The Inherited Hypercholesterolemias

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KEYWORDS

• Inherited hypercholesterolemia • Familial hypercholesterolemia
• Polygenic hypercholesterolemia • Lipoprotein(a) • Familial combined hyperlipidemia

KEY POINTS

- Hypercholesterolemia is greatly influenced by genetic factors.
- Hypercholesterolemic conditions are also dependent on gene–environment interactions.
- Familial hypercholesterolemia (FH) has a high prevalence, is easily diagnosed, and is a treatable and preventable cause of premature atherosclerotic cardiovascular disease (ASCVD). Heterozygous FH is present in 1 in 250 people in the general population.
- FH-mimics include conditions causing high LDL-C (polygenic hypercholesterolemia [PH], familial combined hyperlipidemia [FCH], extreme hyper-lipoprotein(a) levels [hyper-Lp(a)], medications, hypothyroidism) and conditions causing xanthomas (sitosterolemia, cerebrotendinous xanthomatosis (CTX)).
- Hyper-Lp(a) is common, affecting 20% of the population, and under potent genetic control. At markedly elevated plasma levels (5%–10% of the population), it is likely *the* major monogenic risk factor for ASCVD.

INTRODUCTION

Hypercholesterolemias have both genetic and environmental origins.[1] Major monogenic defects include familial hypercholesterolemia (FH) and elevated lipoprotein(a) [Lp(a)]. Polygenic conditions, such as familial combined hyperlipidemia (FCH) and common or polygenic hypercholesterolemia (PH), have by far stronger environmental influences. We review recent advances in understanding these 4 hypercholesterolemic conditions and their clinical care. We also briefly review sitosterolemia and cerebrotendinous xanthomatosis (CTX), as they are important differential diagnoses in FH.

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FAMILIAL HYPERCHOLESTEROLEMIA

Prevalence

Among inherited hypercholesterolemias, FH is the most clinically important because of its high prevalence, ease of diagnosis, and high phenotypic penetrance leading to premature ASCVD. FH is classified as a Tier 1 condition by the Center for Disease Control and Prevention, meaning that there is very strong evidence that ASCVD is preventable, with a significant impact on public health. Yet only around 10% of patients with FH are diagnosed.[2] FH is 2-fold more common in the general population than previously considered; 1 in 250 have heterozygous FH (HeFH) and 1 in 300,000 homozygous FH (HoFH).[2–5] The prevalence is up to 1% in certain founder populations (Afrikaners, French Canadians, Lebanese), up to 10% of patients with hyperlipidemia and ASCVD, and up to 20% of patients with premature ASCVD.[5,6]

Genetic Defects

FH is a monogenic cause of elevated plasma LDL cholesterol concentration (LDL-C) due to impaired LDL catabolism, with LDL-C ranging from 8 to 26 mmol/L (≈300–1000 mg/dL) in HoFH and 5 to 12 mmol/L (191–460 mg/dL) in HeFH (**Fig. 1**).[7] FH is codominantly inherited with high penetrance.[5,8] About 80% to 85% of FH is caused by *LDLR* gene mutations, with greater than 1200 *LDLR* mutations identified to date. The absence of functional LDL receptors or synthesis of ineffective receptors leads to impaired LDL clearance from plasma.[9] *APOB* gene missense mutations in the LDL receptor-binding domain of apolipoprotein B-100 (otherwise known as familial defective apolipoprotein B-100) account for another 5% to 10%.[2] Gain-of-function mutations in *PCSK9* account for about 1%.[2,5] *PCSK9* encodes proprotein convertase subtilisin/kexin type 9 enzyme, a key player in the hepatic internalization and degradation of LDL receptors. Rarely, mutations in *LDLRAP1,* which encodes LDL receptor adaptor protein 1, cause an autosomal recessive form of FH.[10]

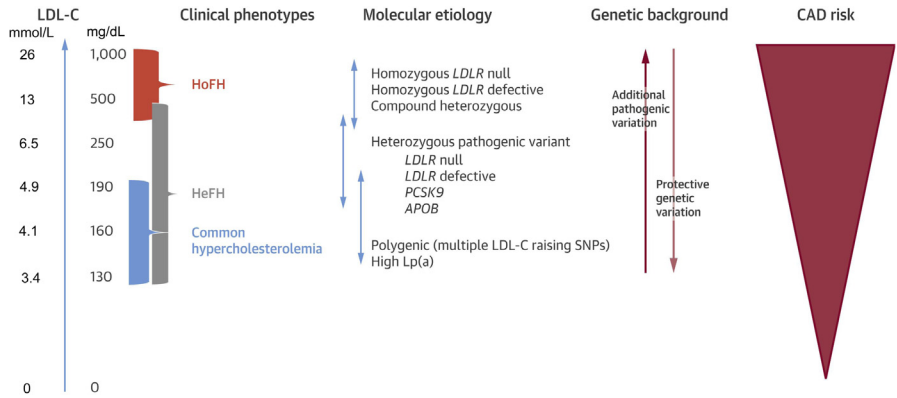

Fig. 1. Phenotypic spectrum of familial hypercholesterolemia. (*From* Sturm AC, Knowles JW, Gidding SS, Ahmad ZS, Ahmed CD, Ballantyne CM, Baum SJ, Bourbon M, Carrié A, Cuchel M, de Ferranti SD, Defesche JC, Freiberger T, Hershberger RE, Hovingh GK, Karayan L, Kastelein JJP, Kindt I, Lane SR, Leigh SE, Linton MF, Mata P, Neal WA, Nordestgaard BG, Santos RD, Harada-Shiba M, Sijbrands EJ, Stitziel NO, Yamashita S, Wilemon KA, Ledbetter DH, Rader DJ; Convened by the Familial Hypercholesterolemia Foundation. Clinical Genetic Testing for Familial Hypercholesterolemia: JACC Scientific Expert Panel. J Am Coll Cardiol. 2018 Aug 7;72(6):662-680; with permission.)

Clinical Diagnostic Criteria and Genetic Testing

The 2 most widely used clinical approaches for diagnosing FH are the Simon Broome Register (SBR) criteria[11] and the Dutch Lipid Clinic Network (DLCN) criteria, with varying weighting given to different criteria (**Table 1**). However, both these criteria and MED-PED criteria were derived for use in Western populations. The LDL-C to diagnose FH should be lower in Asians.[12,13] The Japan Atherosclerosis Society recommends a minimum LDL-C cut-off ≥4.7 mmol/L (180 mg/dL) rather than 5 mmol/L (191 mg/dL) and the use of X-ray imaging to determine Achilles tendon hypertrophy to diagnose HeFH[14] (see **Table 1**). The DLCN criteria should not be used in children and adolescents.[15] Secondary causes of raised LDL-C, such as hypothyroidism, use of corticosteroids, extreme cholesterol-raising diets (eg, coconut oil), nephrotic syndrome, and obstructive liver disease, should always be excluded before making a diagnosis of FH.

International guidelines strongly recommend genetic testing for FH in all adult index cases to facilitate diagnosis, prognosis, management, and cascade screening.[12,15–17] Genetic testing for FH should be carried out in an accredited laboratory, ideally using massively parallel sequencing.[15] Tendon xanthomata are present in approximately 13% and corneal arcus in approximately 30% of patients with HeFH.[18] A positive family history of FH is crucial as it increases the yield of diagnosis of the condition.[19] Genetic testing in patients with LDL-C >5 mmol/L alone without other diagnostic criteria for FH or presence of ASCVD, has a very low detection rate of 2% to 3% for pathogenic gene variants.[17] Approximately 30% of patients with probable/definite DLCN criteria test negative for the 3 most common pathogenic variants (*LDLR, APOB, PCSK9*); the reasons include variants of unclear significance, unidentified causative variants, or rare variants not in the genetic test panel (eg, *LDLRAP1*), and PH.[2,15,16] Hence, absence of a positive genetic test does not exclude FH if the phenotypic features are strongly suggestive of the condition.[15,16] Phenotypic FH-mimics include conditions causing xanthomata or xanthelasma such as sitosterolemia, CTX, familial dysbetalipoproteinaemia, and FCH. In patients without phenotypic FH, alternative diagnoses to consider include PH, hyper-Lp(a), and secondary causes of elevated LDL-C. Earlier diagnosis of FH allows for earlier cholesterol-lowering treatment, which can lead to a 10-fold lower risk of ASCVD in adults.[20]

Severity of Coronary Artery Disease

The higher cumulative lifetime exposure of LDL-C increases the risk of ASCVD (mainly coronary artery disease (CAD)) in adults with FH mutations compared with those without. Owing to the accelerated accumulation of LDL starting from birth, in untreated patients with HoFH, CAD starts in early childhood and can lead to premature death due to atherosclerotic CAD before 25 years of age. CAD in untreated HeFH manifests between 30 and 60 years[7]; 30 to 50% untreated individuals with FH have a fatal or nonfatal cardiac event by 50 years of age in men and 60 years of age in women.[2] The relative risk of CAD in patients with FH compared with non-FH in men less than 40 years old is > 20-fold.[21]Among patients with LDL>5 mmol/L (191 mg/dL), CAD risk is increased by more than 3-fold in those with an FH mutation.[17] Thus, diagnosis of FH in patients of young onset CAD and raised LDL-C is essential.[22] The CAD risk in women is lower than in men and increases exponentially after menopause.[21]

Atherosclerotic Cardiovascular Disease Risk

Although LDL is important in the pathogenesis of all ASCVD, the increased risk in FH seems to differ according to the type of ASCVD. The association with CAD is the

Table 1
Clinical criteria for the diagnosis of familial hypercholesterolemia

Clinical criteria for the diagnosis of Familial Hypercholesterolemia

	Simon Broome Register 1991[11]	Dutch Lipid Clinic Network 1990s	MED-PED 1993	CCS 2018[16]	JAS 2018[14]
Likelihood	Definite: a + (b or c) Possible: (a + d) or (a +e)	Definite >8 Probable 6-8 Possible 3-5 Unlikely <3	HeFH is diagnosed if total cholesterol > cut-off	Definite FH: DNA mutation or xanthomas + LDL levels below or LDL≥8.5	HeFH (≥15yr old): LDL ≥6.5mmol/l strongly suggest FH
Criteria				Probable FH: 1st degree relative with LDL>5 or premature ASCVD in proband or 1st degree relative (men<55yr, women<65yr) and LDL>5 if ≥ 40yr LDL≥4.5 if 18-40yr LDL≥4 if <18yr	Diagnostic criteria for HeFH adults: 1.LDL≥4.7mmol/l 2.Tendon xanthomas 3.Family history of FH or premature CAD (within 2nd degree relative) Note: Xanthelasma is not included as criteria Archilles tendon hypertrophy: ≥9mm on Xray

	Simon Broome	Score	Dutch Lipid	Score
Total cholesterol (mmol/L)	>7.5 (adult) >6.7 (child)	a a	-	
LDL cholesterol (mmol/L)	>4.9 (adult) >4.0 (child)	a a	≥8.5 6.5-8.4 5.0-6.4 4.0-4.9	8 5 3 1
Physical	Tendon xanthoma	b	Tendon xanthoma Arcus cornealis<45yr	6 4
Personal History			Premature CAD Premature cerebral or PVD	2 1
Family history	1° relative or 2° relative: Tendon xanthoma 2° relative<50yr with MI or 1° relative <60yr 1° relative or 2° relative: LDL>7.5 (LDL>6.7 in sibling<16yo)	b d e	1° relative with tendon xanthoma or arcus cornealis OR children<18yr with LDL>95th percentile 1° relative with Premature CAD or vascular disease, or LDL>95th percentile	2 1
Genetics	*LDLR, APOB*, or *PCSK9* mutation	c	*LDLR, APOB*, or *PCSK9* mutation	8

1° relative: 1st degree relative, 2° relative: 2nd degree relative
MI: myocardial infarction, Premature disease: men aged<55yr, women aged<60yr
PVD: peripheral vascular disease

Age	1st FH	2nd FH	3rd FH	NFH*
<20	5.7	5.9	6.2	7.0
20-29	6.2	6.5	6.7	7.5
30-39	7.0	7.2	7.5	8.8
≥40	7.5	7.8	8.0	9.3

Total cholesterol in mmol/l
1° FH: 1st degree relative with FH
2° FH: 2nd degree relative with FH
3° FH: 3rd degree relative with FH
NFH*: absent family history of FH

All units of LDL and non-HDL in mmol/L.To convert LDL cholesterol from mmol/L to mg/dL, multiply by 38.67

All units of LDL and non-HDL are in mmol/L.To convert LDL cholesterol from mmol/L to mg/dL, multiply by 38.67. a and b inside the Table 1 reflects the Score of the clinical criteria for simon broome.

highest. In a large prospective registry study of a Norwegian population with FH, the risk of aortic stenosis was increased in patients with FH compared with the general population, with a standardized incidence ratio of 7.9.[23] However, the risk of ischemic stroke and cerebrovascular disease were not increased in patients with FH in the same population.[24] The Copenhagen General Population study showed that patients with clinical FH by DLCN have increased but different risks of peripheral artery disease and chronic kidney disease.[25]

Not all patients with FH have the same ASCVD risk. Risk factors for severity in FH include (i) clinical risk factors such as degree of untreated LDL-C, age, gender(male), Lp(a) level, diabetes, obesity, hypertension, and smoking and (ii) presence of subclinical atherosclerosis (eg, thickened carotid intima-media thickness, positive coronary calcium score[CAC]).[26] ASCVD risk scores derived from the general population (eg, Framingham, Pooled Cohort Equation, European SCORE) should not be used in patients with FH because the risk is underestimated.[16] Instead, risk scores specific for FH should be used; the SAFEHEART risk equation developed in Spanish patients with FH accurately predicts 5 and 10 yr ASCVD risk[27]; The FH-Risk-Score developed from a prospective cohort study of 5 registries of patients without the history of cardiovascular events also accurately predicts 10 year ASCVD risk in patients with FH without prior ASCVD events.[28] The addition of CAC to the SAFEHEART risk equation further improves the risk prediction of ASCVD.[29]

Models of Care

The models of care for FH should be informed by the best contemporary evidence and specify roles for cardiac and lipid specialists, GPs, and allied health workers.

Implementation practice remains a challenge. Guidelines have evolved to simplify diagnostic pathways, emphasize early detection, and improve ASCVD risk prediction (**Table 2**). Universal screening of children (with child–parent testing) and population genomic screening have been recently promulgated, but the feasibility of implementation and effectiveness of ASCVD risk reduction need to be established.

Therapies

Firstly, lifestyle modification with a heart-healthy diet, regular exercise, antismoking advice, weight regulation, and stress management should be advised for all patients with hyperlipidemia. Secondary causes of elevated LDL-C and other ASCVD risk factors should be treated. There is a progressive shift for lower LDL-C targets in adults with FH (see **Table 2**). The EAS/ESC 2019 guideline recommends LDL less than 1.8 mmol/L (70 mg/dL) for primary prevention and LDL less than 1.4 mmol/L (54 mg/dL) for secondary prevention in patients with FH. In patients with FH and recurrent ASCVD events within 2 years, LDL-C <1 mmol/L (40 mg/dL) is recommended by European and Australian guidelines,[15,30] **Table 2**. The guidelines do not specify different targets for HeFH and HoFH.

High-intensity statin followed by or simultaneously[31] with ezetimibe should be prescribed if LDL-C remains above target. However, most patients with FH cannot attain low LDL-C target levels with maximal tolerated doses of statin, ezetimibe, and diet.[8] Bile acid sequestrants (BAS), niacin, probucol,[14] and fibrates can also lower LDL-C, but their use is hampered by side effects, lower effectiveness compared with statins and insufficient evidence for ASCVD prevention in patients with FH. Bempedoic acid (oral ATP-citrate lyase inhibitor) which can lower LDL-C by 20% was approved by the FDA in 2020 for use in people with HeFH with or without ASCVD even when intolerant to statin. A PCSK9 monoclonal antibody at 2 or 4 weekly injections (eg, evolocumab, alirocumab) recommended for those not achieving LDL-C targets, cause additional lowering of LDL-C around 50% to 60% in HeFH and 25% to 40% in HoFH. PCSK9 inhibition has an additional benefit of approximately 25% lowering of Lp(a)[32] which is often raised in FH. Inclisiran, a small interfering RNA given twice-yearly subcutaneously, lowers LDL-C by around 40% in patients with HeFH.[33] In patients with HoFH and severe HeFH, lipoprotein apheresis remains an important and effective method of lowering LDL-C, Lp(a) and arterial inflammation[34] and enhances the potential benefits of novel treatments. Lomitapide, an inhibitor of MTP, is approved for use in patients with HoFH and reduces LDL-C by approximately 40%.[35] Evinacumab, a monoclonal antibody that inhibits angiopoietin-related protein 3 (ANGPTL3), given via intravenous infusion every 4 weeks, can lower LDL-C by 50% even in HoFH with no LDL receptor activity.[36] Evinacumab was approved for HoFH by the FDA (2021). Ongoing studies including gene editing or vaccines targeting PCSK9[37,38] and ANGPLT3,[39] will likely change the landscape of LDL-lowering in patients with FH and severe hyperlipidemia.

Special Groups

Women with HoFH and HeFH with ASCVD have high-risk pregnancies and should be managed by a multidisciplinary specialist team.[40] BAS and lipoprotein apheresis are approved for use in pregnancy. Statins, fibrates, ezetimibe, and PCSK9 inhibitors are not approved for use in pregnancy although the use of statins in a small group of pregnant women with HoFH was reported to be safe for the fetus.[41] Use of a statin, particularly a hydrophilic statin, pravastatin, in the later trimesters of pregnancy in women with HoFH may be considered as pravastatin does not cross the placenta significantly.[40]

Table 2
Summary of recent guideline and consensus statement concerning treatment targets for primary and secondary prevention in familial hypercholesterolemia (FH)

	Guidelines and Consensus Statements					
	AHA 2015,[12] AHA/ ACC/NLA 2018 [64]	**JAS (Japan) 2018[14]**	**AACE 2020[135]**	**Australia 2020[15]**	**ESC/EAS 2019[30]**	**CCS 2021[108]**
All advocate lowering of LDL by 50% as the initial step (except for AACE 2020 which did not explicitly mention)						
Primary Prevention	LDL-C <2.5 mmol/L	LDL<2.6 mmol/L	LDL-C <1.8 mmol/L Non–HDL-C<2.6 mmol/L ApoB<0.80 g/L	LDL-C <2.5 mmol/L if absent ASCVD LDL-C <1.8 mmol/L if imaging of ASCVD or other major ASCVD risk factors present	LDL-C <1.8 mmol/L Non–HDL-C <2.6 mmol/L ApoB <0.80 g/L	LDL-C <2.5 mmol/L Non–HDL-C <3.2 mmol/L ApoB <0.85 g/L
Secondary Prevention	LDL-C <1.8 mmol/L Non–HDL-C <2.6 mmol/L	LDL<1.8 mmol/L	LDL-C <1.4 mmol/L Non–HDL-C <2.1 mmol/L ApoB<0.7 g/L	LDL-C <1.4 mmol/L Non–HDL-C <2.2 mmol/L ApoB <0.65 g/L Recurrent ASCVD within 2 yr: LDL-C <1.0 mmol/L Non–HDL-C <1.8 mmol/L ApoB <0.5 g/L	LDL-C <1.4 mmol/L Non–HDL-C <2.2 mmol/L ApoB <0.65 g/L Recurrent ASCVD within 2 yr: LDL-C <1.0 Non–HDL-C<1.8 mmol/L ApoB <0.55 g/L	LDL-C <1.8 mmol/L Non–HDL-C <2.4 mmol/L ApoB <0.7 g/L

b. All units of LDL and non-HDL in mmol/L.To convert LDL cholesterol from mmol/L to mg/dL, multiply by 38.67.
Abbreviations: ApoB, apolipoprotein B; LDL-C, low-density lipoprotein cholesterol.

Statins should be initiated early, as young as 8 to 10 years old in children with FH, because this reduces ASCVD risk.[42] The target should be 50% reduction of LDL-C or less than 3.5 mmol/L (130 mg/dL).[43] Ezetimibe, and the PCSK9 inhibitor evolocumab are approved by the FDA for children ≥10 years old with HeFH and HoFH. In 2021, Evinacumab was approved by the FDA in 2021 for children ≥12 years old with HoFH.

Gaps in Care

The major gaps in clinical care include (i) low detection of FH (especially in the young), (ii) access to new therapies (especially HoFH and severe FH), and (iii) the need for improved health policy and financing integrated models of care for FH.

POLYGENIC HYPERCHOLESTEROLEMIA

PH, with a very high polygenic risk score, can masquerade as phenotypic FH. These patients bear multiple common genetic variants that each increases LDL-C by a small amount and collectively have a significant cumulative LDL-C raising effect. Although these traits are highly heritable (50%–80%), they are also readily modifiable by environmental factors and expression of hypercholesterolemia occurs later in life than with monogenic hypercholesterolemias.[1,7] At any given LDL level, patients without FH mutation have lower risk of CAD than those with an FH mutation.[17] However, with novel polygenic risk scores based on millions of SNVs (so-called multigenic risk scores), patients above the 95th percentile have an increased risk of premature myocardial infarction comparable with patients with FH mutations.[44] This is potentially clinically relevant, since the prevalence of PH is 10-fold greater than definite FH.[44,45] Patients with FH mutations *and* a high polygenic risk score have an even higher mean LDL-C than those with monogenic mutations alone,[44] explaining the variability of LDL-C observed in patients despite carrying the same monogenic mutation. As there is overlap between phenotypic FH (by DLCN) and genetic FH, genetic testing for FH and multigenic risk scores for PH could be useful,[45] but this is not usual practice at present.

Gaps in Care

Although utilization of polygenic scores has potential for further risk classification of patients with and without FH, gold standard scoring criteria, and studies evaluating patient outcomes, behavior, and risk stratification are lacking.[46] Unlike monogenic FH, there is a potentially lower detection rate of PH by cascade testing. Further studies may be useful in families with probands with polygenic cholesterol scores above the 95th percentile.[7]

FAMILIAL COMBINED HYPERLIPIDEMIA

Prevalence and Genetics

FCH is more common than FH [0.5%–2%[47] versus 0.3%–0.4%[2]] and is also a frequently missed diagnosis.[30] Unlike FH, FCH is polygenic in origin, mixed hyperlipidemia being due to the interaction of multiple susceptibility genes with environmental factors.[47,48] It typically manifests as the elevation of LDL-C, triglycerides (TG) and apoB, with reciprocal reduction in HDL-C. There is significant phenotypic heterogeneity between and within families.[48] More than 35 genes have now been implicated as FCH susceptibility genes, including *USF1* (regulates hepatic VLDL synthesis), *APOA1* and *CETP* (regulates TG), *LDLR* (effect on LDL clearance) and *HSL* and *PNPLA2* (control of adipose tissue lipolysis and hepatic steatosis).[47] From kindred studies, various dyslipidemic patterns of FCH have been observed, including

predominant accumulation of small dense LDLs,[49] increased VLDL production,[49,50] and hypertriglyceridemia due to additional impairment of lipoprotein lipase activity.[51] Metabolic dysregulation in FCH can be related to increased supply of fatty acids to the liver, and overproduction and impaired clearance of apoB-containing particles, which are associated with dysfunctional adipose tissue and hepatic insulin resistance.[47]

Clinical Diagnosis

The Atherosclerosis and Metabolic Diseases Study Group has defined the clinical diagnosis of FCH as hypercholesterolemia [LDL-C greater than 4.1 mmol/L (160 mg/dL), or raised plasma apoB and/or hypertriglyceridemia [TG greater than 2.3 mmol/L (200 mg/dL)] in at least 2 members of the same family.[52] A diagnostic nomogram using total cholesterol, TG and apoB levels for FCH has also been proposed,[53] but this relies on untreated plasma lipid levels and requires validation and simplification for clinical use. Raised apoB level is a useful diagnostic and prognostic factor in patients with FCH.[52–54] The Spanish Foundation for Hypercholesterolemia (2014) proposed phenotypic criteria based on LDL-C greater than 4.14 mmol/L (160 mg/dL) and/or TG greater than 2.25 mmol/L (200 mg/dL)] and at least 2 first-degree relatives with mixed hyperlipidemia.[55] The ESC/EAS guideline suggested the combination of apoB greater than 120 mg/dL and TG greater than 1.5 mmol/L (>133 mg/dL) with a family history of premature CVD to identify patients most likely to have FCH.[30]

The diagnosis of FCH is challenging and requires a clearer definition. FCH overlaps with other common metabolic conditions; such as central obesity,[56] metabolic syndrome,[57] and T2DM,[58] all of which have heritable components. The pattern of dyslipidemia in FCH is similar to that in diabetic dyslipidemia and metabolic syndrome.[52] An important differential diagnosis is familial dysbetalipoproteinemia (ie, type III hyperlipoproteinemia) due to homozygosity for 2 defective apolipoprotein E2 alleles, so-called E2E2 homozygosity. This condition is typically exacerbated by secondary factors, such as insulin resistance, obesity, and metabolic syndrome. This leads to accumulation in the circulation of remnants of TG-rich lipoproteins due to decreased hepatic clearance and manifests as mixed dyslipidemia (typically with equimolar lipid concentrations on a standard lipid profile) and xanthomata.[59] Plasma lipid and lipoprotein concentrations in FCH can fluctuate within an individual over time affecting the precision of diagnosis.[54] The penetrance of FCH increases with age and obesity.[52] Genetic testing does not have a role in the diagnosis of FCH.

Clinical Significance

Patients with FCH are at significantly high ASCVD risk, specifically premature CAD.[57] Risk is dependent on the severity of dyslipidemia and presence of comorbidities, such as metabolic syndrome.[57] Approximately 65% of FCH have metabolic syndrome.[57] Patients with FCH are 6-times more likely to develop T2DM compared with their spouses.[58] Longitudinal studies show that first-degree relatives of patients with FCH have an increased risk of dying from cardiovascular disease.[60,61] Patients with FCH and family members also have an increased risk of hepatic steatosis. *USF1* is a key genetic regulator of lipid and glucose metabolism, including processes that induce nonalcoholic fatty liver disease[62] and hypertriglyceridemia,[47] such as the regulation of hepatic synthesis and secretion of VLDL.

Management

The strong association of FCH with CAD makes FCH an important risk-enhancer of ASCVD.[60] In patients at low-to-intermediate absolute risk of ASCVD, the phenotypic

diagnosis of FCH (or some of its component criteria) could be used as a risk-enhancing factor. While FCH per se is not highlighted as a risk-enhancer in the recent guidelines,[30,63,64] the factors characterizing FCH that is, presence of family history of premature ASCVD,[64] persistent hypertriglyceridemia,[63,64] metabolic syndrome,[64] and elevated apoB,[64] are *all* risk-enhancing factors supporting statin initiation/intensification in patients with FCH in primary prevention. In the presence of ASCVD, aggressive LDL-C and apoB lowering should be undertaken.[30]

Lifestyle modification should be advised, and secondary causes of elevated LDL-C and other ASCVD risk factors treated aggressively. Statins are the first-line treatment to lower LDL-C in FCH; statins can also lower TG by approximately 10% to 30%.[65] In patients with ASCVD or T2DM with persistent fasting TG $\geq$ 1.7 mmol/L (150 mg/dL), high dose icosapent ethyl, an EPA only omega-3-fatty acid)should be considered to reduce ASCVD risk.[63] Addition of fibrates or icosapent ethyl to a statin may be considered when plasma TG exceed 2.3 mmol/L (200 mg/dL).[31] The European guidelines recommend the use of combination of statin ($\pm$ezetimibe) and fenofibrate for patients with T2DM with TG greater than 2.3 mmol/L (200 mg/dL).[31] RNA therapeutics targeted at apo C-III and ANGPTL3 are currently being tested and developed to profoundly and durably lower hypertriglyceridemia[63] and could in future provide tailored treatment of higher risk patients with FCH receiving a statin.

Gaps in Care

The gaps in the core of FCH include under-detection, absence of definite diagnostic criteria, and lack of accurate methods for ASCVD risk stratification in primary prevention. The role of imaging for subclinical atherosclerosis (eg, CAC) and other biomarkers (eg, Lp(a)) in FCH is unclear. Because FCH is polygenic in nature, with variable penetrance, cascade genetic testing is unlikely to be cost-effective. However, adult relatives of patients with FCH and CAD should be tested with a full plasma lipid profile and assessed for other modifiable risk factors associated with FCH for example, T2DM, HTN, central obesity.

HYPER-LP(A)

Epidemiology

Lp(a) is an LDL-like lipoprotein with a single molecule of apolipoprotein B-100 (apoB) covalently bound to apolipoprotein(a). Partly owing to apoB, the plasminogen-like properties of apo(a), and a high particle content of oxidized phospholipids, Lp(a) has unique proatherogenic, prothrombotic and proinflammatory properties.[66] Epidemiologic, Mendelian randomization and prospective studies across multiple populations conclusively show that Lp(a) increases the risk of CVD events, stroke and calcific aortic valvular stenosis (CAVD).[67–74] Oxidized phospholipids within Lp(a) may be particularly important in the pathogenesis of ASCVD and CAVD.[75]

The distribution of Lp(a) is positively skewed to the right. Lp(a) < 30 mg/dL is considered normal. A large meta-analysis by the Emerging Risk Factors Collaboration of 126,634 participants in 36 prospective studies showed that Lp(a) greater than 30 mg/dL is associated with increased risk of ASCVD.[69] People in the top 20th percentile of the general population are considered to have hyper-Lp(a) (50 mg/dL $\approx$ 100–125 nmol/L), a level above which the risk of ASCVD increases significantly.[76] Extreme plasma concentrations of Lp(a) are associated with high ASCVD[70,74] and CAVD[68] risk. Lp(a) > 95th percentile in the Danish general population ($\geq$120 mg/dL) was associated with a 3- to 4-fold increase in the risk of acute myocardial infarction, with an absolute 10-year risk of 20% and 35% in higher-risk women and men, respectively.[70] Similarly,

for CAVD, extreme Lp(a) levels greater than 90 mg/dl were associated with the highest risk of aortic valve stenosis (hazard ratio 2.9).[68] Patients with FH have an increased likelihood of having hyper-Lp(a).[77]

Nongenetic Causes

Because Lp(a) is predominantly under genetic control (70%–90%), the plasma concentration is largely heritable with lesser contributions from dietary saturated fat and carbohydrate, exercise, endocrine changes (eg, pregnancy, menopause, thyroid) and renal function.[66] Lp(a) is synthesized in and secreted exclusively by the liver and the clearance of Lp(a) is by liver and kidney. The plasma concentration of Lp(a) is predominantly determined by the rate of hepatic secretion of the Lp(a) particle.[78] Renal clearance is important as chronic kidney disease, including proteinuria, is associated with elevated Lp(a) levels, with renal transplantation lowering the elevated levels of Lp(a).[79] Other secondary causes of hyper-Lp(a) including overt hypothyroidism,[80] menopause,[81] and nephrotic syndrome.[79] Lp(a) levels are suppressed in obstructive liver disease due to cholestasis.[82] Conditions related to female and male hormones may affect Lp(a); Lp(a) increases in pregnancy and menopause, and is reduced with estrogen and testosterone replacement therapies, but the exact mechanisms are unclear.[81] The LDL receptor may also play a modest role in the clearance of Lp(a) because PCSK9 inhibitors lower plasma Lp(a) by about 25%.[32,83] By contrast, statins tend to have no effect and may even increase Lp(a) concentrations.[84,85] The relationship between ethnicity and Lp(a) is discussed later in discussion.

Genetics

The heritability of Lp(a) is autosomal codominant, with individuals inheriting alleles that determined apo(a) isoform sizes.[86,87] The KIV-2 copy number variation determines apo(a) isoform size, accounting for 25% to 50% variability in Lp(a) concentrations,[72] while single-nucleotide polymorphisms (SNP), in particular rs10455872 in the *LPA* gene, explain 24% to 29% of the variability.[67,88,89] Recent studies show that polygenic risk scores including multiple SNPs derived from GWAS can explain 44% to 63% of the Lp(a) variance.[88–91] Lp(a) is likely the most potent genetic risk factor for CAD, more so than LDL and PCSK9-related variants,[84,92] and arguably the most common monogenic cause of premature ASCVD and the only monogenic risk factor to date for CAVD.[93]

Apart from apo(a) isoforms, the prevalence of *LPA* SNPs is also ethnic-specific.[94] SNP rs10455872 and rs3798220 together may explain 36% of the Lp(a) variance and increased CAD risk in European cohort (OR: 2.57).[67] However, the prevalence of these 2 SNPs differs greatly among other ethnicities[94–97]: Prevalence of SNP rs3798220 varies from 4% (Whites) to 42% (Hispanics), while SNP rs10455872 varies from to less than 2% (Blacks) to 14% (Whites) in population-based Dallas Heart Study,[95] Both SNPs are rare and not associated with Lp(a) in a Chinese population.[96] The population attributable risk of specific threshold of Lp(a) for AMI varies among different ethnicities,[73,94] suggesting the need for further studies to clarify ethnic-specific values and risk thresholds. Currently, the use of apo(a) isoforms and SNPs do not have a clearly defined role in clinical practice.

Issue with Laboratory Measurements

Lp(a) is currently difficult to measure accurately and precisely. This is due to multiple copies of Kringle IV type 2 domain of the apo(a) isoform.[72,78,98] It is technically challenging to create a truly isoform-insensitive or "total particle variation insensitive" assay,[99] so that hitherto none is commercially available. Assays based on Denka

reagents calibrated in molar concentration (nmol/L) and traceable to WHO/IFCC reference material are closest to an isoform-insensitive method.[100,101] Conversion factors for mass to molar units is erroneous.[102] Assays that measure Lp(a) by mass (mg/dL) alone have been discouraged.[93,99,103,104]

The estimation of LDL-C would also encompass the contribution from the cholesterol concentration of Lp(a).[84] This is especially problematic with hyper-Lp(a) levels (>80th percentile) as Lp(a) can contribute to 25% to 50% of LDL-C.[105] This could explain why some poor responders to high dose statin have high calculated LDL-C. A novel method has recently been developed to differentiate the cholesterol content of Lp(a) from LDL, VLDL and HDL.[106] This new assay showed that using a correction factor of 30% (derived from Lp(a) mass) for correcting LDL-C is not valid.[106] The formula ([Lp(a) in nmol/L]/[plasma apoB in nmol/L] x 100) can be used to estimate the percentage of apo-B containing lipoproteins that is actually Lp(a) in the plasma.[93] Utility of this approach remains uncertain.

Management

Risk threshold

Regardless of the type of apo(a) isoforms and SNPs, it is the plasma mass or molar concentration of Lp(a) that is most important in predicting ASCVD risk,[91,94] although recent evidence has pointed to a role for Lp(a) polygenic risk scores.[46] Clinical guidelines now tend to define risk threshold using Lp(a) in molar concentration (**Tables 3** and **4**). While the AHA/ACC 2018 guideline recommends a risk threshold of $\geq$125 nmol/L[107], the NLA 2019 guideline recommends a universal value of 100 nmol/L,[104] **Table 3**. The ESC/EAS 2019 guideline recommends that Lp(a) should be measured at least once in a person's lifetime to identify those with extreme Lp(a) results greater than 430 nmol/L (>180 mg/dL), which has the same ASCVD risk as HeFH, but is 2-fold more prevalent.[30,90] The CCS (2021) recommended measuring Lp(a) once in a lifetime as part of initial lipid screening, without specifying screening of selected groups of people.[108] There is an ongoing discussion on the role of measuring Lp(a) in youth to reduce lifetime ASCVD risk.[109,110] By about 5 years of age, plasma Lp(a) reaches adult levels and may contribute to residual risk despite the optimal reduction of other risk factors.[104,109]

Risk enhancer

As recommended by major international guidelines, Lp(a) is a risk-enhancer that may be useful in improving ASCVD risk prediction in both primary and secondary prevention,[30,64,103,104,108] and specifically FH.[26–28] Elevated Lp(a) may be useful in risk stratification in people with intermediate risk of ASCVD and those with low risk who have a family history of ASCVD.[103,109,111] Treatment decisions may be enabled regarding initiating risk reduction therapy (such as statins) in primary prevention and intensifying therapy (such as adding ezetimibe to a statin, or adding a PCSK inhibitor to a statin plus ezetimibe). In patients with hyper-Lp(a), a thorough history of personal and family history of ASCVD and CAVD should be obtained. Secondary causes of hyper-Lp(a) should be excluded, for example, hypothyroidism and chronic kidney disease. Physical examination may identify arcus cornealis, aortic systolic murmur, and/or signs of PAD. In asymptomatic patients with raised Lp(a) and strong family history of premature ASCVD, a CT calcium score, CT coronary angiography, and/or carotid ultrasound may be considered to assess the presence and burden of ASCVD. If subclinical atherosclerosis is present, this could further enable a decision to initiate/intensify statin therapy to lower LDL-C, initiate aspirin, and optimizing control of other risk factors including diabetes mellitus, hypertension, and smoking. Although diet and exercise do

Table 3
Summary of major cholesterol management guidelines and position statements on Lp(a)

	Mighty Medic Group 2017[136]	AHA/ACC and Group 2018[64]	NLA 2019[104]	EAS/ESC 2019[30]	HEART-UK 2019[103]	AACE 2020[135]	Lipid Association of India 2020[137]	CCS 2021[108] (Canada)
Detection	Targeted screening: • Intermediate/ high-risk patients with CVD with premature CVD • FH • Family history of premature CVD without elevated LDL • Recurrent CVD with statin therapy	Targeted screening: • Family history of premature ASCVD • Personal history of ASCVD not explained by major risk factors	Targeted screening: • 1st-degree relatives with premature ASCVD (male<55 yr, female<65 yr) • Personal history of premature ASCVD • Primary severe hypercholesterolemia (LDL ≥190 mg/dL) or suspected FH • Very high-risk ASCVD to better define benefit from PCSK9inhibitor Measurement may be reasonable: • Borderline or intermediate 10 yr ASCVD risk in primary prevention • Less than anticipated LDL lowering to LDL lowering treatment • Family history of high Lp(a) • Calcific valvular aortic stenosis • Recurrent or progressive ASCVD, despite optimal treatment	Universal screening: • At least once in adult person's lifetime to identify Lp(a) > 180 mg/dL (>430 nmol/L) Targeted screening: • Family history of premature CVD • For reclassification in people who are borderline between moderate and high-risk category	Targeted screening: • Personal history of premature ASCVD (<60 yr) • Family history of premature ASCVD (<60 yr) • 1st-degree relative with Lp(a) > 200 nmol/L • FH or other genetic dyslipidemia • Calcific valvular aortic stenosis • Borderline increased but <15% 10 yr risk of CVD	Targeted: • ASCVD especially premature or recurrent despite LDL-lowering • Family history of premature ASCVD and/or high Lp(a) • South Asian or African ancestry, especially family history of ASCVD or increased Lp(a) • 10 yr ASCVD≥10% (primary prevention) to stratify risk • Personal or family history of aortic valve stenosis • refractory elevations of LDL-C despite aggressive LDL-C lowering	Universal screening: • At the time of initial screening at 18 years old Targeted: • premature ASCVD • FH • family history of premature ASCVD and/or high Lp(a) • Recurrent ASCVD • Patients after acute coronary syndrome	Universal screening: • At least once in a lifetime as part of the initial lipid screening

Threshold above which risk increased	>30 mg/dL or >45 nmol/L	≥50 mg/dL or ≥125 nmol/L	≥50 mg/dL or ≥100 nmol/L in Caucasian patients Acknowledges it is unclear what ethnic-specific risk threshold should be	>180 mg/dL or >430 nmol/L equivalent to lifetime ASCVD risk of HeFH	Minor: 32–90 nmol/L Moderate: 90–200 nmol/L High: 200–400 nmol/L Very high: >400 nmol/L	>50 mg/dL	Moderate: 20–49 mg/dL High risk: ≥50 mg/dL	≥50 mg/dL or ≥100 nmol/L
Management	• Niacin or, if refractory, selective apheresis	• Use Lp(a) as a risk-enhancing factor to favor statin initiation	• Use Lp(a) as a risk-enhancing factor to favor more intensive LDL lowering therapy • Niacin is not recommended to reduce ASCVD risk in patients receiving moderate to high intensity and/or ezetimibe and LDL<80 mg/dL • HRT is not recommended to use to lower Lp(a) to reduce ASCVD risk in women	Extreme Lp(a) levels can help reclassify borderline cases between moderate and high-risk	If Lp(a) > 90 nmol/L, • Reduce overall ASCVD risk • Control hyperlipidemia • Consider apheresis if Lp(a) > 150 nmol/L (if LDL-C >3.3 mmol/L despite maximal LDL-lowering therapy) • Aim for non-HDL-C <2.5 mmol/L (100 mg/dL)	• Lipoprotein apheresis in extreme cases • Aggressive lowering LDL-C	• Secondary prevention: consider PCSK9 inhibitor	• Primary prevention: earlier, more intensive health behavior modification and ASCVD risk factors management • Secondary prevention: consider PCSK9inhibitor
Childhood and Adolescent	None specified	None specified	Measurement may be reasonable<20 yr: • Suspected FH • 1st-degree relatives with premature ASCVD • Unknown cause of ischaemic stroke • A parent or sibling with high Lp(a)	None specified	None specified		Universal screening: • >2 yr old with family history of FH and premature ASCVD	None specified

Table 4
Similarities and differences between FH, FCH, polygenic hypercholesterolemia (PH) and hyper-Lp(a)

Variables	Heterozygous FH (HeFH)	Hyper-Lp(a)	Familial Combined Hyperlipidemia (FCH)	Polygenic Hypercholesterolemia(PH)
Clinical Characteristics				
Main lipoproteins affected	LDL-C	Lp(a)	Apo-B containing particles (LDL-C, VLDL-C) TG-rich lipoproteins	LDL-C
High TG and Low HDL-C	No	No	Yes	No
High LDL-C in early childhood	Yes	No	No	No
Prominent cause of high LDL-C in adults	Yes	No (unless extreme level)	Yes	Yes (most common)
Tendon xanthomata	Yes	No	No	No
Arcus cornealis	Yes	Yes	Yes	Yes
Prevalence and Association				
Prevalence in general population	1 in 250	1 in 5	1 in 100	1 in 20
Prevalence in premature CAD	1 in 10	1 in 6	1 in 5–10	> common than FH[17]
Increased risk of premature CAD	Yes	Yes	Yes, but lower than FH	Yes, but lower than FH
Often associated with HTN and T2DM	No	No	Yes	No
Genetics				
Mode of inheritance	Autosomal codominant	Autosomal codominant	Polygenic	Polygenic
Founder effects described	Yes	No	No	No
Well-defined dominant trait mapped to a major gene locus	Yes	Yes	No	No

Suitable for cascade screening	Yes	Yes	No	No
Current gene testing useful for diagnosis	Yes	No	No	No
Multiplicative interactions with other CAD risk factors	Yes	Yes	Yes	Yes
Management				
Well-defined model of care	Yes	No	No	No
Require lifestyle modification	Yes	Yes	Yes	Yes
Require statins	Yes	No	Yes	Yes
May require ezetimibe	Yes	No	Yes	Yes
May require PCSK9 inhibition	Yes	Yes	Yes	Yes
Often require 3 medications to achieve LDL-C target	Yes	N/A	No	No
Can require apheresis	Yes	Yes	No	No
Lipid targets often achieved with standard drugs and dietary intervention	Yes	No	Yes	Yes

Abbreviations: CAD, coronary artery disease; FCH, familial combined hyperlipidemia; HTN, hypertension; Lp(a), lipoprotein(a); T2DM, type 2 diabetes mellitus.

Adapted from Ellis KL, Hooper AJ, Burnett JR, Watts GF. Progress in the care of common inherited atherogenic disorders of apolipoprotein B metabolism. Nat Rev Endocrinol. 2016 Aug;12(8):467-84.

not lower Lp(a), healthy diet and exercise should be advocated, because a healthy lifestyle may significantly reduce cardiovascular risk in patients with high Lp(a) levels,[112] illustrating the principle of environmental modification of genetically mediated risk of ASCVD.

Treatment

It is estimated that the reduction of high plasma Lp(a) concentration by 80% to 90% is needed to achieve a clinically meaningful reduction in ASCVD risk, that is approximately 20% which is equivalent to a 1 mmol/L reduction in LDL-cholesterol.[90] Currently, no medication is approved specifically for hyper-Lp(a). Statins can increase Lp(a) by almost 50% in patients with small apo(a) isoforms, but mechanisms are unclear.[85] PCSK9 monoclonal antibodies can lower Lp(a) by 20% to 30%,[32,113] suggesting enhanced clearance of Lp(a) via LDL receptors. However, Lp(a) reduction may also be seen with PCSK9 inhibitors in true HoFH,[114] pointing to a mechanism involving LDL receptor-independent pathways. Post hoc analyses of PSCK9 inhibitor clinical outcome trials that reductions in Lp(a) may contribute to the lowering ASCVD events.[32,113] Niacin can lower Lp(a) by 20% to 30%,[115] but this agent did not reduce ASCVD risk in large clinical trials.[103,104] Lipoprotein apheresis lowers plasma Lp(a) levels acutely by 60% to 65%, but the postapheresis rebound is rapid and the mean inter-apheresis reduction of Lp(a) is approximately 30%.[116] The ASCVD benefits of the reduction in Lp(a) with apheresis may entail anti-atherosclerotic, anti-inflammatory, and antithrombotic effect.[116] Other agents that lower Lp(a) include mipomersen (c. 20%–30%),[117] and the CETP inhibitor anacetrapib (c. 38%),[118] but these agents are not in clinical use. Hormone replacement therapy in postmenopausal women[81] and thyroxine replacement in hypothyroidism[80] also lower Lp(a) concentrations. Less potent Lp(a) lowering agents (<10%) include fibrates, ascorbic acid, aspirin, angiotensin-converting enzyme inhibitor, and calcium antagonist.[76]

Novel therapies

APO(a)-L_{RX}, a $GalNac_3$-conjugated ASO targeted at *LPA* mRNA (Pelacarsen), that is selectively taken up by hepatocytes lower Lp(a) by 80% with 98% of patients achieving plasma concentrations less than 50 mg/dL (125 nmol/L).[119] Inhibiting apo(a) synthesis in the liver decreases the assembly of Lp(a) and the hepatic secretion of Lp(a) particles.[119] The randomized controlled trial HORIZON is currently investigating the effect of APO(a)-L_{RX} (TQJ230), 80 mg s.c. monthly, (NCT04023552) in patients with established CAD on maximally treated statin and ezetimibe. Following the successful results reported in a phase 1 clinical trial,[120] a phase 2 study of the $GalNac_3$-conjugated-siRNA (Olpasiran) targeting apo(a) and thus Lp(a) production is also currently undergoing (NCT04270760).

Gaps in Care

Major gaps include: (1) lack of data showing ASCVD risk reduction with specific lowering of Lp(a), (2) lack of availability of isoform-independent and well standardized assays for measuring Lp(a) molar concentrations, (3) inadequate information on ethnic-specific risk thresholds,[99] (4) the need for justification of screening programs for high Lp(a), and (5) lack of awareness of Lp(a) at patient, family, health care professional, organizational, and population levels.

SITOSTEROLEMIA

Sitosterolemia (or phytosterolemia) is an autosomal recessive disorder characterized by high plasma levels of plant sterols, particularly sitosterol, and to a lesser extent

stigmasterol and campesterol.[121] The primary genetic defects involve two ATP-binding cassette subfamily G members, *ABCG5* and *ABCG8.*[122,123] These genes encode the sterol efflux transporters that outport plant sterols into the intestinal lumen, and transport plant sterols into bile.[122] This leads to an increase in gastrointestinal absorption of plant sterols from less than 5% in normal individual to 15% to 60% in patients with sitosterolemia.[123] This causes a phenotypic spectrum from asymptomatic, normocholesterolemia to severe hypercholesterolemia with tendon xanthoma, hematological abnormalities and premature atherosclerosis.[121,124,125] Homozygous sitosterolemia is estimated to occur in 1 per 200,000 in the population.[125] Sudden cardiac death has been reported in 5 years old and teenagers with sitosterolemia.[126] Heterozygotes are usually asymptomatic with normal to slightly increased plasma plant sterol concentrations, with a possible 2-fold increase in risk of CAD.[127] Sitosterolemia has been reported in breastfed infants, presumably due to increased cholesterol absorption from breast milk.[128]

Plasma concentrations of plant sterols should be measured in hypercholesterolemic patients with xanthomata that do not have FH, are poor responders to statins, are hyper-responsive to ezetimibe, or have unexplained hemolytic anemia. Management of sitosterolemia involves restricting dietary plant sterol and cholesterol intake, use of a sterol absorption inhibitor (ezetimibe), and BAS. Food rich in plant sterols including vegetable oil, nuts, avocado, seeds, margarine, shellfish, and seaweed should be avoided. Ezetimibe, which inhibits Niemann-Pick C1-Like 1 (NPCL1) efficiently lowers gastrointestinal absorption and thus of plasma sterols by 40% to 50% in homozygous sitosterolemia.[129] The BAS cholestyramine has been reported to reduce plasma sterols level by 20%.[130]

Cerebrotendinous Xanthomatosis

CTX is a rare autosomal recessive disorder of bile acid synthesis involving a deficiency in sterol 27-hydroxylase (cytochrome P450 *CYP27A1*) causing accumulation of cholestanol and cholesterol in plasma, tendons, lenses, and brain.[131] The prevalence is 3 to 5 per 100,000 in Caucasians but varies with ethnicity.[131] The presence of 2 of 4 hallmark criteria (premature cataract, chronic diarrhea, neurologic signs, tendon xanthomata) is a clue to the diagnosis of CTX.[132] Tendon xanthomata, which generally present by age 30, is seen in 70% of patients.[133] Neurologic abnormalities, seen in 48% to 74% of cases,[134] include impaired intellect, dementia, seizures, and psychiatric issues.[131,133] CTX can present in neonates as liver failure, but more commonly as nonspecific symptoms initially.[133] Approximately 7% to 20% of patients with CTX have premature CAD.[133,134] Diagnosis is confirmed by extremely elevated plasma cholestanol concentrations.[133] Patients with CTX have low/normal plasma levels of LDL-C with elevated plant sterols.[131] Treatment is with chenodeoxycholic acid (CDCA) 250 mg 3 times a day for adults and 15 mg/kg per day for children.[133] Early initiation of treatment prevents neurologic deficits, whereas late treatment may not reverse complications.[133,134] Statins may also be useful by decreasing synthesis of cholesterol and cholestanol, but this may potentially be offset by increased hepatic cholesterol uptake by the liver, so their use is not established in CTX other than for co-existent hypercholesterolemia.

SUMMARY

FH, PH, FCH, and hyper-Lp(a) are common inherited disorders of the metabolism of apo B-100 frequently seen in patients and families with premature ASCVD.

Sitosterolemia and CTX should be considered in the differential diagnosis of severe hypercholesterolemia or HoFH, but otherwise are exceptionally rare monogenic defects and best cared for in highly specialized clinics.

Lifetime risk of CAD is highest with FH, the most common Tier 1 genomic condition that requires early detection, preferably with genetic testing, and treatment with lifestyle and multiple cholesterol-lowering therapies. The case for screening for high Lp(a) is weakened by lack of effective therapies, but testing may be justified to risk-stratify people at intermediate absolute risk of ASCVD or those at low risk with a positive family history of ASCVD, thereby leading to risk-reduction treatments, such as statins. Cardiovascular outcome trials with RNA-based therapeutics targeted at apo(a) synthesis may change perceptions about the value of screening for high Lp(a) in secondary prevention. PH and FCH are polygenic conditions that should be treated according to general lipid guidelines with lifestyle modifications and pharmacotherapies primarily targeted at LDL-C and apoB-100, followed possibly by therapies for residual hypertriglyceridemia; FCH may be viewed as a forerunner of diabetes and managed accordingly by treating and preventing obesity. Knowledge of polygenic risk scores in FH and FCH may enable risk stratification but has no role at present in genetic cascade testing of family members, who should nevertheless be offered a nonfasting lipid profile in the first instance. All four disorders may coexist within an individual, placing them at particularly high lipoprotein-mediated risk of ASCVD.

Models of care are most developed for FH. These may be adapted, as indicated by new evidence, for managing hyper-Lp(a) and FCH. As new evidence accrues, the measurement of polygenic lipid and CAD risk scores may be incorporated into evolving models for care for FH, hyper-Lp(a), and FCH. Implementation of evidence-informed best clinical practice remains a major challenge, even for conditions like FH. Gaps in implementation need to be addressed at patient, population, health care professional, organizational, and government levels.

CLINICS CARE POINTS

- Secondary causes of raised plasma concentrations of LDL-cholesterol, such as hypothyroidism, use of corticosteroids, extreme cholesterol-raising diets, nephrotic syndrome, and obstructive liver disease, should always be excluded before making a diagnosis of FH.
- A well-curated family history is an essential component of the diagnosis of FH and guides the efficient use of genetic cascade testing.
- Risk stratification should only be carried out using ASCVD algorithms specific to FH (eg, SAFEHEART risk equation and FH-Risk-Score); coronary artery calcium scoring may be particularly useful when combined with the SAFEHEART equation.
- Lp(a) is a risk-enhancer that may be useful in improving ASCVD risk prediction in both primary and secondary prevention, particularly in patients with FH; elevated Lp(a) may be useful in risk re-stratification of people at intermediate absolute risk of ASCVD and low-risk people with a family history of ASCVD.
- Secondary causes of hyper-Lp(a) should be excluded and corrected for example, hypothyroidism and nephrotic range proteinuria. Currently available lipid regulating drugs do not effectively lower elevated Lp(a) levels; this will require the use of RNA therapeutics, currently in clinical trials.

- Plasma concentrations of plant sterols should be measured to exclude sitosterolemia in hypercholesterolemic patients with xanthomata that do not have FH, are poor responders to statins, are hyper-responsive to ezetimibe, or have unexplained hemolytic anemia.
- Polygenic hypercholesterolemia (PH) and familial combined hyperlipidemia (FCH) can mimic FH and are important differential diagnoses when genetic testing does not confirm a pathogenic variant for FH. However, patients with a frank phenotypic diagnosis of FH in whom a gene variant has not been identified should still be considered to have FH.
- The care of patients with PH and FCH should be based on guidelines for general lipid management. Lifestyle modifications are essential, and all modifiable causes of elevated cholesterol and other ASCVD risk factors must be corrected.
- Polygenic lipid and cardiovascular risk scores may identify patients particularly susceptible to ASCVD in all the 3 conditions (FCH, PH, and hyper-Lp(a)), but these scores are not yet ready for prime time.
- Evidence-informed guidelines should be followed regarding LDL-cholesterol treatment targets and the sequential use of statins, ezetimibe (or bempedoic acid), and a PCSK9 inhibitor; in very high-risk patients, such as those with FH and ASCVD, early use of combination therapy should be considered.

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