mmol/l and were therefore suspected of having FH. Of these, 18% had clinical FH according to the DLCN criteria and 26% had FH according to the Simon Broome criteria. In the general Danish population, clinical FH using the DLCN criteria has been estimated to be 1:223 (0.45%) [10] and other studies have found clinical Simon Broome FH to be more prevalent than DLCN FH [8]. A high degree of concordance was seen between DLCN and Simon Broome diagnosis among patients with definite FH. A positive gene test was frequent in these individuals (28 were mutation positive), which surely contributed to the high degree of concordance between these groups. In contrast, we observed a low degree of concordance between DLCN and Simon Broome diagnosis among patients with probable or possible FH. Thus, the choice of FH algorithm in clinical practice plays a major role for overall FH classification.

The data presented in Figure 1 indicates that when applying the Simon Broome criteria in clinical practice, you will catch more patients with clinical FH than when using DLCN as a diagnostic tool. This, however, does not necessarily correspond to identifying patients with an FH causing mutation. In the general Danish population, the DLCN criteria have been shown to have a higher mutation detection rate [8] than the Simon Broome criteria, but the detection rate of FH gene mu-

tations stratified according to clinical diagnosis among patients referred with LDL-C concentration ≥ 5.0 mmol/l is unknown and needs further investigation.

We found more patients with clinical FH who had IHD without a previous MI (29% and 22% for DLCN and Simon Broome, respectively) than patients who had AMI (7.2% and 6%), indicating that a large portion of FH patients may be within this population. FH patients were younger than non-FH patients whether the DLCN or the Simon Broome criteria were used. However, this was only significant for the DLCN. The younger age at diagnosis may be a result of cascade screening of family members of patients with known FH or with suspicion of FH.

Notably, more than 40% of patients with LDL-C concentration ≥ 5.0 mmol/l and clinical FH did not use statins at referral (DLCN 41.2%; Simon Broome 43.4%). Thus, their LDL-C levels were well above the European Society of Cardiology's treatment targets for LDL concentration < 2.6 mmol/l (age < 40 at FH diagnosis) or < 1.8 mmol/l (age > 40 at FH diagnosis and/or known IHD) [5, 7]. This indicates a need to improve the management of patients with clinical FH.

Only six patients had tendon xanthomas at their physical examination although previous studies have reported that the rate may reach 29% among patients with FH gene mutations [11]. None of the patients were identified with arcus cornealis before the age of 45 years, even though 85 of the patients were in this age group with 27 having probable/definite DLCN FH and/or possible/definite Simon Broome FH. Clinical examination for xanthomas and arcus cornealis is highly dependent on the physician performing the physical examination.

In our study, 62.3% with DLCN FH and 70% with Simon Broome FH did not have CVD at the time of referral, which shows the potential benefit in making an early diagnosis and initiating LLT.

Limitations

This was a retrospective study. As noted, it was not possible to obtain all the necessary information to achieve a complete clinical FH score. Furthermore, data regarding former transient cerebral ischaemia, carotid stenosis or the presence of xantelasmata were not available. Genetic testing did not include *PCSK9* mutations, which account for approximately 2% of FH gene mutations [12]. The highest recorded cholesterol levels were used to determine untreated levels; some of these may have been recorded while on statins. Statin intensity at referral was not known why the above method was used rather than cholesterol level correction. Information regarding blood pressure was unavailable in 61 patients; all data on other variables were nearly complete.

Data on tendon xanthoma and cholesterol levels among relatives were unknown. These variables are central to the Simon Broome criteria and may cause bias, underestimating the prevalence of Simon Broome FH compared with DLCN FH.

The included patients were highly selected since they represent patients in whom suspicion of FH had been raised in either the primary or the secondary healthcare sector. The clinical FH scores of referred patients may be influenced by several factors such as regional FH awareness and country, making the results subject to further investigation in similar settings.

CONCLUSIONS

Clinical FH is a common finding (18% using the DLCN and 26% using the Simon Broome criteria) among patients with LDL-C concentration ≥ 5.0 mmol/l referred to a large Danish lipid clinic. However, the concordance of clinical FH between the DLCN and the Simon Broome criteria is low. It would be very interesting to prospectively evaluate the mutation detection rate of genetically verified FH by these broad referral criteria. Evaluated by statin use and LDL-C levels at referral, patients with clinical DLCN FH and Simon Broome FH are undertreated, showing the need for increased identification and treatment.

CORRESPONDENCE: *Morten Hostrup Martinsen.*
E-mail: Morten.Martinsen@dadlnet.dk

ACCEPTED: 25 September 2019

CONFLICTS OF INTEREST: Disclosure forms provided by the authors are available with the full text of this article at Ugeskriftet.dk/dmj

LITERATURE

1. Austin MA, Hutter CM, Zimmern RL et al. Familial hypercholesterolemia and coronary heart disease: a HuGE association review. Am J Epidemiol 2004;160:421-9.
2. Mundal L, Sarancic M, Ose L et al. Mortality among patients with familial hypercholesterolemia: a registry-based study in Norway, 1992-2010. J Am Heart Assoc 2014;3:e001236.
3. Singh S, Bittner V. Familial hypercholesterolemia - epidemiology, diagnosis, and screening. Curr Atheroscler Rep 2015;17:482.
4. Scientific Steering Committee on behalf of the Simon Broome Register Group. Risk of fatal coronary heart disease in familial hypercholesterolaemia. Bmj 1991;303:893-6.
5. Hovingh GK, Davidson MH, Kastelein JJ et al. Diagnosis and treatment of familial hypercholesterolaemia. Eur Heart J 2013;34:962-71.
6. Migliara G, Baccolini V, Rosso A et al. Familial Hypercholesterolemia: a systematic review of guidelines on genetic testing and patient management. Front Public Health 2017;5:252.
7. Nordestgaard BG, Chapman MJ, Humphries SE et al. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease: consensus statement of the European Atherosclerosis Society. Eur Heart J 2013;34:3478-3490a.
8. Benn M, Watts GF, Tybjaerg-Hansen A et al. Mutations causative of familial hypercholesterolaemia: screening of 98 098 individuals from the Copenhagen General Population Study estimated a prevalence of 1 in 217. Eur Heart J 2016;37:1384-94.
9. Versmissen J, Oosterveer DM, Yazdanpanah M et al. Efficacy of statins in familial hypercholesterolaemia: a long term cohort study. BMJ 2008;337:a2423.
10. Benn M, Watts GF, Tybjaerg-Hansen A et al. Familial hypercholesterolemia in the danish general population: prevalence, coronary artery disease, and cholesterol-lowering medication. J Clin Endocrinol Metab 2012;97:3956-64.
11. Civeira F, Castillo S, Alonso R et al. Tendon xanthomas in familial hypercholesterolemia are associated with cardiovascular risk independently of the low-density lipoprotein receptor gene mutation. Arterioscler Thromb Vasc Biol 2005;25:1960-5.
12. Sharifi M, Futema M, Nair D et al. Genetic architecture of familial hypercholesterolaemia. Curr Cardiol Rep 2017;19:44.