Familial hypercholesterolemia and its manifestations: Practical considerations for general practitioners

Panagiotis Anagnostis[1], Christina Antza[1*], Matilda Florentin[2*], Vasileios Kotsis[1]

[1]3rd Department of Internal Medicine, Medical School, Aristotle University of Thessaloniki, "Papageorgiou" General Hospital Thessaloniki, Thessaloniki, Greece
[2]Department of Internal Medicine, Faculty of Medicine, University of Ioannina, Ioannina, Greece
*Both authors equally contributed to the study

Correspondence to:
Panagiotis Anagnostis, MD, MSc, PhD, FRSPH,
3rd Department of Internal Medicine,
Medical School, Aristotle University of Thessaloniki,
"Papageorgiou" General Hospital Thessaloniki,
564 29 Thessaloniki, Greece,
phone: +30 2310 257150,
e-mail: pan.anagnostis@gmail.com

DOI: 10.33963/v.kp.97845

Received:
September 9, 2023

Accepted:
October 13, 2023

Early publication date:
October 16, 2023

ABSTRACT

Familial hypercholesterolemia (FH) is the most common genetic disorder of lipid metabolism, affecting almost 1 in 250 individuals worldwide. It is usually inherited via the autosomal dominant way and is characterized by aberrantly high total and low-density lipoprotein cholesterol (LDL-C) concentrations from early childhood, predisposing to increased risk of premature atherosclerotic cardiovascular disease (ASCVD), mostly coronary heart disease (CHD). Despite its high prevalence in the general population and the high ASCVD risk, FH is often underdiagnosed and undertreated. Genetic diagnosis is not always necessary since specific criteria, taking into account the patient's individual and family history, clinical signs, and untreated LDL-C concentrations, may be used for prompt diagnosis. Except for CHD, which may be already evident at diagnosis, leading to increased mortality, other non-CHD morbidities, such as stroke, peripheral artery disease, carotid artery stenosis, and aortic valve calcification may be also present, substantiating the need for prompt intervention. Statins constitute the mainstay of treatment both in adults and children >8 years old. In cases of statin intolerance or not achieving the LDL-C target despite maximally tolerated statin dose, ezetimibe and/or proprotein convertase subtilisin-kexin type 9 inhibitors may be used. The advent of recently approved medications, such as inclisiran and bempedoic acid, either as monotherapy or as add-on therapy to statins, has further enhanced the therapeutic armamentarium that can be used in FH patients. The purpose of this narrative review is to provide practical considerations regarding the diagnostic and therapeutic approach to FH patients.

Key words: atherosclerosis, cardiovascular disease, ezetimibe, familial hypercholesterolemia, statins, xanthomas

INTRODUCTION

Familial hypercholesterolemia (FH) is the most common genetic disorder of lipid metabolism, characterized by very high total (TC) and low-density lipoprotein (LDL) cholesterol (LDL-C) concentrations [1, 2]. This chronic exposure to hypercholesterolemia from early childhood predisposes the individual to increased risk of premature cardiovascular disease (CVD), mainly attributed to coronary heart disease (CHD) (hazard ratio [HR], 10.6; 95% confidence interval [CI], 9.8–11.5) [3]. Moreover, an increased risk of other non-CHD complications, such as peripheral artery disease (PAD), aortic valve calcification (AVC), and non-alcoholic fatty liver disease, has been reported in FH patients [4, 5]. These data necessitate early pharmaceutical intervention, even from childhood, to forestall these complications.

The purpose of this article is to provide a brief overview of FH for the general practitioner, focusing on the epidemiology, clinical manifestations, and therapeutic management of this common clinical entity.

GENETICS, EPIDEMIOLOGY, AND DIAGNOSIS

In the vast majority of cases, FH is usually a monogenic disease inherited by the autosomal dominant way (although the frequency of detectable mutations is 60%–80%) [6], mainly due to loss-of-function mutations in the LDL-receptor (*LDLR*) gene (90% of detectable

cases) or apolipoprotein B (*APOB*) (5%) gene, or gain of function of the proprotein convertase subtilisin/kexin type 9 (*PCSK9*) (<1%) gene [1, 2, 6]. Autosomal recessive mutations in the LDLR adaptor protein (*LDLRAP1*) gene have also been reported [1, 2]. No causative mutations may be identified in ≥20% of cases diagnosed as FH with clinical criteria. In such cases, a polygenic type of inheritance may be suspected, which involves multiple small-effect common variants, which raise plasma LDL-C concentrations [6, 7].

The clinical phenotype and the degree of LDL-C elevation seem to be largely dependent on the genetic background of FH and the residual LDLR activity. In particular, *LDLR* mutations are associated with higher LDL-C concentrations compared to pathogenetic variants of the *APOB* or *PCSK9* genes [8]. Of course, the presence of other cholesterol-affecting factors as well as dietary habits also moderate the magnitude of LDL-C elevation [8].

The estimated prevalence of heterozygous FH (HeFH) is 1:200 to 1:250 individuals worldwide, with LDL-C concentrations ranging between 190 mg/dl (4.9 mmol/l) and 400 mg/dl (10.3 mmol/l). The estimated prevalence of homozygous FH (HoFH) is much lower, ranging from 1:160 000 to 1:300 000 individuals in the general population [1, 2, 6]. According to the European Atherosclerosis Society Familial Hypercholesterolaemia Studies Collaboration, median LDL-C levels in patients with HeFH are 206.3 mg/dl (5.4 mmol/l) (interquartile range [IQR], 163.4–254.6 mg/dl [4.3–6.7 nmol/l]) [9], whereas the respective values in patients with HoFH according to the HoFH International Clinical Collaborators registry are 558.6 mg/dl (14.7 mmol/l) (IQR, 440.8–699.2 mg/dl [11.6–18.4 mmol/l]) [10].

However, what matters most is that FH is often underdiagnosed. According to the European Atherosclerosis Society Familial Hypercholesterolaemia Studies Collaboration, a considerable delay in diagnosis is often observed since the median age at diagnosis is 44.4 (32.5–56.5) years, with 40.2% of patients being <40 years when diagnosed [9]. FH should be highly suspected in cases of LDL-C >190 mg/dl (4.9 mmol/l) in adults and LDL-C >150 mg/dl (3.9 mmol/l) in children [8]. In any case, secondary causes of hypercholesterolemia, such as hypothyroidism, nephrotic syndrome, cholestasis, pregnancy, or medication-induced (i.e., diuretics, β-blockers, corticosteroids), should be initially excluded and treated when feasible [6]. Cascade screening is recommended in adults or cases with 1st degree relative with TC >310 mg/dl (>8 mmol/l) without treatment, premature CHD, or tendon xanthomas [6]. In children, FH diagnosis is established when LDL-C is >160 mg/dl (>4 mmol/l) with a positive family history of high cholesterol or premature CVD. The diagnostic cut-off for a child with a parent carrying a known genetic defect is >130 mg/dl (>3.5 mmol/l) [6].

Genetic diagnosis is not available worldwide. Therefore, FH diagnosis can be based on a combination of criteria, including LDL-C levels, physical signs, individual or family history of hypercholesterolemia, and/or premature atherosclerotic CVD (ASCVD). The most commonly used criteria are the Dutch Lipid Clinic Network (DLCN) criteria, which are in 85% of cases aligned with the genetic diagnosis of the disease [11]. Briefly, these include the presence or absence of one of the following items: (1) positive family history (LDL-C >95th percentile, premature CVD, tendon xanthomas, and/or corneal arcus); (2) individual history of premature CVD; (3) physical examination (tendon xanthomas and/or corneal arcus before the age of 45 years); (4) high LDL-C levels without treatment; (5) DNA analysis. Each item contributes with 1–8 points, yielding a "definite" FH diagnosis when >8 points are present, a "probable" FH diagnosis with 6–8 points, and a "possible" FH diagnosis when the patient is in the range of 3–5 points [6].

Interestingly, lipoprotein (a) (Lp[a]) concentrations, which are independently associated with increased risk of CVD, may also be increased in FH patients, compared to the general population [12]. In particular, the estimated prevalence of Lp(a) >30 mg/dl (>72 nmol/l) or >50 mg/dl (>120 nmol/l) is 29%–40.7% and 22%–29.4% of HeFH patients [13, 14]. Vice versa, patients with Lp(a) concentrations >30 mg/dl are more likely to be diagnosed with definite/probable FH than those with Lp(a) <30 mg/dl (odds ratio [OR], 2.37; 95% CI, 1.78–3.17]) [15]. Increased Lp(a) (>55 mg/dl; >132 nmol/l) independently augments ASCVD in FH patients [14].

CLINICAL MANIFESTATIONS

Signs

During physical examination of a patient with a possible or confirmed FH diagnosis, the clinician should search for the accumulation of cholesterol in different body parts. Even in apparently healthy individuals, physical examination can lead to the suspicion and/or diagnosis of FH.

During skin examination, the most common findings are xanthomas (tendon or tuberous) and xanthelasmas [16]. Tendon xanthomas are nodules, commonly observed subcutaneously in the Achilles tendon or hands, elbows and knees (Figures 1 and 2). In subjects with HoFH, tendon xanthomas are present earlier in life while in HeFH, these usually appear during adulthood [16]. Their prevalence ranges from 5% to 20%, which underscores the importance of clinical examination in these patients [17–19]. As thickening can be observed in the Achilles tendon, ultrasound examination (>5.8 mm for males, >5.5 mm for females) could be useful to confirm a suspicious palpation [20]. Xanthelasmas are cutaneous yellow, slightly uplifted signs, usually evident on the upper inner part of the eyelid. Their prevalence (5%–9%) is less than that reported for xanthomas [18, 21].

Regarding eye examination, a corneal arcus may be found, which is characterized by a differently colored (usually gray) ring around the cornea. FH registries have reported a prevalence of up to 33%. When it is observed in patients <45 years old, further investigation is needed [21, 22].

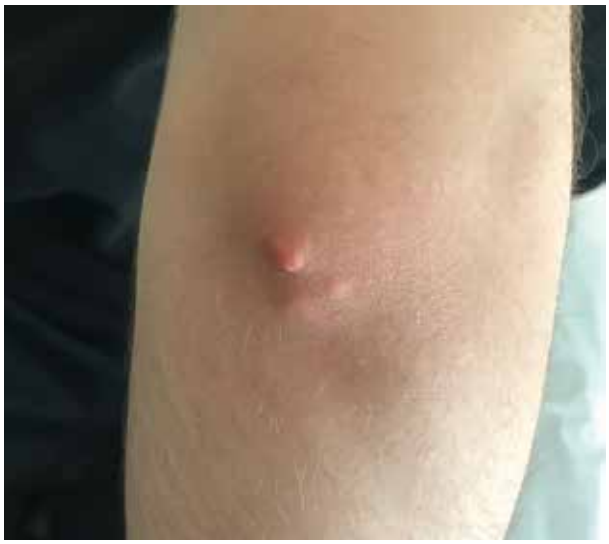

Figure 1. Tendon xanthoma of the elbow in a patient with familial hypercholesterolemia

Figure 2. Achilles tendon xanthoma in a patient with familial hypercholesterolemia

Long-term complications

Patients, with either HoFH or HeFH are generally free of symptoms until atherosclerotis develops and one or more of the following clinical manifestations are present [4]:

Coronary heart disease, atrial fibrillation, and heart failure

Globally, CHD is the most common type of atherosclerotic CVD, involving about 17% of FH adults, with premature cases present also at high rates (11.3%). This prevalence may be even higher (i.e., 23%) in the Japanese population, as reported in the Familial Hypercholesterolemia Expert Forum (FAME) Study [23]. In particular, the adjusted HR for CHD in patients with LDL-C >190 mg/dl (>4.9 mmol/l) compared to individuals with LDL-C <130 mg/dl (3.4 mmol/l) is 5.1 (95% CI, 1.1–21.7) and 3.1 (95% CI, 1.8–5.5) for the age range of 20–29 and 30–39, respectively [24].

Except for untreated high LDL-C levels, aging and male sex are also independent risk factors for CHD in FH patients [25]. As CHD mortality is high in FH patients (even in those treated with statins), early detection of CHD is of major importance. Therefore, detailed clinical history and clinical examination are mandatory. Electrocardiography (in rest and exercise), as well as echocardiography, have to be performed and, in cases of a high possibility of CHD, patients should be referred to a specialized cardiology center [26]. The need for early clinical diagnosis has become more compelling, as recent data also indicate a 2-fold higher risk of hospitalization for atrial fibrillation or heart failure in the FH population than in the general population [27].

Stroke

Stroke may also be a clinical manifestation of FH. Globally, its prevalence in the FH population is reported to be 2.1% [25] while a recently published cohort study showed that the risk of stroke/transient ischemic attack is almost 7-fold higher than in the age- and sex-matched general population [3]. If clinical symptoms occur, brain computed tomography (CT) and referral to a stroke physician are needed.

Peripheral artery disease (PAD)

A recently published meta-analysis, evaluating data from more than 170 000 HeFH patients, showed that the risk of PAD in this population is almost 3.5-fold higher than in healthy individuals [28]. Hence, clinical evaluation of FH patients should include questions to assess possible weakness or pain after walking and physical examination to detect coldness in the lower leg or lack of arterial pulses. If any of these are observed, the ankle-brachial index measurement and ultrasound of the arteries of the lower extremities have to be performed [26, 29]. As the probability and severity of PAD increase with age, more caution has to be taken in the elderly population [30].

Carotid artery stenosis (CAS)

FH patients appear to be at high risk of CAS. In a recently published prospective cohort study, CAS was detected in 32% of the FH population with ultrasound [31]. In the general population, the global prevalence of CAS is lower (1.5%; 95% CI, 1.1–2.1), reaching up to 6.9% (95% CI, 5.2–9.3) in males aged 75–79 years old [32]. In patients experiencing a myocardial infarction episode, carotid intima-media thickness was also higher in the HeFH population compared to those with mixed hyperlipidemia [33]. Thus, a careful physical examination to exclude the presence of a bruit in the carotid artery is of major importance. In the case of positive signs, carotid echocardiography may be considered before referring the patient to magnetic resonance or CT angiography [26]. If there are no clinical

signs, further parameters have to be examined when considering referring the patient for ultrasound. For example, women, as well as individuals with monogenic FH type, are at higher ASCVD risk compared to men and polygenic FH type, respectively [34, 35].

Calcium deposition

The development of aortic valve calcification (AVC) is quite common in the FH population due to the increased LDL-C levels. In particular, the reported prevalence of AVC in HoFH patients may reach up to 100%, whereas it varies between 3% and 61% in those with HeFH [36–38]. Therefore the coronary artery calcium score should be measured and referral to a cardiologist for echocardiographic assessment — especially in homozygous cases — is imperative, and, in the case of pathological findings, further management/follow-up is recommended [26, 39]. In patients with confirmed AVC, Lp(a) should also be measured since high levels (>50 mg/dl; 120 mmol/l) may further increase the AVC and ASCVD risk in FH patients [4, 40].

Aortic disease

In general, a positive association between FH and aortic disease (defined either as aortic stenosis or aortic aneurysm) has been described in the literature. However, studies are limited, are of small sample size, and could not confirm causality [41]. The strongest determinants of this association seem to be aging and higher values of recorded blood pressure [41, 42]. Therefore, guidelines recommend X-ray and abdominal ultrasound, especially in elderly FH patients, in this regard [26].

Renal artery disease and chronic kidney disease

Regarding the association between FH and renal artery or chronic kidney disease, a positive correlation has been shown although data are again limited, mainly emerging from studies with small sample sizes [4, 41]. Therefore, there is no evidence to support further evaluation of this aspect in the FH population unless other symptoms or risk factors co-exist. However, taking into account the cost-effectiveness of the estimated glomerular filtration rate (eGFR) calculation, this could be used during follow-up visits of FH patients, especially in the elderly.

THERAPEUTIC MANAGEMENT

Dietary and lifestyle measures should be addressed in all FH patients, but most frequently multidrug treatment will be required to achieve the therapeutic targets of LDL-C. These measures include not only a hypolipidemic diet and regular exercise but also counseling on the importance of not smoking or vaping and maintaining healthy body weight. Of course, cardiovascular risk factors and comorbidities (e.g. hypertension, diabetes mellitus [DM]) should be treated accordingly.

Statins

Statin therapy is the initial pharmaceutical approach to the management of hypercholesterolemia in FH patients. Indeed, current guidelines recommend treatment with the maximally tolerated dose of a high-potency statin [6]. However, the recommended LDL-C levels (i.e., <70 mg/dl [1.8 mmol/l] and <55 mg/dl [1.4 mmol/l]) in FH patients without and with established ASCVD, respectively, are commonly not attained with statin monotherapy.

The most fundamental mechanism of statin action is the increased hepatic expression of LDLR. Therefore, homozygous FH patients with null mutations on the *LDLR* gene are not expected to respond to statin therapy. However, they do respond to statins, but to a lesser extent compared to (double) heterozygous FH patients, as statins appear to exert alternative mechanisms of action, such as very low-density lipoprotein (VLDL) and subsequently LDL synthesis reduction [43]. Specifically, a reduction in LDL-C by approximately 20% has been demonstrated in such patients [44].

Based on current guidelines, children with FH should start statin therapy from the age of 8–10 years, initially with low doses and subsequently with higher doses aiming to reach the recommended LDL-C levels [6]. Statins have proven safety and efficacy in children [45] while evidence suggests a reduced risk of CVD in adulthood in statin-treated FH children [46, 47]. Overall, statins are very safe and are currently used by millions of patients. True statin intolerance, due to transaminase or creatine kinase (CK) elevation and/or myalgias, is not frequent [48], and, usually, patients can tolerate at least a low dose of one or more statins even on alternate days [49]. Before the initiation of a statin, it is prudent to measure baseline transaminase and CK levels; therapy should be withheld in patients with transaminase >3 times the upper limit normal (ULN) or CK >5 ULN. Regarding an increased risk of new-onset DM, this is, indeed, a consistent, dose-related effect of (mainly potent) statin treatment [50]; however, absolute cardiovascular risk reduction in high-risk patients clearly outweighs this small increase in the incidence of DM [51].

Ezetimibe

Ezetimibe is the second agent that is used in addition to statins in FH patients if the LDL-C therapeutic goal is not achieved. This drug inhibits the intestinal uptake of dietary and biliary cholesterol, thus reducing the amount of cholesterol that is delivered to the liver. Consequently, hepatic LDLR expression is upregulated, leading to increased clearance of LDL from the circulation. Importantly, absorption of fat-soluble nutrients is not affected by the administration of ezetimibe. When added to ongoing statin therapy, ezetimibe further reduces LDL-C levels by approximately 21%–27% [52] although its LDL-C lowering capacity is smaller than monotherapy. The complementary

mechanisms of action of these drugs probably explain why they work in synergy.

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors

About 8 years ago, a game changer in the pharmacological management of lipid disorders, a family of PCSK9 inhibitors, was added to our therapeutic armamentarium. The monoclonal antibodies alirocumab and evolocumab have been consistently shown to induce robust reductions in LDL-C levels by simultaneously achieving a significant decrease in cardiovascular events [53, 54]. FH patients who have very high baseline cholesterol levels very often require these agents to reach their LDL-C target levels as they do not attain them with the combination of statin with ezetimibe.

More recently another PCSK9 inhibitor, inclisiran, which is a small interfering RNA, was also approved for HeFH patients and for patients with established ASCVD who do not attain their LDL-C treatment targets with maximally tolerated statin with or without ezetimibe. Specifically, inclisiran was approved by the European Medicines Agency (EMA) in December 2020 and by the Food and Drug Administration (FDA) in December 2021 [55, 56]. This agent has been found to effectively lower LDL-C levels and has a favorable safety profile [57, 58], and a recent analysis of major inclisiran clinical trials suggests potential benefits for a reduction in major adverse cardiovascular events [59].

Bempedoic acid

Quite recently, a novel agent that also impedes cholesterol biosynthesis in the liver, bempedoic acid, was approved for the treatment of hypercholesterolemia. This agent inhibits adenosine triphosphate-citrate lyase, i.e., it acts at an earlier level in the cascade of cholesterol biosynthesis compared to statins [58, 60]. It is a prodrug for oral administration with intracellular activation, mainly in the liver and, to a lesser extent, kidney cells, and it is absent from the adipose tissue and muscle cells. Therefore, it lacks the muscle-related side effects of statins [60]. It has been recently approved by both the FDA and the EMA as a lipid-lowering drug in combination with diet, statins, or other hypolipidemic drugs in patients with hypercholesterolemia (including FH subjects), mixed dyslipidemia, statin intolerance, or contraindication to statins.

Overall, we should aim to achieve each patient's LDL-C treatment target with any of these available agents or their combinations, beginning with statins with or without ezetimibe and adding PCSK9 inhibitors accordingly. In very high-risk patients, i.e. those with a second ASCVD event within 2 years, a treatment goal of LDL-C <40 mg/dl may be considered [6].

Pharmaceutical options for Lp(a) lowering

As previously mentioned, FH patients frequently have increased Lp(a) levels; this population has an even greater risk of ASCVD. Phase II studies with antisense oligonucleotides and small interfering RNAs targeting apolipoprotein (a) have demonstrated remarkable reductions in Lp(a) levels of up to 80% [61, 62]. Currently, phase III studies with cardiovascular outcomes are ongoing, and their results are eagerly awaited.

Therapeutic options for patients with HoFH

LDL apheresis

LDL-C apheresis should be considered in all patients with HoFH with LDL-C >300 mg/dl (7.76 mmol/l) and started as soon as possible, ideally at the age of 3 and not later than 8 years, depending on appropriate venous access [63]. Limitations of this treatment include variable access, high cost, and a time-consuming procedure affecting patients' quality of life, while LDL-C levels acutely decrease and then rebound following apheresis [63].

Lomitapide

Lomitapide is an inhibitor of microsomal triglyceride transfer protein (MTP), an enzyme responsible for the synthesis of VLDL in the liver and chylomicrons in the intestine. This agent has been approved by the FDA and the EMA for the treatment of hypercholesterolemia in adult patients with HoFH. Lomitapide reduces LDL-C levels by around 40% in these patients on top of statin treatment with or without LDL apheresis. It has an acceptable safety and tolerance profile, with gastrointestinal symptoms being the most frequent adverse events, which, however, decrease in the long term [58.64]. Notably, an increase in liver fat may occur with lomitapide therapy; therefore, screening for liver steatosis, steatohepatitis, and fibrosis should take place before treatment initiation [58, 64].

Angiopoietin-like protein 3 (ANGPTL3) inhibitors

The ANGPTLs are a family of proteins consisting of members 1–8 of the angiopoietins. ANGPTL3, ANGPTL4, and ANGPTL8 are essential for the metabolism of triglyceride-rich lipoproteins, i.e., chylomicrons and VLDL, as they inhibit the activity of lipoprotein lipase (LPL) [65]. ANGPTL3 also reduces the activity of endothelial lipase that hydrolyzes the phospholipids of high-density lipoproteins [66]. The inhibition of ANGPTL3 is a novel therapeutic option to reduce both LDL-C and triglycerides. Evinacumab, a fully monoclonal human antibody, has been shown to induce reductions of >50% in LDL-C with a favorable safety profile [58, 67] and was approved by the FDA and the EMA in 2021 for the treatment of patients ≥12 years with HoFH [68]. Studies with small interfering RNAs targeting ANGPTL3 are also underway.

These treatments are usually provided by specialized centers for FH with experience in their use.

The LDL-C lowering capacity of these treatment options is summarized in Table 1.

Table 1. Low-density lipoprotein cholesterol-lowering capacity of currently available lipid-lowering agents and drugs under development

Drug Class		Compound	LDL-C reduction
Statins	Low potency	Lovastatin (20–40 mg)	24%–27%
		Pravastatin (10–40 mg)	20%–29%
		Pitavastatin (1–4 mg)	33%–46%
		Fluvastatin (80 mg)	33%
		Simvastatin (10–80 mg)	28%–47%
	High potency	Rosuvastatin (5–40 mg)	45%–63%
		Atorvastatin (10–80 mg)	37%–50%
Intestinal Cholesterol Absorption Inhibitor		Ezetimibe	18%–20% as monotherapy +21%–27% of statin-achieved reduction
PCSK9 inhibitors Monoclonal antibodies		Evolocumab Alirocumab	55%–75% 46%–63%
siRNAs		Inclisiran	40%–51%
ACL blocker		Bempedoic Acid	22%
MTP Inhibitor		Lomitapide	40%
ANGPTL3 inhibitors		Evinacumab	47%
ASO against apolipoprotein (a)		Pelacarsen	35%–80% reduction in Lp(a)

Abbreviations: ACL, adenosine triphosphate-citrate lyase; ANGPTL3, angiopoietin like protein 3; ASO, antisense oligonucleotide; LDL-C, low density lipoprotein cholesterol; Lp(a), lipoprotein (a); MTP, microsomal triglyceride transfer protein; PCSK9, proprotein convertase subtilisin/kexin type 9; siRNA, small interfering RNA

CONCLUSIONS: PRACTICAL CONSIDERATIONS

FH is the most common genetic disorder which, however, is underrecognized and undertreated worldwide. FH patients are at increased risk of premature ASCVD; therefore, timely treatment initiation is of major importance. Physicians should always suspect FH in patients with very high LDL-C levels. In such cases, careful taking of a family history and physical examination are often sufficient for diagnosis. In less clear cases, genetic testing may be required. Cascade screening is very important to detect as many individuals with FH as possible and treat them accordingly. Potent statins, usually combined with ezetimibe, are the cornerstone of treatment. PCSK9 inhibitors are also frequently required to achieve therapeutic targets. HoFH patients should be referred to specialized lipid centers for treatment and follow-up.

Article information

Conflict of interest: None declared.

Funding: None.

REFERENCES

1. 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(45): 3478–90a, doi: 10.1093/eurheartj/eht273, indexed in Pubmed: 23956253.
2. Wilemon K, Patel J, Aguilar-Salinas C, et al. Reducing the clinical and public health burden of familial hypercholesterolemia. JAMA Cardiology. 2020; 5(2): 217, doi: 10.1001/jamacardio.2019.5173.
3. Iyen B, Qureshi N, Kai J, et al. Risk of cardiovascular disease outcomes in primary care subjects with familial hypercholesterolaemia: A cohort study. Atherosclerosis. 2019; 287: 8–15, doi: 10.1016/j.atherosclerosis.2019.05.017, indexed in Pubmed: 31181417.
4. Anagnostis P, Vaitsi K, Mintziori G, et al. Non-coronary atherosclerotic cardiovascular disease in patients with familial hypercholesterolaemia. Curr Med Res Opin. 2020; 36(5): 731–740, doi: 10.1080/03007995.2020.1734783, indexed in Pubmed: 32096673.
5. Anagnostis P, Rizos CV, Skoumas I, et al. Prevalence of non-coronary heart disease in patients with familial hypercholesterolemia: an analysis from the HELLAS-FH. Curr Pharm Des. 2021; 27(21): 2537–2544, doi: 10.2174/1381612827666210216151645, indexed in Pubmed: 33593250.
6. Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J. 2020; 41(1): 111–188, doi: 10.1093/eurheartj/ehz455, indexed in Pubmed: 31504418.
7. Talmud PJ, Shah S, Whittall R, et al. Use of low-density lipoprotein cholesterol gene score to distinguish patients with polygenic and monogenic familial hypercholesterolaemia: a case-control study. Lancet. 2013; 381(9874): 1293–1301, doi: 10.1016/S0140-6736(12)62127-8, indexed in Pubmed: 23433573.
8. Lui DTW, Lee ACH, Tan KCB. Management of familial hypercholesterolemia: current status and future perspectives. J Endocr Soc. 2021; 5(1): bvaa122, doi: 10.1210/jendso/bvaa122, indexed in Pubmed: 33928199.
9. EAS Familial Hypercholesterolaemia Studies Collaboration (FHSC). Global perspective of familial hypercholesterolaemia: a cross-sectional study from the EAS Familial Hypercholesterolaemia Studies Collaboration (FHSC). Lancet. 2021; 398(10312): 1713–1725, doi: 10.1016/S0140-6736(21)01122-3, indexed in Pubmed: 34506743.
10. Tromp TR, Hartgers ML, Hovingh GK, et al. Worldwide experience of homozygous familial hypercholesterolaemia: retrospective cohort study. Lancet. 2022; 399(10326): 719–728, doi: 10.1016/S0140-6736(21)02001-8, indexed in Pubmed: 35101175.
11. Civeira F, Ros E, Jarauta E, et al. Femoral atherosclerosis in heterozygous familial hypercholesterolemia: influence of the genetic defect. Arterioscler Thromb Vasc Biol. 2008; 28(3): 580–586, doi: 10.1161/ATVBAHA.107.153841, indexed in Pubmed: 18096825.
12. Anagnostis P, Siolos P, Krikidis D, et al. Should we consider lipoprotein (a) in cardiovascular disease risk assessment in patients with familial hypercholesterolaemia? Curr Pharm Des. 2018; 24(31): 3665–3671, doi: 10.2174/1381612824666181010150958, indexed in Pubmed: 30317988.
13. Alonso R, Andres E, Mata N, et al. Lipoprotein(a) levels in familial hypercholesterolemia: an important predictor of cardiovascular disease independent of the type of LDL receptor mutation. J Am Coll Cardiol.

2014; 63(19): 1982–1989, doi: 10.1016/j.jacc.2014.01.063, indexed in Pubmed: 24632281.
14. Anagnostis P, Rizos CV, Skoumas I, et al. Achieving low-density lipoprotein cholesterol targets as assessed by different methods in patients with familial hypercholesterolemia: an analysis from the HELLAS-FH registry. Lipids Health Dis. 2020; 19(1): 114–330, doi: 10.1186/s12944-020-01289-5, indexed in Pubmed: 32466791.
15. Rizos CV, Athyros V, Bilianou E, et al. An insight into familial hypercholesterolemia in Greece: rationale and design of the Hellenic Familial Hypercholesterolemia Registry (HELLAS-FH). Hormones (Athens). 2017; 16(3): 306–312, doi: 10.1007/BF03401525, indexed in Pubmed: 30091117.
16. Rallidis LS, Iordanidis D, Iliodromitis E. The value of physical signs in identifying patients with familial hypercholesterolemia in the era of genetic testing. J Cardiol. 2020; 76(6): 568–572, doi: 10.1016/j.jjcc.2020.07.005, indexed in Pubmed: 32741655.
17. Rizos CV, Elisaf MS, Skoumas I, et al. Characteristics and management of 1093 patients with clinical diagnosis of familial hypercholesterolemia in Greece: Data from the Hellenic Familial Hypercholesterolemia Registry (HELLAS-FH). Atherosclerosis. 2018; 277: 308–313, doi: 10.1016/j.atherosclerosis.2018.08.017, indexed in Pubmed: 30270064.
18. Mata N, Alonso R, Badimón L, et al. Clinical characteristics and evaluation of ldl-cholesterol treatment of the spanish familial hypercholesterolemia longitudinal cohort study (SAFEHEART). Lipids Health Dis. 2011; 10: 94, doi: 10.1186/1476-511X-10-94, indexed in Pubmed: 21663647.
19. deGoma EM, Ahmad ZS, O'Brien EC, 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(3): 240–249, doi: 10.1161/CIRCGENETICS.116.001381, indexed in Pubmed: 27013694.
20. Michikura M, Ogura M, Yamamoto M, et al. Achilles tendon ultrasonography for diagnosis of familial hypercholesterolemia among Japanese subjects. Circ J. 2017; 81(12): 1879–1885, doi: 10.1253/circj.CJ-17-0041, indexed in Pubmed: 28652530.
21. Bujo H, Takahashi K, Saito Y, et al. Clinical features of familial hypercholesterolemia in Japan in a database from 1996-1998 by the research committee of the ministry of health, labour and welfare of Japan. J Atheroscler Thromb. 2004; 11(3): 146–151, doi: 10.5551/jat.11.146, indexed in Pubmed: 15256765.
22. Perez de Isla L, Alonso R, Watts GF, et al. Attainment of LDL-Cholesterol Treatment Goals in Patients With Familial Hypercholesterolemia: 5-Year SAFEHEART Registry Follow-Up. J Am Coll Cardiol. 2016; 67(11): 1278–1285, doi: 10.1016/j.jacc.2016.01.008, indexed in Pubmed: 26988947.
23. Yamashita S, Masuda D, Harada-Shiba M, et al. Effectiveness and safety of lipid-lowering drug treatments in Japanese patients with familial hypercholesterolemia: Familial Hypercholesterolemia Expert Forum (FAME) study. J Atheroscler Thromb. 2022; 29(5): 608–638, doi: 10.5551/jat.62764, indexed in Pubmed: 33980760.
24. Perak AM, Ning H, de Ferranti SD, et al. Long-Term risk of atherosclerotic cardiovascular disease in US adults with the familial hypercholesterolemia phenotype. Circulation. 2016; 134(1): 9–19, doi: 10.1161/CIRCULATIONAHA.116.022335, indexed in Pubmed: 27358432.
25. EAS Familial Hypercholesterolaemia Studies Collaboration (FHSC). Global perspective of familial hypercholesterolaemia: a cross-sectional study from the EAS Familial Hypercholesterolaemia Studies Collaboration (FHSC). Lancet. 2021; 398(10312): 1713–1725, doi: 10.1016/S0140-6736(21)01122-3, indexed in Pubmed: 34506743.
26. Harada-Shiba M, Arai H, Ohmura H, et al. Guidelines for the diagnosis and treatment of adult familial hypercholesterolemia 2022. J Atheroscler Thromb. 2023; 30(5): 558–586, doi: 10.5551/jat.CR005, indexed in Pubmed: 36682773.
27. Hovland A, Mundal LJ, Igland J, et al. Increased risk of heart failure and atrial fibrillation in heterozygous familial hypercholesterolemia. Atherosclerosis. 2017; 266: 69–73, doi: 10.1016/j.atherosclerosis.2017.09.027, indexed in Pubmed: 28992466.
28. Akioyamen LE, Tu JV, Genest J, et al. Risk of ischemic stroke and peripheral arterial disease in heterozygous familial hypercholesterolemia: a meta-analysis. Angiology. 2019; 70(8): 726–736, doi: 10.1177/0003319719835433, indexed in Pubmed: 30871330.
29. Aboyans V, Ricco JB, Bartelink MEL, et al. 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS): Document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteriesEndorsed by: the European Stroke Organization (ESO)The Task Force for the Diagnosis and Treatment of Peripheral Arterial Diseases of the European Society of Cardiology (ESC) and of the European Society for Vascular Surgery (ESVS). Eur Heart J. 2018; 39(9): 763–816, doi: 10.1093/eurheartj/ehx095, indexed in Pubmed: 28886620.
30. Austin MA, Hutter CM, Zimmern RL, et al. Familial hypercholesterolemia and coronary heart disease: a HuGE association review. Am J Epidemiol. 2004; 160(5): 421–429, doi: 10.1093/aje/kwh237, indexed in Pubmed: 15321838.
31. Bea AM, Civeira F, Jarauta E, et al. Association between the presence of carotid artery plaque and cardiovascular events in patients with genetic hypercholesterolemia. Rev Esp Cardiol (Engl Ed). 2017; 70(7): 551–558, doi: 10.1016/j.rec.2017.01.023, indexed in Pubmed: 28215923.
32. Song P, Fang Z, Wang H, et al. Global and regional prevalence, burden, and risk factors for carotid atherosclerosis: a systematic review, meta-analysis, and modelling study. Lancet Glob Health. 2020; 8(5): e721–e729, doi: 10.1016/S2214-109X(20)30117-0, indexed in Pubmed: 32353319.
33. Rallidis LS, Kosmas N, Tsirebolos G, et al. Prevalence of heterozygous familial hypercholesterolemia and combined hyperlipidemia phenotype in very young survivors of myocardial infarction and their association with the severity of atheromatous burden. J Clin Lipidol. 2019; 13(3): 502–508, doi: 10.1016/j.jacl.2019.02.007, indexed in Pubmed: 30956097.
34. Sharifi M, Higginson E, Bos S, et al. Greater preclinical atherosclerosis in treated monogenic familial hypercholesterolemia vs. polygenic hypercholesterolemia. Atherosclerosis. 2017; 263: 405–411, doi: 10.1016/j.atherosclerosis.2017.05.015, indexed in Pubmed: 28549500.
35. Tada H, Kawashiri MA, Okada H, et al. Assessments of carotid artery plaque burden in patients with familial hypercholesterolemia. Am J Cardiol. 2017; 120(11): 1955–1960, doi: 10.1016/j.amjcard.2017.08.012, indexed in Pubmed: 28947310.
36. Duell PB, Gidding SS, Andersen RL, et al. Longitudinal low density lipoprotein cholesterol goal achievement and cardiovascular outcomes among adult patients with familial hypercholesterolemia: The CASCADE FH registry. Atherosclerosis. 2019; 289: 85–93, doi: 10.1016/j.atherosclerosis.2019.08.007, indexed in Pubmed: 31487564.
37. Fahed AC, Shibbani K, Andary RR, et al. Premature valvular heart disease in homozygous familial hypercholesterolemia. Cholesterol. 2017; 2017: 3685265, doi: 10.1155/2017/3685265, indexed in Pubmed: 28761763.
38. Smith JG, Luk K, Schulz CA, et al. Association of low-density lipoprotein cholesterol-related genetic variants with aortic valve calcium and incident aortic stenosis. JAMA. 2014; 312(17): 1764–1771, doi: 10.1001/jama.2014.13959, indexed in Pubmed: 25344734.
39. Cuchel M, Raal FJ, Hegele RA, et al. 2023 Update on European Atherosclerosis Society Consensus Statement on Homozygous Familial Hypercholesterolaemia: new treatments and clinical guidance. Eur Heart J. 2023; 44(25): 2277–2291, doi: 10.1093/eurheartj/ehad197, indexed in Pubmed: 37130090.
40. Cegla J, Neely RD, France M, et al. HEART UK consensus statement on Lipoprotein(a): A call to action. Atherosclerosis. 2019; 291: 62–70, doi: 10.1016/j.atherosclerosis.2019.10.011, indexed in Pubmed: 31704552.
41. Yagi K, Hifumi S, Nohara A, et al. Difference in the risk factors for coronary, renal and other peripheral arteriosclerosis in heterozygous familial hypercholesterolemia. Circ J. 2004; 68(7): 623–627, doi: 10.1253/circj.68.623, indexed in Pubmed: 15226625.
42. Kita Y, Shimizu M, Sugihara N, et al. Abdominal aortic aneurysms in familial hypercholesterolemia--case reports. Angiology. 1993; 44(6): 491–499, doi: 10.1177/000331979304400610, indexed in Pubmed: 8503516.
43. Raal FJ, Pappu AS, Illingworth DR, et al. Inhibition of cholesterol synthesis by atorvastatin in homozygous familial hypercholesterolaemia. Atherosclerosis. 2000; 150(2): 421–428, doi: 10.1016/s0021-9150(99)00435-9, indexed in Pubmed: 10856535.
44. Stein EA, Dann EJ, Wiegman A, et al. Efficacy of rosuvastatin in children with homozygous familial hypercholesterolemia and association with underlying genetic mutations. J Am Coll Cardiol. 2017; 70(9): 1162–1170, doi: 10.1016/j.jacc.2017.06.058, indexed in Pubmed: 28838366.
45. Anagnostis P, Vaitsi K, Kleitsioti P, et al. Efficacy and safety of statin use in children and adolescents with familial hypercholesterolaemia: a system-

atic review and meta-analysis of randomized-controlled trials. Endocrine. 2020; 69(2): 249–261, doi: 10.1007/s12020-020-02302-8, indexed in Pubmed: 32333266.
46. Luirink IK, Wiegman A, Kusters DM, et al. 20-Year follow-up of statins in children with familial hypercholesterolemia. N Engl J Med. 2019; 381(16): 1547–1556, doi: 10.1056/NEJMoa1816454, indexed in Pubmed: 31618540.
47. Kusters DM, Braamskamp MJ, Langslet G, et al. Effect of rosuvastatin on carotid intima-media thickness in children with heterozygous familial hypercholesterolemia: the CHARON study (Hypercholesterolemia in Children and Adolescents Taking Rosuvastatin Open Label). Circulation. 2017; 136(4): 359–366, doi: 10.1161/CIRCULATIONAHA.116.025158, indexed in Pubmed: 28592434.
48. Naci H, Brugts J, Ades T. Comparative tolerability and harms of individual statins: a study-level network meta-analysis of 246 955 participants from 135 randomized, controlled trials. Circ Cardiovasc Qual Outcomes. 2013; 6(4): 390–399, doi: 10.1161/CIRCOUTCOMES.111.000071, indexed in Pubmed: 23838105.
49. Keating AJ, Campbell KB, Guyton JR. Intermittent nondaily dosing strategies in patients with previous statin-induced myopathy. Ann Pharmacother. 2013; 47(3): 398–404, doi: 10.1345/aph.1R509, indexed in Pubmed: 23482733.
50. Mach F, Ray KK, Wiklund O, et al. Adverse effects of statin therapy: perception vs. the evidence: focus on glucose homeostasis, cognitive, renal and hepatic function, haemorrhagic stroke and cataract. Eur Heart J. 2018; 39(27): 2526–2539, doi: 10.1093/eurheartj/ehy182, indexed in Pubmed: 29718253.
51. Collins R, Reith C, Emberson J, et al. Interpretation of the evidence for the efficacy and safety of statin therapy. Lancet. 2016; 388(10059): 2532–2561, doi: 10.1016/S0140-6736(16)31357-5, indexed in Pubmed: 27616593.
52. Morrone D, Weintraub WS, Toth PP, et al. Lipid-altering efficacy of ezetimibe plus statin and statin monotherapy and identification of factors associated with treatment response: a pooled analysis of over 21,000 subjects from 27 clinical trials. Atherosclerosis. 2012; 223(2): 251–261, doi: 10.1016/j.atherosclerosis.2012.02.016, indexed in Pubmed: 22410123.
53. Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. N Engl J Med. 2017; 376(18): 1713–1722, doi: 10.1056/NEJMoa1615664, indexed in Pubmed: 28304224.
54. Schwartz GG, Steg PG, Szarek M, et al. Alirocumab and cardiovascular outcomes after acute coronary syndrome. N Engl J Med. 2018; 379(22): 2097–2107, doi: 10.1056/NEJMoa1801174, indexed in Pubmed: 30403574.
55. https://www.fda.gov/drugs/news-events-human-drugs/fda-approves-add-therapy-lower-cholesterol-among-certain-high-risk-adults [accessed: September 1, 2023].
56. https://www.ema.europa.eu/en/medicines/human/EPAR/leqvio [assessed: September 1, 2023].
57. Ray KK, Troquay RPT, Visseren FLJ, et al. Long-term efficacy and safety of inclisiran in patients with high cardiovascular risk and elevated LDL cholesterol (ORION-3): results from the 4-year open-label extension of the ORION-1 trial. Lancet Diabetes Endocrinol. 2023; 11(2): 109–119, doi: 10.1016/S2213-8587(22)00353-9, indexed in Pubmed: 36620965.
58. Atar D, Langslet G, Tonstad S. Do we need new lipid-lowering agents in the era of PCSK9 inhibitors? Recent advances. Kardiol Pol. 2022; 80(7–8): 741–749, doi: 10.33963/KP.a2022.0117, indexed in Pubmed: 35521719.
59. Ray KK, Raal FJ, Kallend DG, et al. Inclisiran and cardiovascular events: a patient-level analysis of phase III trials. Eur Heart J. 2023; 44(2): 129–138, doi: 10.1093/eurheartj/ehac594, indexed in Pubmed: 36331326.
60. Agarwala A, Goldberg AC. Bempedoic acid: a promising novel agent for LDL-C lowering. Future Cardiol. 2020; 16(5): 361–371, doi: 10.2217/fca-2020-0016, indexed in Pubmed: 32463301.
61. O'Donoghue ML, Rosenson RS, Gencer B, et al. Small Interfering RNA to Reduce Lipoprotein(a) in Cardiovascular Disease. N Engl J Med. 2022; 387(20): 1855–1864, doi: 10.1056/NEJMoa2211023, indexed in Pubmed: 36342163.
62. Tsimikas S, Karwatowska-Prokopczuk E, Xia S, et al. Lipoprotein(a) reduction in persons with cardiovascular disease. N Engl J Med. 2020; 382(3): 244–255, doi: 10.1056/NEJMoa1905239, indexed in Pubmed: 31893580.
63. Cuchel M, Raal FJ, Hegele RA, et al. 2023 Update on European Atherosclerosis Society Consensus Statement on Homozygous Familial Hypercholesterolaemia: new treatments and clinical guidance. Eur Heart J. 2023; 44(25): 2277–2291, doi: 10.1093/eurheartj/ehad197, indexed in Pubmed: 37130090.
64. Alonso R, Cuevas A, Mata P. Lomitapide: a review of its clinical use, efficacy, and tolerability. Core Evid. 2019; 14: 19–30, doi: 10.2147/CE.S174169, indexed in Pubmed: 31308834.
65. Dijk W, Kersten S. Regulation of lipid metabolism by angiopoietin-like proteins. Curr Opin Lipidol. 2016; 27(3): 249–256, doi: 10.1097/MOL.0000000000000290, indexed in Pubmed: 27023631.
66. Khetarpal SA, Vitali C, Levin MG, et al. Endothelial lipase mediates efficient lipolysis of triglyceride-rich lipoproteins. PLoS Genet. 2021; 17(9): e1009802, doi: 10.1371/journal.pgen.1009802, indexed in Pubmed: 34543263.
67. Rosenson RS, Burgess LJ, Ebenbichler CF, et al. Evinacumab in patients with refractory hypercholesterolemia. N Engl J Med. 2020; 383(24): 2307–2319, doi: 10.1056/NEJMoa2031049, indexed in Pubmed: 33196153.
68. Evkeeza. Available at https://www.ema.europa.eu/en/medicines/human/EPAR/evkeeza [accessed: September 1, 2023].