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Reducing cardiovascular risk in patients with familial hypercholesterolemia: Risk prediction and lipid management

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ABSTRACT

Familial hypercholesterolemia (FH) is a frequent genetic disorder characterized by elevated low-density lipoprotein (LDL)-cholesterol (LDL-C) levels and early onset of atherosclerotic cardiovascular disease. FH is caused by mutations in genes that regulate LDL catabolism, mainly the LDL receptor (*LDLR*), apolipoprotein B (*APOB*) and gain of function of proprotein convertase subtilisin kexin type 9 (*PCSK9*). However, the phenotype may be encountered in individuals not carrying the latter monogenic defects, in approximately 20% of these effects of polygenes predominate, and in many individuals no molecular defects are encountered at all. These so-called FH phenocopy individuals have an elevated atherosclerotic cardiovascular disease risk in comparison with normolipidemic individuals but this risk is lower than in those with monogenic disease. Individuals with FH are exposed to elevated LDL-C levels since birth and this explains the high cardiovascular, mainly coronary heart disease, burden of these subjects. However, recent studies show that this risk is heterogenous and depends not only on high LDL-C levels but also on presence of previous cardiovascular disease, a monogenic cause, male sex, smoking, hypertension, diabetes, low HDL-cholesterol, obesity and elevated lipoprotein(a). This heterogeneity in risk can be captured by risk equations like one from the SAFEHEART cohort and by detection of subclinical coronary atherosclerosis. High dose high potency statins are the main stain for LDL-C lowering in FH, however, in most situations these medications are not powered enough to reduce cholesterol to adequate levels. Ezetimibe and PCSK9 inhibitors should also be used in order to better treat LDL-C in FH patients.

Contents

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CAC, coronary artery calcium; CHD, coronary heart disease; CI, confidence interval; CGPS, Copenhagen General Population Study; CCHS, Copenhagen City Heart Study; CVD, cardiovascular disease; DLCN, Dutch Lipid Clinic Network; FH, familial hypercholesterolemia; HDL-C, HDL-cholesterol; HeFH, heterozygous familial hypercholesterolemia; HR, hazard ratio; IMT, intima media thickness; LDL, low-density lipoprotein; LDL-C, LDL-cholesterol; LDLR, LDL receptor; Lp(a), lipoprotein(a); LPA, lipoprotein(a) gene; MEDPED, Make Early Diagnosis Prevent Early Death; NNT, number needed to treat; OR, odds ratio; RR, relative risk; PCSK9, proprotein convertase subtilisin kexin type 9; SAFEHEART, Spanish Familial Hypercholesterolemia Cohort Study; SPIRE, Studies of PCSK9 Inhibition and the Reduction of vascular Events.

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Familial hypercholesterolemia (FH) is an autosomal codominant disorder characterized by high low-density lipoprotein (LDL)-Cholesterol (LDL-C) and elevated lifetime risk of coronary heart disease (CHD).[1] One of the earliest descriptions of FH was made at the end of the 19th century[2] and the first description of FH heritability was made by Khachadurian in 1964 in Lebanese FH families.[3] Khachadurian demonstrated that individuals from affected families could present with 3 types of lipid profiles: blood cholesterol increased by 4-fold the normal; cholesterol increased by 2-fold the normal or normal cholesterol concentrations.[3] From this description appeared evidence of the homozygous and heterozygous forms of the disease.

FH is caused by mutations in genes that regulate LDL catabolism, mainly the LDL receptor (*LDLR*), apolipoprotein B (*APOB*) and gain of function of proprotein convertase subtilisin kexin type 9 (*PCSK9*). However, the phenotype may be encountered in individuals not carrying the latter monogenic defects, in approximately 20% of these effects of polygenes predominate, and in many individuals no molecular defects are encountered at all.[4,5] These so called FH phenocopy individuals have an elevated atherosclerotic cardiovascular disease (CVD; ASCVD) risk in comparison with normolipidemic individuals but this risk is lower than in those with monogenic disease.[6–8]

FH is one of the most common genetic lipid disorders and its prevalence is around 1/250 in general population and probably there are between 14 and 34 million individuals with FH worldwide.[9] Unfortunately, FH is underdiagnosed and undertreated in most countries.[9,10] Data from the 1999 to 2014 National Health and Nutrition Examination Survey estimated that only 52.3% of US adults with definite/probable FH were taking statins.[11] Therefore, awareness from patients and physicians about this disease is very important and might have implications for public health. In this review we discuss topics involving risk prediction and how to reduce CVD in FH population.

ASCVD risk

Individuals with FH are exposed to elevated LDL-C levels since birth. This explains the high ASCVD burden of these subjects. Natural history of CHD risk in FH population can be extrapolated from data of the Simon Broome cohort.[12] In this study 3553 patients were followed up between 1 January 1980 and 31 December 2015. FH diagnosis was done using clinical criteria either by Simon Broome or by using the Dutch Lipid Clinic Network (DLCN) criteria.[12] Definitive and possible FH individuals from all ages had 3.19-fold excess CHD mortality risk (95% CI 2.23–4.41, $p < 0.0001$) compared to the population in England and Wales pre 1992, before lipid-lowering therapy with statins was used routinely.

CVD risk is highest in younger FH compared to non-FH populations. For example, in a Norwegian registry including 5518 patients with genotyped FH, standardized mortality ratio for total CVD deaths occurring out of hospital, was 12.35 (95% CI 5.14–29.70) for those aged 20–39 years and decreased to 2.17 (95% CI 1.17–4.03) and 1.19 (95% CI 0.53–2.65) for, respectively, 40–59 and 60–69 years.[14]

ASCVD risk in FH patients is mainly driven by CHD. Stroke risk in FH remains controversial. The relationship of FH with ischemic stroke was studied by Beheshti et al.[13] The authors analyzed 2 large Danish cohorts: Copenhagen General Population Study (CGPS) and Copenhagen City Heart Study (CCHS). They found that the cumulative incidences in individuals in the CGPS with and without FH causative mutations were similar for ischemic stroke ($p = 0.50$). Similarly, in the CCHS also there was no association between FH mutations and risk of ischemic stroke ($p = 0.61$).[14] Using Simon Broome or US MEDPED (Make Early Diagnosis Prevent Early Death) criteria, there was no association between FH and risk of ischemic stroke. However, using DLCN criteria, there was an association between clinical FH and increased risk of ischemic stroke, with a HR of 1.30 (95% CI 1.08–1.56) for possible FH and 2.50 (95% CI 1.33–4.69) for definite or probable FH. This difference between clinical criteria used probably is explained by the personal premature ischemic heart disease at baseline item in DLCN criteria. The Spanish Familial Hypercholesterolemia Cohort Study (SAFEHEART) where only molecularly diagnosed heterozygous FH (HeFH) patients are included, mostly undergoing lipid lowering therapy, has shown results in the same direction, with no differences with controls regarding cerebrovascular events occurrence.[15]

Possibly peripheral arterial disease is more frequent in FH subjects. A Brazilian cross-sectional study included 202 HeFH patients (91% with molecular diagnosis) which were compared to 524 normolipidemic controls.[16] Peripheral arterial disease was diagnosed by ankle-brachial index values ≤0.90. The authors found that the prevalence of peripheral arterial disease was 17.3% and 2.3% respectively in FH and controls ($p < 0.001$). This result persisted after matching FH and controls by a propensity score. Also in the same direction, the SAFEHEART registry showed a greater prevalence of symptomatic peripheral arterial disease in FH patients than in controls: 1.4% versus 0.2% ($p < 0.001$).[15]

Classical risk factors and ASCVD

Despite the indisputable role played by elevated LDL-C in FH, other classical risk factors contribute for ASCVD risk in the FH population.[17] A retrospective Dutch cohort study included 2400 FH patients. The diagnosis of FH was based on the presence of an LDLR mutation or upon strict clinical criteria.[18] The following ASCVD risk factors were associated with CVD in FH subjects: male gender (RR 2.82, 95% CI 2.37–3.36), smoking (RR 1.67, 95% CI 1.40–1.99), hypertension (RR 1.36, 95% CI 1.06–1.75), diabetes mellitus (RR 2.19, 95% CI 1.36–3.54) and low high-density lipoprotein cholesterol (HDL-C; RR 1.37, 95% CI 1.15–1.63).[18]

A systematic review and meta-analysis of 27 full-text articles, representing 41,831 participants with 6629 ASCVD events, confirmed the importance of classical CVD risk factors. The authors found that age (OR: 1.07; 95% CI: 1.03, 1.10), male sex (OR: 1.95; 95% CI: 1.68, 2.23), hypertension (OR: 2.11;95% CI: 1.64, 2.58), diabetes (OR: 1.95; 95% CI: 1.33, 2.57), body mass index (OR: 1.04; 95% CI:1.03, 1.05), smoking (OR: 1.71; 95% CI: 1.30, 2.12), elevated lipoprotein(a) [Lp(a)] (OR: 1.90; 95% CI:1.10, 2.71), low HDL-C (OR: 1.39; 95% CI: 1.24, 1.53), and a family history of CVD (OR: 1.83, 95% CI: 1.58, 2.07) were significant ASCVD risk factors in FH.[19] Thus, undoubtedly classical CVD risk

factors should always be considered in ASCVD risk stratification of FH population.

Nontraditional CVD risk factors

Xanthomas

Tendon xanthomas are cholesterol deposits in tendons and may be detected by clinical examination and imaging studies.[20] Achilles tendon xanthoma is a very specific physical examination sign in FH subjects and is a criterion for FH clinical diagnosis in the DLCN score. In the past, xanthomas were described in 20–80% of FH patients, however, in contemporary molecularly proven FH populations where statin use is more prevalent, they are described in only around 15% of patients.[15,21]

Tendon xanthomas probably are markers of long-term exposure to high LDL-C levels and possibly share pathophysiological pathway with atherosclerosis. Homozygous FH develop tendon xanthomas early in life before age of 10 years old.[1] The association of Achilles tendon xanthomas and CVD was shown in previous cross-sectional studies. Mangili et al. demonstrated that Achilles tendon xanthomas are independently associated with the extension of subclinical coronary atherosclerosis quantified by tomographic scores in molecularly proven FH patients asymptomatic for CVD.[22] A previous meta-analysis showed that FH patients with xanthomas present a three-fold greater prevalence of previous ASCVD compared to subjects not having xanthomas.[22] The importance of tendon xanthomas in FH-CVD risk stratification was highlighted in the National Lipid Association Expert Panel on Treatment of adults with FH which includes tendon xanthoma as a CVD risk factor in individuals with FH.[23] Possibly intensive lipid lowering therapy could contribute to tendon xanthoma regression. A previous study observed a 5% reduction in tendon xanthoma thickness with PCSK9 inhibitors during a mean treatment period of almost 3 years.[24]

Lipoprotein(a) or Lp(a)

Lp(a) consists of an LDL particle with an additional apolipoprotein named apolipoprotein(a) [apo(a)] which is covalently linked to the apolipoprotein B-100 (ApoB) moiety of the LDL particle.[25] Plasma concentrations of Lp(a) are mainly determined by the *LPA* gene (90%). Elevated levels of Lp(a) are strong and independent risk markers for myocardial infarction (MI), stroke, and aortic valve stenosis in the general population.[26–28]

There is much evidence that high Lp(a) also increases ASCVD in FH subjects. A sub-study from SAFEHEART analyzed the role of Lp(a) as a predictor of ASCVD and the relationship with the type of *LDLR* gene mutation in 1960 He FH with molecular diagnosis.[29] Lp(a) was an independent predictor of ASCVD (OR: 1.007; 95% CI: 1.004 to 1.011; $p < 0.0001$) and patients carrying null mutations and Lp(a) levels >50 mg/dL showed the highest CVD risk compared with patients carrying either defective mutations and higher Lp(a) or null mutations with lower Lp (a). A retrospective, multi-center, Dutch cohort study included 2400 FH patients and showed that elevated Lp(a) levels proved to be one of the independent ASCVD risk factors (RR 1.50, 95% CI 1.20–1.79). Other studies also support these findings (Table 1).

ASCVD risk stratification

Fig. 1 indicates biomarkers or conditions associated with a higher ASCVD risk in FH individuals. In the general population, ASCVD risk stratification is based on risk scores, such as the Framingham Risk Score or the Pooled Cohort Equation (AHA/ACC). The variables included in these scores are the classical risk factors: age, HDL-C, total cholesterol, systolic blood pressure, smoking and diabetes. However, these scores are not designed to be applied in FH subjects and possibly underestimate ASCVD risk in this population. This occurs due to lifelong exposure to high LDL-C in FH that is not considered on these scores.

Two risk scores were specifically designed for FH populations. The first one was the Montreal risk score.[30] This Canadian score was based on a total of 670 adult Caucasian subjects with a known mutation in the LDLR gene. The authors identified the strongest predictors of CVD in patients with FH and developed a score to identify FH patients at very high ASCVD risk. They showed that age ($\beta = 0.75$), HDL-C ($\beta = -0.27$), male gender ($\beta = 0.25$), hypertension ($\beta = 0.19$) and smoking ($\beta = 0.12$) were independent predictors of ASCVD risk.[30] Subsequently they elaborated a score (Montreal-FH-SCORE) that significantly predicted ASCVD (AUC of 0.840 (0.808–0.872), $p < 0.0001$). FH subjects with Montreal-FH-SCORE score above 20 presented a significant 10.3-fold higher odds of presenting ASCVD events compared to subjects in the lower score group (95% CI 6.7–17 15.7, $p < 0.0001$). Paquette et al. validated this score in a cohort of 718 adult FH individuals.[30] They found an area under the receiver operating characteristic curve of 0.799 (95% CI 0.766–0.832, $p < 0.0001$). The main limitation of this score was that it was based on a cross sectional design study and included only Caucasian subjects. This score needs to be validated in a larger and prospective study of multiethnic cohorts.

The second score was the SAFEHEART risk equation.[31] The SAFEHEART is a Spanish multicenter, prospective cohort study of a molecularly defined population with FH with or without previous ASCVD. The authors elaborated a risk equation to predict 5 and 10-year ASCVD risk based on variables associated to ASCVD in the SAFEHEART registry. This study identified increased age, male sex, history of ASCVD, high blood pressure, increased body mass index, active smoking, LDL-C and Lp(a) levels as independent prospective predictors of increased risk of incident ASCVD in patients with FH, which were

Table 1
Lp(a) and ASCVD risk in FH populations.

Country/year of publication	FH diagnosis	Study design	N	Outcome	OR or RR for Lp(a)	Findings
Canada/1996[69]	Molecular (French-Canadian >10-kb deletion of the LDL receptor gene)	Case-control	98 FH subjects and 66 healthy first- and second-degree relatives	Atherosclerotic vascular disease	N/A	No difference in Lp(a) values
Dutch/2004[18]	Molecular or clinical criteria	Retrospective, cohort study.	2400 FH	Cardiovascular mortality and CVD.	RR 1.50, (95% CI 1.20–1.79)	Lp(a), male gender, smoking, hypertension, diabetes mellitus, low HDL-c were independent CVD risk factors
Spain/2014[29]	Molecular	Cross sectional	1960 FH and 957 non-FH	CVD	OR 1.008 (95% CI 1.005–1.010)	Lp(a) is an independent predictor of CVD in men and women with FH
Canada/2019[70]	Molecular	Retrospective, cohort study; association of rs10455872 *LPA* gene with CVD	668 FH	CVD	OR: 1.97; (95% CI 1.05–3.68)	*LPA* variant rs10455872 is a good predictor of premature CVD risk in FH

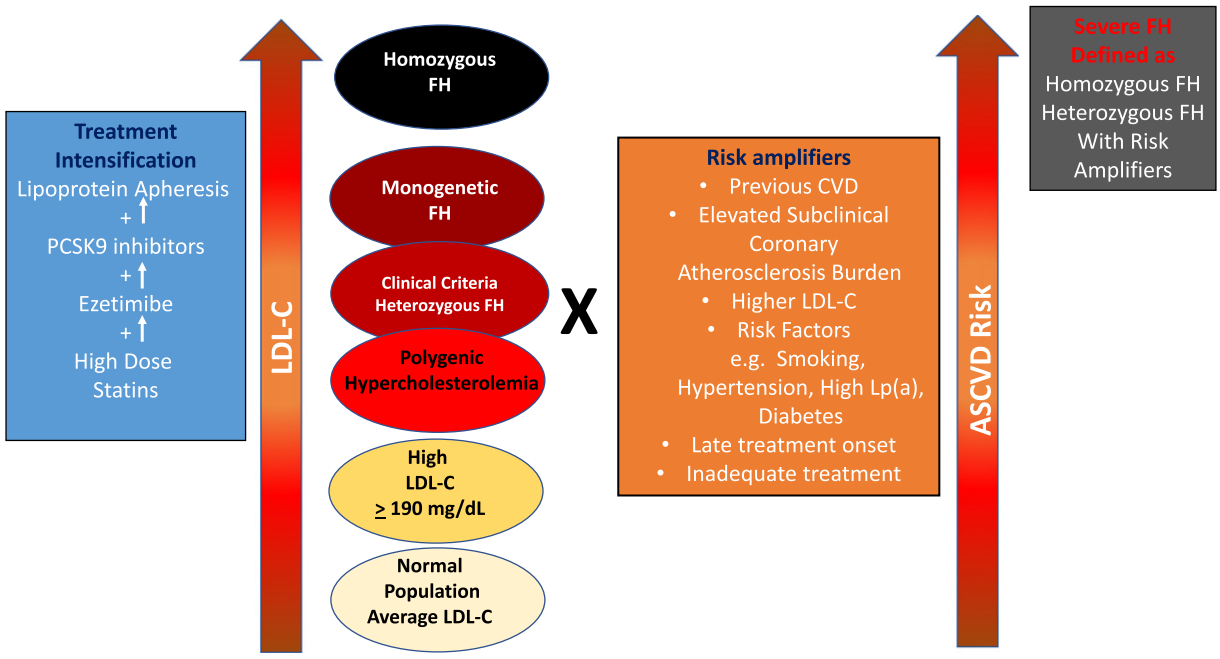

Fig. 1. Biomarkers, genetic backgrounds, conditions and treatments associated with higher atherosclerotic cardiovascular disease risk in Familial hypercholesterolemia. ASCVD risk is proportional to LDL-C levels, previous cardiovascular disease, elevated subclinical atherosclerosis burden, monogenic defects and presence of classic risk biomarkers. The higher the risk and LDL-C, additional LDL-C lowering therapies to statins are recommended.

subsequently used to develop the SAFEHEART risk equation.[31] The Harrell C index respectively for SAFEHEART risk equation, Framingham risk score and the American College of Cardiology/American Heart Association ASCVD Pooled Cohort Risk Equations for discrimination of ASCVD in patients without an established diagnosis of ASCVD before enrollment in the registry were respectively: 0.81, 0.78, and 0.8. The differences between the SAFEHEART risk equation and the other 2 were significant ($p = 0.023$ and $p = 0.045$). The authors developed equations for both individuals with or without a previous ASCVD manifestation. A clinical practice application of potential use of SAFEHEART equation risk in deciding about PCSK9 inhibitors treatment was published by Perez de Isla et al.[32] The authors showed that the number needed to treat (NNT) were dependent of both baseline predicted risk and LDL-C levels. The smallest NNT ($n = 12$) for PCSK9 inhibitors was observed among those FH subjects with 5-year risk of ≥5% and LDL-C ≥160 mg/dL. Despite the apparent potential use of these risk scores in FH subjects, external validation is still needed in larger cohorts to a more widespread use of these tools in FH ASCVD risk stratification.

Genetics

Historically FH was considered as a disease characterized by an individual with high LDL-C with either family history of premature CHD or high LDL-C.[1] Phenotype was so important that the presence of a mutation was not a mandatory criterion in many FH clinical diagnosis criteria (US MEDPED, Simon Broome and DLCN). However, more recent evidence reveals that a pathogenic FH mutation carries importance not only for diagnosis and cascade screening but also for prognosis.[4]

Patients with high LDL-C but absence of monogenic defects possibly have polygenic hypercholesterolemia or another etiology, which in general has a better prognosis compared to monogenic FH. Khera et al. showed that patients with high LDL-C (>190 mg/dL) and no FH mutations had a 6-fold higher risk for CHD and those with both high LDLC and a FH mutation had a 22-fold higher risk compared to subjects with normal LDL-C and no mutation.[6] Sharifi et al. expanded this knowledge to subclinical atherosclerosis (carotid intima media thickness-intima media thickness or cIMT and coronary artery calcium-CAC) and found that after adjustment for age and gender, the mean of cIMT measurements and CAC scores were significantly greater in the monogenic than the polygenic patients: carotid IMT mean: 0.74 mm vs. 0.66 mm, $p = 0.038$ and CAC score mean: 24.5 vs. 2.65 Agatston units, $p = 0.0004$.[7]

A Canadian registry enrolled patients that had a clinical diagnosis of FH according to the DLCN score and genotyped them for monogenic FH mutations and a polygenic score (those with a weighted polygenic score ≥80th percentile were considered to have polygenic hypercholesterolemia).[8] The authors included 626 patients and mean follow-up was 7.2 years. Those with monogenic defects had higher LDL-C levels than those with high polygenic scores and those with no molecular defects associated with high LDL-C. The study confirmed that monogenic causes of FH were associated with a marked greater risk of premature ASCVD (adjusted HR: 1.96; 95% CI: 1.24 to 3.12; $p = 0.004$). However, risk of ASCVD in patients with polygenic hypercholesterolemia was not significantly different compared with patients in whom no genetic cause of FH was identified. Interestingly the elevated polygenic risk score potentiated ASCVD risk in patients with monogenic FH (adjusted HR: 3.06; 95% CI: 1.56 to 5.99; $p = 0.001$)[8] despite no differences in LDL-C from those with monogenic disease and a low score.

These studies strongly suggest the role played by the monogenic defect in ASCVD development in hypercholesterolemic subjects. Indeed, the definition of FH itself is challenged by the fact that in 40% of individuals with the phenotype no molecular defects are encountered despite the advanced molecular technologies.[4] In addition to a greater ASCVD risk, monogenic defects are also a marker of better cost effectiveness of cascade screening, considering the heterogenous inheritance of polygenes.[5]

Subclinical atherosclerosis

Coronary calcium score

CAC scores reflect the degree of coronary atherosclerotic plaque burden and there is indisputable evidence that this biomarker is independently associated to CHD events. Subjects with CAC score of zero have low risk of suffering a CHD event in 10 years,[33] on the other hand

subjects with very high CAC scores have CHD risk that is similar to secondary prevention patients.[34] CAC improves CHD risk stratification as it also improves discrimination and reclassification of clinical risk scores and is recommended as an additional tool for risk stratification.[35]

FH individuals have increased CAC compared to non-affected subjects.[36–38] Martinez et al. showed that the determinants of CAC as a continuous variable were male sex and the LDL-C year score (a marker of exposition to LDL-C for lifetime) ($r^2 = 0.32$).[36] A French study showed similar association of CAC with cholesterol burden.[39] The authors included 112 genetically diagnosed FH patients and showed that total cholesterol burden (calculated as total cholesterol × age at diagnosis plus annually assessed total cholesterol) was independently associated to CAC after multivariate analysis.

However, how could CAC help on ASCVD risk stratification of FH subjects? Is there any evidence that CAC could be associated to ASCVD in this population? An insight about these questions was approached by our group that evaluated the possible role of CAC as a predictor of ASCVD events in a prospective cohort of subjects with asymptomatic HeFH.[40] Miname et al. included a total of 206 molecularly proven FH subjects undergoing standard lipid lowering therapy that were followed for a median of 3.7 years (interquartile range: 2.7 to 6.8 years). CAC was positive in 105 (51%), a fact also seen in other cohorts[41] and, 15 ASCVD events (7.2%) were documented. Interestingly subjects with zero CAC did not experience an ASCVD event, on the other hand a high CAC was associated with high ASCVD incidence. In multivariate Cox regression analysis, log(CAC score + 1) was independently associated with incident ASCVD events (HR: 3.33; 95% CI: 1.635 to 6.790; $p = 0.001$) where LDL-C was not. These results indicate that CAC could improve ASCVD risk stratification in FH subjects. However, we still need more studies to prove if this method could be used to select those that probably should benefit from more intensive lipid lowering therapy with PCSK9 inhibitors.

Computed coronary tomography angiography

Computed coronary tomography angiography (CTCA) allows the identification of both artery wall and lumen diseases, e.g. lumen obstructions. CTCA had some advantages and disadvantages compared to CAC. The advantages are information about lumen obstructions, visualization of non-calcified plaques, a theoretical advantage in younger individuals, and information about plaque composition. Main disadvantages are higher costs, necessity of intravenous contrast injection, higher radiation exposure and costs.

Most evidence shows that this imaging methodology could be useful in evaluation of symptomatic patients to rule out CHD as cause of symptoms.[42] For asymptomatic individuals we still do not have evidence that CTCA could improve outcome due to treatment guided by findings of this test. CTCA, however, helped to chart a pattern profile of subclinical coronary atherosclerosis in FH subjects. Miname et al. described for the first-time subclinical atherosclerosis patterns with CTCA in HeFH.[37] They studied 102 asymptomatic FH subjects (36% male, 45 ± 13 years, mean LDL-C 280 mg/dL) and 35 age and gender normolipidemic matched controls (mean LDL-C 103 mg/dL). HeFH subjects had a greater atherosclerotic burden represented by higher numbers of patients with: plaques (48% vs. 14%, $p = 0.0005$), coronary stenosis (19% vs. 3%, $p = 0.015$), segments with plaques (2.05 ± 2.85 vs. 0.43 ± 1.33, $p = 0.0016$) and CAC scores (55 ± 129 vs.38 ± 140, $p = 0.0028$). After multivariate analysis, determinants of plaque presence were increasing age (OR = 2.06, for age change of 10 years, 95% CI: 1.38–3.07, $p < 0.001$) and total cholesterol levels (OR = 1.86, for change in 1SD of cholesterol levels, 95% CI: 1.09–3.15, $p = 0.027$). CAC score was associated with the presence of stenosis (OR = 1.54; 95 CI%: 1.27–1.86, $p < 0.001$, for doubling the calcium score). Neefjes et al. also showed higher coronary plaque burden presence detected by CT angiography in HeFH subjects.[43] The median total CAC score was higher in patients with FH than in non-FH subjects (Agatson score 87 vs. 7, $p < 0.001$). The severity and extent of obstructive disease on a per patient and a per segment level was also significantly higher in patients with FH. The number of coronary segments with non-obstructive or obstructive coronary disease was higher in patients with FH in all age groups and increased with higher age. The same authors subsequently published a prospective cohort study of an extended patient population of 140 asymptomatic HeFH patients (90 men; mean age 52 ± 8 years), who had been treated with high statin dosages, with a clinical follow-up of 29 ± 8 months.[38] The CAC score was 0 in 21% of the patients. In 16% there was no CT evidence of any coronary artery disease while 24% had obstructive disease. After multivariate analysis, plaque burden was directly related to male gender and post treatment LDL-C levels and inversely associated with HDL-C. There was a low incidence of cardiac events and no cardiac death occurred during follow-up.

Perez de Isla et al.[41] in an imaging sub study of SAFEHART showed in 440 FH individuals (mean age 46.4 years, 52% women) that a CAC score of zero was encountered in 46%; 46% also presented with a coronary plaque with lumen involvement. Coronary obstructions 50–70% and >70% were found respectively in 16% and 6% of studied subjects.

All these CTCA studies showed a higher subclinical coronary plaque burden in FH subjects. However, there are still some unanswered questions: is there an association of subclinical atherosclerosis on CTCA with ASCVD events in FH subjects? The information provided by CTCA improves ASCVD stratification risk over classical risk factors or CAC alone in FH subjects? CTCA could help to select FH subjects that would most benefit from more aggressive lipid lowering therapy, for example PCSK9 inhibitors?

A small Japanese study showed that a score based on coronary artery segments with stenosis in CTCA was associated with major adverse cardiac events.[44] However, this study did not give a definite answer due to small sample size and retrospective design.

Carotid intima media thickness (IMT) or cIMT

The cIMT measurement by B-mode ultrasound is defined as the distance between the lumen-intima and the media-adventitia interfaces. Despite not being synonomous for atherosclerosis, cIMT has been used as a surrogate of vascular disease. There is evidence that HeFH subjects have greater IMT values than normolipidemic subjects since the childhood.[45] Some studies assessed cIMT evolution as surrogate end points to track treatment effects in HeFH subjects.[46,47]

Previous evaluations comparing subclinical vascular disease in the coronaries, carotids and the aorta in HeFH subjects and matched controls showed that there was no agreement degree between these vascular sites.[36,37] Of importance, the severity of subclinical carotid disease did not predict the severity of CAC burden suggesting that cIMT might not be a good surrogate of coronary plaque burden. Indeed the MESA study, in non-FH subjects, has shown superiority of CAC over cIMT in predicting CHD events in the general population.[48]

Severe FH concept

In 2016, the International Atherosclerosis Society (IAS) published a consensus statement in order to define severe FH subjects who would benefit from more aggressive cholesterol-lowering treatment.[17] The definition of severe FH is seen in Table 2. Obviously those at highest risk are those with the homozygous FH phenotype (LDL-C usually >400 mg/dL), those with previous manifestation of ASCVD, those with very high LDL-C (usually >310 mg/dL and one risk factor) and those with high LDL-C (>190 mg/dL) with 2 other CVD risk factors. In addition, the presence of advanced subclinical atherosclerosis also indicates a higher risk FH individual. The authors proposed that severe FH subjects who are not at ideal goal or <50% LDL-C reduction should be treated more intensively with triple drug therapy (associate PCSK9 inhibitor to maximum tolerated statin plus ezetimibe).[17] Recently in the Simon Broome registry[49] the definition of severe FH proposed by the IAS[17]

Table 2
Severe FH criteria according to the International Atherosclerosis Society.[17]

Criteria:	Treatment recomendation[a]
a) At presentation (untreated LDL cholesterol): LDL-C >400 mg/dL or LDL-C >310 mg/dL and one high-risk feature or LDL-C >190 mg/dL and two high-risk features	Realistic goal is to reduce LDL-C by ≥50%; the ideal goal is to achieve LDL-C <100 mg/dL.
b) Presence of advanced subclinical atherosclerosis: CAC score >100 Agatston units or >75th percentile for age and sex; or CT angiography with obstructions >50% or presence of non-obstructive plaques in more than one vessel	Realistic goal is to reduce LDL-C by ≥50%; the ideal goal is to achieve LDL-C <70 mg/dL
c) Presence of clinical atherosclerotic cardiovascular disease: Clinical atherosclerotic cardiovascular disease defined as previous myocardial infarction, angina, coronary revascularization, non-embolic ischemic stroke, or transitory ischemic attack, and intermittent claudication.	Realistic goal is to reduce LDL-C by ≥50%; the ideal goal is to achieve LDL-C <70 mg/dL

High-risk biomarkers or conditions are: age >40 years without treatment; smoking; male sex; lipoprotein(a) >75 nmol/L (50 mg/dL); HDL cholesterol 40 mg/dL; hypertension; diabetes mellitus; family history of early cardiovascular disease in first-degree relatives (age <55 years in men and <60 years in women); chronic kidney disease (i.e., estimated glomerular filtration rate <60 mL/min per 1.73 m^2; and BMI >30 kg/m^2).

[a] Calcium scores calculated using criteria from the Multi-Ethnic Study of Atherosclerosis.

was validated in 2929 FH individuals followed by 24 years. Those with severe FH diagnosis, not only by higher LDL-C levels, but also by the presence of the classical atherosclerosis risk factor had a 1.93 (95% CI 1.33–2.79) higher standardized mortality ratio than those with non-severe forms, p = 0.0005. This risk was mostly attributed to the presence of risk factors other than high cholesterol.

Treatment

Lifestyle measures should be initiated for all FH subjects: a diet low in saturated and trans fats with emphasis in mono and polyunsaturated fats, complex carbohydrates, fruits, low fat dairy products, lean meats and fish and vegetables is very important. Counselling regarding smoking cessation, regular exercise and appropriate calorie intake must be provided. Additional ASCVD risk factors, including hypertension and diabetes mellitus, should also be assessed and treated appropriately if necessary.

The treatment of FH includes aggressive lipid lowering therapy because patients frequently have 2–4-fold higher LDL-C than normolipidemic individuals.[1] Obviously there are no randomized clinical trials of lipid lowering therapy in FH subjects because of disease frequency and because this should be unethical, however there are observational data that show ASCVD risk reduction in FH subjects with LDL-C reduction by either statins or PCSK9 inhibitors.[12,50–53]

Statins

Statins are the main lipid lowering treatment in FH subjects and high doses of high-potency medications (atorvastatin 40–80 mg and rosuvastatin 20–40 mg) are preferred, owing to their superior efficacy. Although there is no randomized trial with statin in FH population, data from observational studies show that the introduction of these medications changed the natural history of FH. The UK Simon Broome Register has shown that since the introduction and widespread use of statins, the prognosis for patients with HeFH has improved markedly, with a reduction in coronary mortality of about a third.[12]

An observational Dutch study showed that after additional adjustment for other cardioprotective medication, the hazard ratio for statins was found to be protective for CHD and all-cause mortality (HR: 0.56; 95% CI: 0.33 to 0.96).[51] A Danish study showed that the odds ratio for coronary artery disease off cholesterol-lowering medication was 13.2 (95% CI 10.0–17.4) in definite/probable FH compared with non-FH subjects, after adjusting for other risk factors and the corresponding adjusted odds ratio for coronary artery disease in FH subjects on cholesterol-lowering medication reduced to 10.3 (95% CI 7.8–13.8).[53]

Ezetimibe

Ezetimibe is a cholesterol-lowering medication that acts by inhibiting enteric absorption via binding to Niemann-Pick C1-Like 1 (NPC1L1) protein.[54] Ezetimibe reduces LDL-C by around 18%.[54] The combination of statin and ezetimibe promotes additive LDL-C reduction by acting on both exogenous (ezetimibe) and endogenous (statin) pathways of cholesterol metabolism. Although the ENHANCE study did not show a reduction in cIMT associated with ezetimibe/simvastatin in patients with FH,[47], the IMPROVE-IT study later proved the clinical benefit of this association by demonstrating a reduction in CVD outcomes with the ezetimibe 10 mg/simvastatin 40 mg combination versus placebo/simvastatin 40 mg in patients after acute coronary syndrome.[55] Due to its safe profile, low-cost and efficacy combined to statin, ezetimibe should be the second option after statin if FH subjects still need additional lipid lowering medication.

PCSK9 inhibitors

PCSK9 became a focus of interest after genetic studies showed that patients with *PCSK9* gain of function mutations had an FH phenotype[56] and patients with loss of function of this protein had lower LDL-C and lower CHD risk.[57]

Inhibition of PCSK9 reduces plasma LDL-C levels by reducing LDLR degradation as previously described.[57]The main technology used for PCSK9 inhibition are monoclonal antibodies. PCSK9 monoclonal antibodies are administered subcutaneously and bind to circulating PCSK9. The PCSK9/monoclonal antibody complex is further metabolized to the reticuloendothelial system with consequent reduction in circulating PCSK9 levels.

Monoclonal antibodies can be humanized (3% murine and 97% human) or fully human. The representative of the first category was bococizumab, which, although initially effective in reducing LDL-C, showed progressive loss of function caused by the production of neutralizing antibodies.[58] Such occurrence led to non-commercialization of this medication. However, in Studies of PCSK9 Inhibition and the Reduction of vascular Events (SPIRE) program, the subgroup of statin-treated cardiovascular FH subjects had a similar magnitude of risk reduction for hard CVD events with bococizumab as did patients without FH, with no evidence of statistical heterogeneity between groups for FH: HR 0.83; 95% CI 0.44–1.54 and for non FH: HR 0.79, 95% CI 0.64–0.97; p for heterogeneity between groups: 0.87.[52]

Two fully human monoclonal antibodies are currently on the market: alirocumab (75–150 mg every 2 weeks or 300 mg once a month) and evolocumab (140 mg every 2 weeks or 420 mg once a month), this one also approved for homozygous FH.[58] Both PCSK9 inhibitors demonstrated efficacy in reducing CVD outcomes in very high-risk populations.[59,60] Previous studies in FH populations showed that both medications were found to significantly reduce LDL-C by >50–60% and also support a lower rate of lipid apheresis in FH patients receiving a PCSK9 inhibitor.[61] In 2017 the ESC/EAS Task Force published a practical clinical guidance for PCSK9 inhibition (Table 3).[62] They recommend that PCSK9 inhibitors persist with high LDL-C levels and high CVD risk.

Other therapies for severe FH forms

Lomitapide and until recently mipomersen (this drug had is approval suspended in August 2019 due to commercial problems and low

Table 3
Recommendations for PCSK9 inhibitor use in FH patients according to the European Societies of Cardiology and Atherosclerosis (ESC/EAS).[61]

	Additional indices of risk severity
a) Clinical ASCVD with LDL-C >100 mg/dL b) Primary prevention and no additional indices of risk severity with LDL-C >180 mg/dL c) Primary prevention with additional indices of risk severity and LDL-C >140 mg/dL	Diabetes mellitus with target organ damage or with a major risk factor; lipoprotein(a) >50 mg/dL; major risk factors: smoking, marked hypertension; >40 years of age without treatment; premature ASCVD in first-degree relatives; imaging indicators of subclinical disease.

tolerability) are alternatives for refractory homozygous FH patients.[1] Lipoprotein apheresis when available remains a robust procedure for LDL-C and Lp(a) lowering in severe forms of FH.[63]

What we can do to improve care of FH?

Awareness and diagnosis

Less than 1% of FH subjects are diagnosed in most countries. The few exceptions are 71% diagnosed in the Netherlands, 43% in Norway, 19% in Iceland, 13% in Switzerland, 12% in the UK, and 6% in Spain.[9] A subanalysis of the "Ten Countries Study" done in Asia-Pacific and Southern Hemisphere showed that in most participating countries <3% of FH cases were diagnosed.[10] There was a gradient with lesser diagnosis in less developed regions of the world in comparison with the UK.

The best approach for the underdiagnosis issue is improving systematic cholesterol screening. The cascade testing of family members of known index cases of FH is cost-effective in detecting FH but this requires identification of index cases.[1] Consistent with this, both systematic and opportunistic detection strategies for FH screening should be developed and incorporated in the health system of each country.

An example of screening program was previously published with children 1 to 2 years of age during routine immunization visits.[64] The authors obtained capillary blood samples to measure cholesterol levels and to test for familial hypercholesterolemia mutations in 10,095 children. They identified 40 children who had positive screening results for familial hypercholesterolemia (0.4% of the children, including 32 children who had a FH mutation and 8 who did not have the mutation but had high cholesterol level) and 40 parents who had positive screening results for FH. The overall mutation prevalence was 1 in 273 children (37 in 10,095; 95% CI, 1 in 198 to 1 in 388).

A previous study already showed that using genetic testing plus measurement of LDL-C and treatment with statins, is a cost-effective means of preventing CHD in families at risk of FH.[65] The main problem is access to genetic testing because it is not yet widely available in most countries. However, physicians should consider FH diagnosis if LDL-C is >190 mg/dL in adults and/or >160 mg/dL in children, mainly if premature CHD is positive in relatives. Clinical diagnostic criteria should be applied, and lipid profile of first-degree relatives must be verified.

Improving treatment

Besides being underdiagnosed, FH subjects also are undertreated. An example of this fact was shown among US adults participating at the National Health and Nutrition Examination Survey.[11] In this study FH was diagnosed using the modified version of the DLCN criteria to identify individuals having definite or probable FH. Statin use was disturbingly low; only 52.3% of adults with definite/probable FH were on a documented statin. Less than half of those on statins (30.3% for definite/probable FH) were prescribed a higher-intensity statin. Data from a multinational, cross-sectional, observational study also included participants with definite or probable FH according to DLCN criteria.[66] They showed that most were receiving statins (99%). However, of these, 57.6% were on high-intensity statin therapy, and 13.0% used a statin associated with a cholesterol absorption inhibitor. Only 32.0% of patients achieved their LDL-C target.[66] In the SAFEHEART cohort although 71.8% of FH subjects were on maximal lipid lowering therapy, an LDL-C treatment target <100 mg/dL was reached by only 11.2% of patients.[67]

How to change this scenario? First of all, increased use of high-intensity statins and combined therapy with ezetimibe should be established in FH care. In this aspect, education of patients about this disease and treatment safety should be reinforced to improve adherence in particular to high dose of medications. Second, physician inertia to treat FH patients and accommodate with high LDL-C levels should be attenuated with medical education. Third, improve ASCVD risk stratification in the FH population in order to select those who will most benefit from more intensive lipid lowering therapy, in particular with PCSK9 inhibitors. Unfortunately, high cost of these medications still is a strong barrier for their access especially in developing regions of the world. A recently published study with real-world observational data indicate that access to PCSK9 inhibitors has an important impact on cardiovascular outcomes in the patients with high risk who are prescribed these medications.[68] In this study the HRs for composite cardiovascular events outcome in propensity score-matched analyses were 1.10 (95% CI, 1.01–1.19; $p = 0.02$) for rejected versus paid PCSK9 inhibitor and 1.12 (95% CI, 1.01–1.24; $p = 0.03$) for abandoned versus paid PCSK9 inhibitor.[68] Another worrying finding in this study is that higher PCSK9 inhibitor rejection rates were observed with women, racial minorities, and lower-income groups. The correct identification of FH subjects that most benefit from PCSK9 inhibitors will improve cost effectiveness of this medication and bring strong arguments for payers.

Conclusions

Although there has been great evolution in FH knowledge and treatment modalities in the last decade, the reality evolving its care is far from ideal. Public health policies for improving diagnosis, cascade screening and treatment should be implemented. Physician and patients' education programs could in part attenuate the problems around FH care.

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References

1. Defesche JC, Gidding SS, Harada-Shiba M, Hegele RA, Santos RD, Wierzbicki AS. Familial hypercholesterolaemia. Nat Rev Dis Primers 2017;3, 17093.
2. Steinberg D. Thematic review series: the pathogenesis of atherosclerosis. An interpretive history of the cholesterol controversy: part II: the early evidence linking hypercholesterolemia to coronary disease in humans. J Lipid Res 2005;46(2):179-190.
3. Khachadurian AK. The inheritance of essential familial hypercholesterolemia. Am J Med 1964;37:402-407.
4. Sturm AC, Knowles JW, Gidding SS, et al. Clinical genetic testing for familial hypercholesterolemia: JACC Scientific Expert Panel. J Am Coll Cardiol 2018;72(6):662-680.
5. 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.
6. Khera AV, Won HH, Peloso GM, et al. Diagnostic yield and clinical utility of sequencing familial hypercholesterolemia genes in patients with severe hypercholesterolemia. J Am Coll Cardiol 2016;67(22):2578-2589.

7. Sharifi M, Higginson E, Bos S, et al. Greater preclinical atherosclerosis in treated monogenic familial hypercholesterolemia vs. polygenic hypercholesterolemia. Atherosclerosis 2017;263:405-411.
8. Trinder M, Li X, DeCastro ML, et al. Risk of premature atherosclerotic disease in patients with monogenic versus polygenic familial hypercholesterolemia. J Am Coll Cardiol 2019;74(4):512-522.
9. 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):3478-3490a.
10. Pang J, Chan DC, Hu M, et al. Comparative aspects of the care of familial hypercholesterolemia in the "Ten Countries Study". J Clin Lipidol 2019;13(2):287-300.
11. Bucholz EM, Rodday AM, Kolor K, Khoury MJ, Prevalence de Ferranti SD. Predictors of cholesterol screening, awareness, and statin treatment among US adults with familial hypercholesterolemia or other forms of severe dyslipidemia (1999-2014). Circulation 2018;137(21):2218-2230.
12. Humphries SE, Cooper JA, Seed M, et al. Coronary heart disease mortality in treated familial hypercholesterolaemia: update of the UK Simon Broome FH register. Atherosclerosis 2018;274:41-46.
13. Beheshti S, Madsen CM, Varbo Benn M, Nordestgaard BG. Relationship of familial hypercholesterolemia and high low-density lipoprotein cholesterol to ischemic stroke. Circulation 2018;138:578-589.
14. Mundal L, Igland J, Ose L, et al. Cardiovascular disease mortality in patients with genetically verified familial hypercholesterolemia in Norway during 1992-2013. Eur J Prev Cardiol 2017;24(2):137-144.
15. Perez de Isla L, Alonso R, Mata N, et al. Coronary heart disease, peripheral arterial disease, and stroke in familial hypercholesterolaemia: insights from the SAFEHEART Registry (Spanish Familial Hypercholesterolaemia Cohort Study). Arterioscler Thromb Vasc Biol 2016;36(9):2004-2010.
16. Pereira C, Miname MH, Makdisse MR, et al. Peripheral arterial disease in heterozygous familial hypercholesterolemia. Atherosclerosis 2015;242(1):174-178.
17. Santos RD, Gidding SS, Hegele RA, et al. Defining severe familial hypercholesterolaemia and the implications for clinical management: a consensus statement from the International Atherosclerosis Society Severe Familial Hypercholesterolemia Panel. Lancet Diabetes Endocrinol 2016;4(10):850-861.
18. Jansen AC, van Aalst-Cohen ES, Tanck MW, et al. The contribution of classical risk factors to cardiovascular disease in familial hypercholesterolaemia: data in 2400 patients. J Intern Med 2004;256(6):482-490.
19. Akioyamen LE, Genest J, Chu A, Inibhunu H, Ko DT, Tu JV. Risk factors for cardiovascular disease in heterozygous familial hypercholesterolemia: a systematic review and meta-analysis. J Clin Lipidol 2019;13(1):15-30.
20. Tsouli SG, Kiortsis DN, Argyropoulou MI, Mikhailidis DP, Elisaf MS. Pathogenesis, detection and treatment of Achilles tendon xanthomas. Eur J Clin Invest 2005;35(4):236-244.
21. Jannes CE, Santos RD, de Souza Silva PR, et al. Familial hypercholesterolemia in Brazil: cascade screening program, clinical and genetic aspects. Atherosclerosis 2015;238(1):101-107.
22. Mangili LC, Miname MH, Silva PRS, et al. Achilles tendon xanthomas are associated with the presence and burden of subclinical coronary atherosclerosis in heterozygous familial hypercholesterolemia: a pilot study. Atherosclerosis 2017;263:393-397.
23. Robinson JG, Goldberg AC, National Lipid Association Expert Panel on Familial H. Treatment of adults with familial hypercholesterolemia and evidence for treatment: recommendations from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. J Clin Lipidol 2011;5(suppl 3):S18-S29.
24. Bea AM, Perez-Calahorra S, Marco-Benedi V, et al. Effect of intensive LDL cholesterol lowering with PCSK9 monoclonal antibodies on tendon xanthoma regression in familial hypercholesterolemia. Atherosclerosis 2017;263:92-96.
25. Gencer B, Kronenberg F, Stroes ES, Mach F. Lipoprotein(a): the revenant. Eur Heart J 2017;38(20):1553-1560.
26. Kamstrup PR, Benn M, Tybjaerg-Hansen A, Nordestgaard BG. Extreme lipoprotein (a) levels and risk of myocardial infarction in the general population: the Copenhagen City Heart Study. Circulation 2008;117(2):176-184.
27. Kamstrup PR, Tybjaerg-Hansen A, Nordestgaard BG. Elevated lipoprotein(a) and risk of aortic valve stenosis in the general population. J Am Coll Cardiol 2014;63(5):470-477.
28. Emerging Risk Factors C, Erqou S, Kaptoge S, et al. Lipoprotein(a) concentration and the risk of coronary heart disease, stroke, and nonvascular mortality. Jama 2009;302(4):412-423.
29. 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.
30. Paquette M, Dufour R, Baass A. The Montreal-FH-SCORE: a new score to predict cardiovascular events in familial hypercholesterolemia. J Clin Lipidol 2017;11(1):80-86.
31. Perez de Isla L, Alonso R, Mata N, et al. Predicting cardiovascular events in familial hypercholesterolemia: the SAFEHEART Registry (Spanish Familial Hypercholesterolemia Cohort Study). Circulation 2017;135(22):2133-2144.
32. Perez de Isla L, Ray KK, Watts GF, et al. Potential utility of the SAFEHEART risk equation for rationalising the use of PCSK9 monoclonal antibodies in adults with heterozygous familial hypercholesterolemia. Atherosclerosis 2019;286:40-45.
33. Budoff MJ, Young R, Burke G, et al. Ten-year association of coronary artery calcium with atherosclerotic cardiovascular disease (ASCVD) events: the multi-ethnic study of atherosclerosis (MESA). Eur Heart J 2018;39(25):2401-2408.
34. Peng AW, Mirbolouk M, Orimoloye OA, et al. Long-term all-cause and cause-specific mortality in asymptomatic patients with CAC >/=1,000: results from the CAC consortium. JACC Cardiovasc Imaging 2019. https://doi.org/10.1016/j.jcmg.2019.02.005 [Epub ahead of print].
35. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2019;73(24):e285-e350.
36. Martinez LR, Miname MH, Bortolotto LA, et al. No correlation and low agreement of imaging and inflammatory atherosclerosis' markers in familial hypercholesterolemia. Atherosclerosis 2008;200(1):83-88.
37. Miname MH, Ribeiro 2nd MS, Parga Filho J, et al. Evaluation of subclinical atherosclerosis by computed tomography coronary angiography and its association with risk factors in familial hypercholesterolemia. Atherosclerosis 2010;213(2):486-491.
38. Neefjes LA, Ten Kate GJ, Alexia R, et al. Accelerated subclinical coronary atherosclerosis in patients with familial hypercholesterolemia. Atherosclerosis 2011;219(2):721-727.
39. Gallo A, Giral P, Carrie A, et al. Early coronary calcifications are related to cholesterol burden in heterozygous familial hypercholesterolemia. J Clin Lipidol 2017;11(3):704-711.e2.
40. Miname MH, Bittencourt MS, Moraes SR, et al. Coronary artery calcium and cardiovascular events in patients with familial hypercholesterolemia receiving standard lipid-lowering therapy. JACC Cardiovasc Imaging 2019;12(9):1797-1804.
41. Perez de Isla L, Alonso R, Muniz-Grijalvo O, et al. Coronary computed tomographic angiography findings and their therapeutic implications in asymptomatic patients with familial hypercholesterolemia. Lessons from the SAFEHEART study. J Clin Lipidol 2018;12(4):948-957.
42. Moss AJ, Williams MC, Newby DE, Nicol ED. The updated NICE guidelines: cardiac CT as the first-line test for coronary artery disease. Curr Cardiovasc Imaging Rep 2017;10(5):15.
43. Neefjes LA, Ten Kate GJ, Rossi A, et al. CT coronary plaque burden in asymptomatic patients with familial hypercholesterolaemia. Heart 2011;97(14):1151-1157.
44. Tada H, Kawashiri MA, Okada H, et al. Assessment of coronary atherosclerosis in patients with familial hypercholesterolemia by coronary computed tomography angiography. Am J Cardiol 2015;115(6):724-729.
45. Wiegman A, de Groot E, Hutten BA, et al. Arterial intima-media thickness in children heterozygous for familial hypercholesterolaemia. Lancet 2004;363(9406):369-370.
46. Smilde TJ, van Wissen S, Wollersheim H, Trip MD, Kastelein JJ, Stalenhoef AF. Effect of aggressive versus conventional lipid lowering on atherosclerosis progression in familial hypercholesterolaemia (ASAP): a prospective, randomised, double-blind trial. Lancet 2001;357(9256):577-581.
47. Kastelein JJ, Akdim F, Stroes ES, et al. Simvastatin with or without ezetimibe in familial hypercholesterolemia. N Engl J Med 2008;358(14):1431-1443.
48. Yeboah J, McClelland RL, Polonsky TS, et al. Comparison of novel risk markers for improvement in cardiovascular risk assessment in intermediate-risk individuals. Jama 2012;308(8):788-795.
49. Humphries SE, Cooper JA, Capps N, et al. Coronary heart disease mortality in severe vs. non-severe familial hypercholesterolaemia in the Simon Broome Register. Atherosclerosis 2019;281:207-212.
50. Versmissen J, Oosterveer DM, Yazdanpanah M, et al. Efficacy of statins in familial hypercholesterolaemia: a long term cohort study. BMJ (Clin Res Ed) 2008;a2423:337.
51. Besseling J, Hovingh GK, Huijgen R, Kastelein JJP, Hutten BA. Statins in familial hypercholesterolemia: consequences for coronary artery disease and all-cause mortality. J Am Coll Cardiol 2016;68(3):252-260.
52. Ridker PM, Rose LM, Kastelein JJP, et al. Cardiovascular event reduction with PCSK9 inhibition among 1578 patients with familial hypercholesterolemia: results from the SPIRE randomized trials of bococizumab. J Clin Lipidol 2018;12(4):958-965.
53. Benn M, Watts GF, Tybjaerg-Hansen A, Nordestgaard BG. Familial hypercholesterolemia in the danish general population: prevalence, coronary artery disease, and cholesterol-lowering medication. J Clin Endocrinol Metab 2012;97(11):3956-3964.
54. Gryn SE, Hegele RA. Ezetimibe plus simvastatin for the treatment of hypercholesterolemia. Expert Opin Pharmacother 2015;16(8):1255-1262.
55. Cannon CP, Blazing MA, Giugliano RP, et al. Ezetimibe added to statin therapy after acute coronary syndromes. N Engl J Med 2015;372(25):2387-2397.
56. Abifadel M, Varret M, Rabès J, et al. Mutations in PCSK9 cause autosomal dominant hypercholesterolemia. Nat Genet 2003;34(2):154-156.
57. Burke AC, Dron JS, Hegele RA, Huff MW. PCSK9: regulation and target for drug development for dyslipidemia. Annu Rev Pharmacol Toxicol 2017;57:223-244.
58. Sabatine MS. PCSK9 inhibitors: clinical evidence and implementation. Nat Rev Cardiol 2019;16(3):155-165.
59. 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.
60. 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.
61. Papademetriou V, Stavropoulos K, Papadopoulos C, Koutsampasopoulos K, Dimitriadis K, Tsioufis K. Role of PCSK9 inhibitors in high risk patients with dyslipidemia: focus on familial hypercholesterolemia. Curr Pharm Des 2018;24(31):3647-3653.
62. Landmesser U, Chapman MJ, Stock JK, et al. 2017 update of ESC/EAS Task Force on practical clinical guidance for proprotein convertase subtilisin/kexin type 9 inhibition in patients with atherosclerotic cardiovascular disease or in familial hypercholesterolaemia. Eur Heart J 2018;39(14):1131-1143.
63. Stefanutti C, Zenti MG. Lipoprotein apheresis and PCSK9-inhibitors. Impact on atherogenic lipoproteins and anti-inflammatory mediators in familial hypercholesterolaemia. Curr Pharm Des 2018;24(31):3634-3637.
64. Wald DS, Bestwick JP, Morris JK, Whyte K, Jenkins L, Wald NJ. Child-parent familial hypercholesterolemia screening in primary care. N Engl J Med 2016;375(17):1628-1637.

65. Ademi Z, Watts GF, Pang J, et al. Cascade screening based on genetic testing is cost-effective: evidence for the implementation of models of care for familial hypercholesterolemia. J Clin Lipidol 2014;8(4):390-400.
66. Blom DJ, Almahmeed W, Al-Rasadi K, et al. Low-density lipoprotein cholesterol goal achievement in patients with familial hypercholesterolemia in countries outside western Europe: the International ChoLesterol management Practice Study. J Clin Lipidol 2019;13(4):594-600.
67. 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.
68. Myers KD, Farboodi N, Mwamburi M, et al. Effect of access to prescribed PCSK9 inhibitors on cardiovascular outcomes. Circulation Cardiovascular Quality and Outcomes 2019;12(8):e005404.
69. Carmena R, Lussier-Cacan S, Roy M, et al. Lp(a) levels and atherosclerotic vascular disease in a sample of patients with familial hypercholesterolemia sharing the same gene defect. Arterioscler Thromb Vasc Biol 1996;16(1):129-136.
70. Paquette M, Bernard S, Thanassoulis G, Baass A. LPA genotype is associated with premature cardiovascular disease in familial hypercholesterolemia. J Clin Lipidol 2019;13(4):627-633.