FAMILIAL HYPERCHOLESTEROLEMIA

What You Need to Know

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Familial Hypercholesterolemia : What You Need to Know

ANCC Accredited NCPD Hours: 3.4 hrs
Target Audience: RN/APRN

Need Assessment

Familial hypercholesterolemia (FH), a relatively common Mendelian genetic disorder, is associated with a dramatically increased lifetime risk of premature atherosclerotic cardiovascular disease due to elevated plasma low density lipoprotein cholesterol (LDL-C) levels. The diagnosis of familial hypercholesterolemia is based on clinical presentation or genetic testing. Early identification of patients with familial hypercholesterolemia is of great public health importance because preventive strategies can lower the absolute lifetime cardiovascular risks and screening can detect affected relatives. However, low awareness detection and control of familial hypercholesterolemia pose hurdles in the prevention of familial hypercholesterolemia related cardiovascular events.

Objectives

After completion of this activity, the candidate should be able to

- Describe different types of familial hypercholesterolemia
- Describe diagnostic criteria and treatment options for familial hypercholesterolemia
- Describe pharmacologic agents for treatment of familial hypercholesterolemia
- Describe non pharmacological measures for management if familial hypercholesterolemia

Goal

The goal of this article is to discuss various aspects of familial hypercholesterolemia including causes, diagnosis, management options and current guidelines.

Introduction

Familial hypercholesterolemia (FH) is an autosomal dominant disorder characterized by high cholesterol levels, specifically very high levels of low-density lipoprotein (LDL, bad cholesterol), in the blood and early cardiovascular disease. Two types of lipoproteins carry cholesterol to and from the cells (as shown in figure 1). One is low density lipoprotein (LDL) and the other is high density lipoprotein (HDL). Triglycerides are the most common type of fat in the body. A high triglycerides level combined with high low density lipoprotein or low high density lipoprotein is linked with fatty build-ups within the artery walls, which increases the risk of heart attack and stroke.

> **"Familial hypercholesterolemia is a genetic condition leading to high cholesterols and high risk for early heart disease"**

In other words, familial hypercholesterolaemia (FH), is the heritable occurrence of severe hypercholesterolaemia with cholesterol deposits in tendons and premature heart disease, is caused by at least four genes (as shown in figure 2) in sterol and lipoprotein pathways and displays varying gene-dose effects. The genes are the low-density lipoprotein (LDL) receptor, apolipoprotein (apo) B, proprotein convertase subtilisin/kexin 9 and the autosomal recessive hypercholesterolaemia (ARH) adaptor protein.

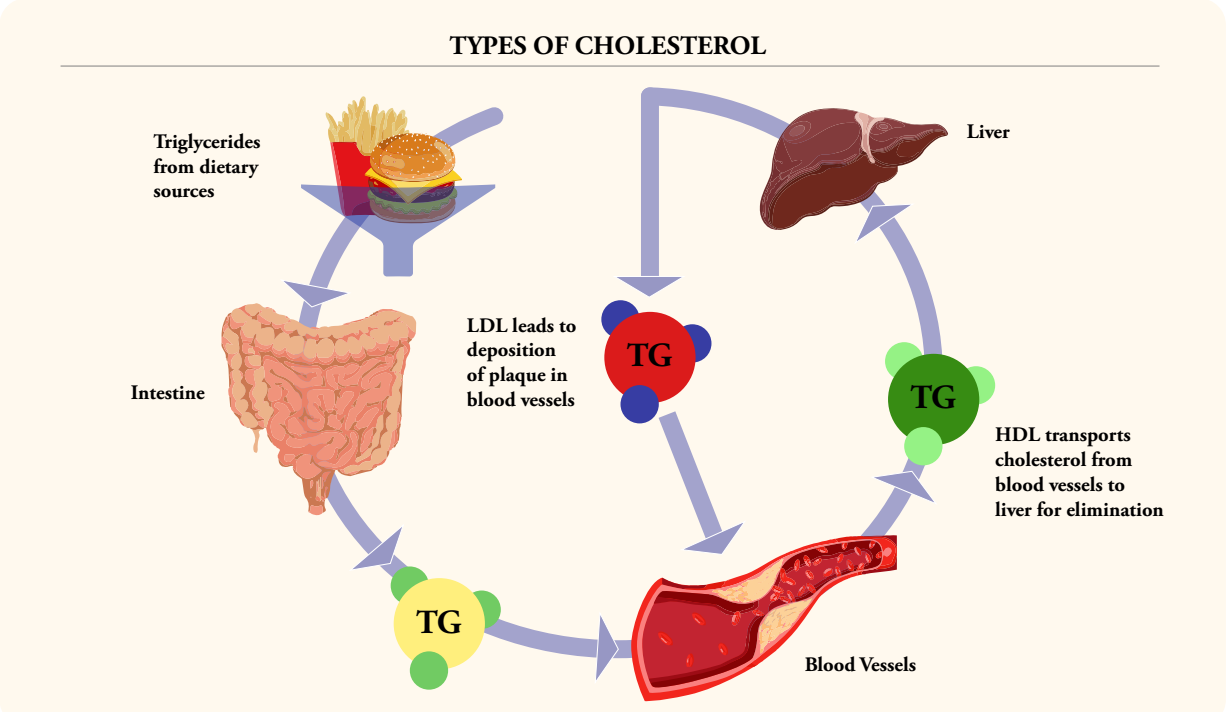

Figure 1: Types of cholesterol

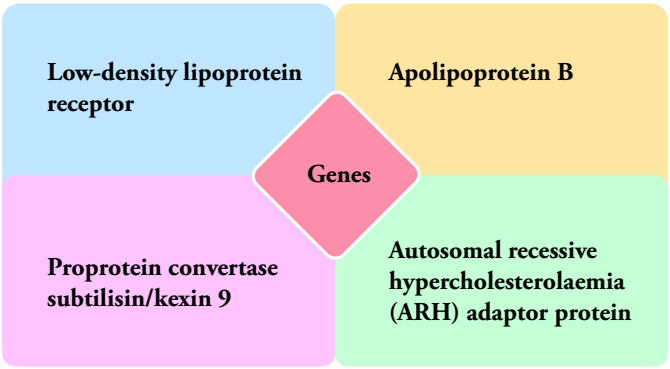

Figure 2: Genes responsible for familial dyslipidemia

All of these disorders have in common defective clearance of low-density lipoprotein within a complex system of lipid and lipoprotein metabolism and regulation. [1, Rank 1]

Classification

Disease	Gene/function
Familial hypercholesterolemia	LDLR/LDL endocytosis
Familial defective Apo B 100	APOB/LDL endocytosis
Autosomal recessive hypercholesterolemia	ARH/LDLR adapter protein
Autosomal dominant hypercholesterolemia	CYP7A/rate limiting enzyme of cholesterol degradation
Autosomal dominant hypercholesterolemia	PSCK9/serum protease that degrades LDLR

Table 1: Disease classification based on gene mutation

Familial hypercholesterolemia is a common inherited dominant autosomal disease caused by defective hepatic clearance of circulating low density lipoprotein particles. Familial hypercholesterolemia results from mutations in specific genes such as low-density lipoprotein (LDL) receptor, apolipoprotein (apo) B, proprotein convertase subtilisin/ kexin 9 (PCSK 9) and the autosomal recessive hypercholesterolaemia (ARH) adaptor protein. There are five types of familial dyslipedemia and each is classified from both the altered lipid profile and by the genetic abnormality (as shown in table 1).

Pathophysiology

Familial cholestrolemia is caused by a reduction or defect in the low density lipoprotein receptor (LDL-R), which is also called the apoB/E receptor because it binds both apolipoprotein B and apolipoprotein E (as shown in figure 3). The low density lipoprotein receptor is responsible for the uptake of low density lipoprotein cholesterol into the liver, which metabolizes approximately 70% of circulating low density lipoprotein cholesterol. Genetic mutations cause alternations in the low density lipoprotein receptor, which lead to inadequate hepatic uptake of low density lipoprotein cholesterol and an increase in the circulating low density lipoprotein cholesterol levels. In homozygous familial hyper-

cholesterolemia (HoFH), mutations reduce the number of normal low density lipoprotein receptors by 50%, while in hetrozygous familial cholestrolemia (HeFH), normal functioning low density lipoprotein receptors may be undetectable.

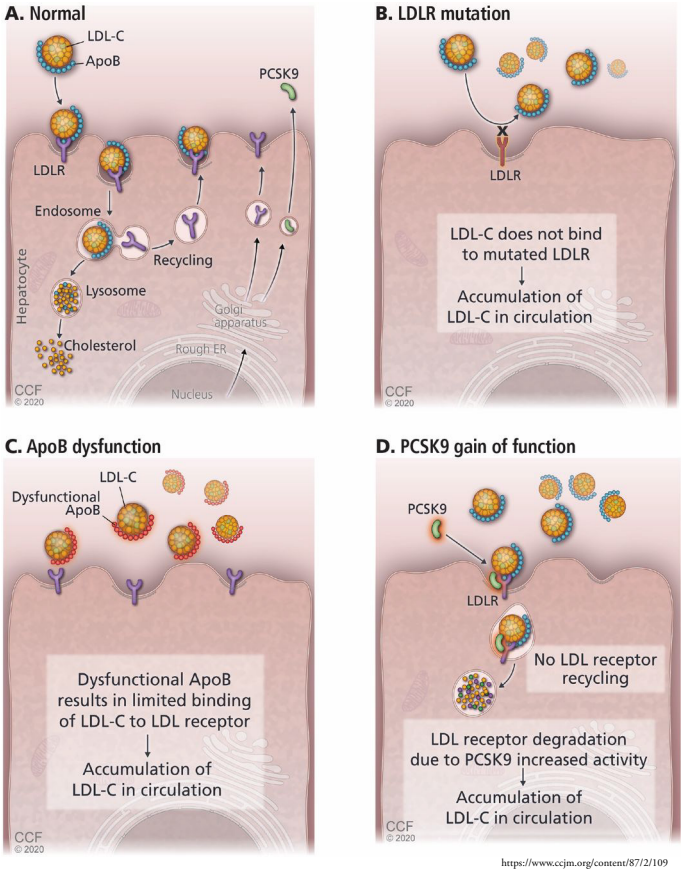

Figure 3: Pathophysiology of FH

High circulating levels of low density lipoprotein cholesterol in these disorders stimulate the uptake of low density lipoprotein cholesterol into non-hepatic cells through cholesterol scavenger pathways. Low density lipoprotein cholesterol is taken up by monocyte/ macrophages into the arterial intima, leading to formation of foam cells and ultimately artherosclerotic plaques in the arterial wall. Low density lipoprotein cholesterol also accumulates in other areas including the skin, cornea, heart valves and other sites causing lesions secondary to its deposition.

Characteristics

Xanthomas (patches of yellowish cholesterol build-up) may worsen with age as a result of extremely high cholesterol levels. Xanthomas can occur around the eyelids and within the tendons of the elbows, hands, knees, and feet. In Familial hypercholesterolemia, the more common cardiovascular disease is coronary artery disease (CAD), which may manifest as angina and myocardial infarction; stroke occurs more rarely. Untreated men are at a 50% risk for a fatal or non-fatal coronary event by age 50 years; untreated women are at a 30% risk by age 60 years.

Familial hypercholesterolemia is best defined as an entity in clinical practice that is

> **“ Familial hypercholesterolemia patients are at significantly increased risk of atherosclerosis as a result of both elevated LDL cholesterol concentrations and exposure from childhood onwards. ”**

recognisable from features in the patient's family and personal history and physical examination, as well as readily available chemical analysis of the blood. The diagnosis of familial hypercholesterolemia is important not only for the prognosis of the patient, but also has implications for the family members who may have inherited the same disorder. The clinical pattern is also an important starting point of research for the biochemist, clinical pathologist, epidemiologist, geneticist or healthcare provider. [2, Rank 3]

Familial hypercholesterolemia may be defined as an heritable disorder, involving a single gene, that produces a clinically recognisable pattern (in the majority of subjects) that consists of severe hypercholesterolaemia due to the accumulation of low-density lipoprotein in the plasma, cholesterol deposition in tendons and occasionally in skin, and a high risk of atherosclerosis manifesting almost exclusively as coronary artery disease (CAD). These disorders all share the mechanism of decreased clearance of low-density lipoprotein, but their inheritance may be autosomal dominant or recessive and not all dominant disorders have a gene-dose effect. [3, Rank 4]

Men who have familial hypercholesterolemia have heart attacks in their 40's to 50's and 85% of men with the disorder have a heart attack by age 60. Women who have familial hypercholesterolemia also have an increased risk for heart attack, but it happens 10 years later than in men (so in their 50's and 60's).

Familial hypercholesterolemia is inherited in families in an autosomal dominant manner. In autosomal dominant inherited conditions, a parent who carries an altered gene that causes the condition has a 1 in 2 (50 percent) chance to pass on that altered gene to each of his or her children. [4, Rank 5]

The altered gene (gene mutation) that causes familial hypercholesterolemia is located on chromosome number 19. It contains the information for a protein called low-density lipoprotein receptor that is responsible to clear up low-density lipoprotein from the blood stream. One in 500 individuals carries one altered gene causing familial hypercholesterolemia. These individuals are called heterozygotes. More rarely, a person inherits the gene mutation from both parents, making them genetically homozygous. Individuals who are homozygous have a much more severe form of hypercholesterolemia, with heart attack and death often occurring before age 30. [5, Rank 2]

> **" The altered gene (gene mutation) that causes familial hypercholesterolemia is located on chromosome number 19 "**

Heterozygous familial hypercholesterolemia Presentation

Vascular Conditions

People with familial hypercholesterolemia have very high levels of low density lipoprotein cholesterol from birth. In children, low-density lipoprotein cholesterol levels are usually > 160 mg/dl and in adults they are usually > 190 mg/dL, which can lead (as shown in table 2), if untreated, to coronary artery disease, cerebrovascular disease, peripheral vascular disease and/or other serious conditions (as shown in figure 4).

NORMAL VALUE		
LDL-C	CHILDREN	> 160 mg/dl
	ADULTS	>190 mg/dL

Table 2: Ideal LDL-C values

Most common is coronary artery disease due to atherosclerotic plaque build-up in the arteries supplying the heart (atherosclerosis), which can result in chest pain or discomfort (angina), heart attack (myocardial infarction) or sudden death. Untreated people with familial hypercholesterolemia have an approximately 10 to 20-fold increased risk for coronary artery disease. [6, Rank 3]

Less common are cerebrovascular disease, peripheral vascular disease and aortic aneurysm. Cerebrovascular disease may occur due to cholesterol build-up in the arteries supplying the brain, which may cause stroke or transient ischemic attack (TIA).

Peripheral vascular disease is due to cholesterol build-up in the arteries supplying the legs which may cause pain when walking that is relieved by rest (claudication) and at its most severe, pain at rest or critical lack of blood flow. [7, Rank 1]

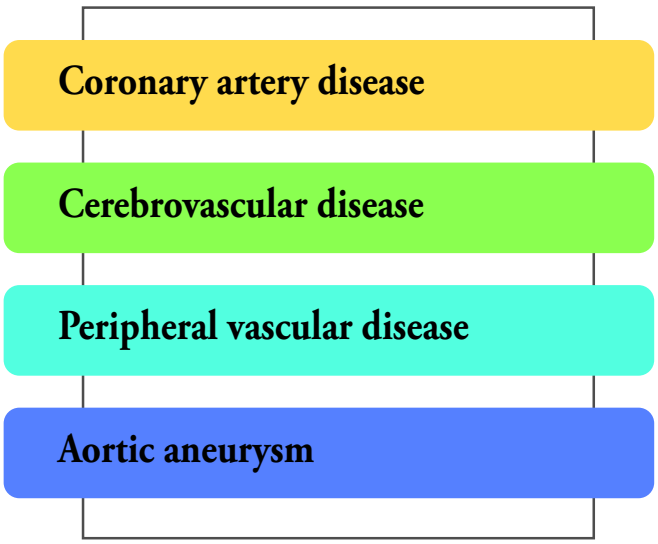

Figure 4: Common vascular conditions associated with FH

Extravascular Conditions

(as shown in figure 5)

Xanthomas are firm nodules caused by cholesterol build-ups a result of the very high levels of low density lipoprotein cholesterol. The most common sites are the Achilles tendon and the tendons on top of the hands. Achilles tendon xanthomas may cause tendonitis, an inflammation of the tendon that

may tear or rupture. Tendon xanthomas are seen in ~20% of individuals with heterozygous familial hypercholesterolemia in the current era and in a much higher percentage of those with homozygous familial hypercholesterolemia.

Xanthesmas are cholesterol deposits on, above or under the eyelids often seen in patients with familial hypercholestrolemia. They may also be seen in individuals with normal cholesterol levels, particularly as they age. [8, Rank 5]

Figure 5: Common extra vascular conditions associated with FH

Corneal arcus is a white, grey or blue opaque ring around the edge of the cornea in the eye, often seen in patients with familial hypercholesterolaemia. Since corneal arcus is common in African Americans with normal cholesterol levels and becomes increasingly common in the general population with age, it is only useful as a diagnostic tool in younger individuals, particularly in those under age 45 (as shown in figure 6). [9, Rank 1]

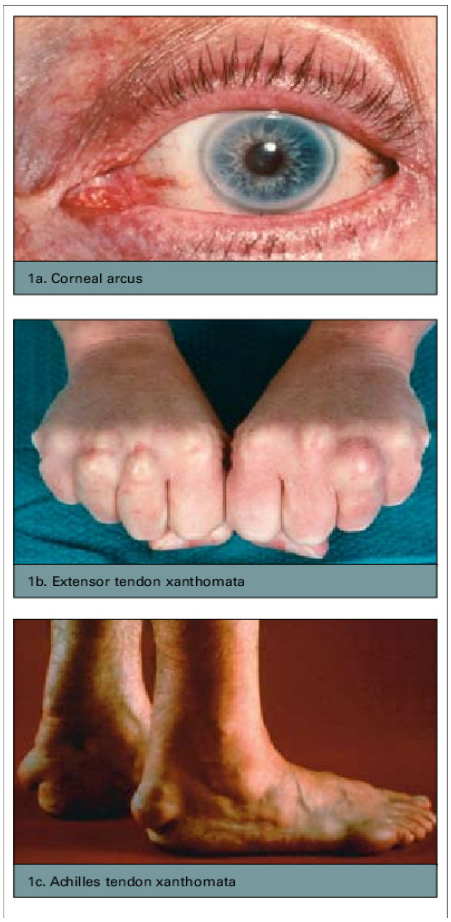

Figure 6: Clinical signs of FH

Homozygous familial hypercholesterolemia – Presentation

Individuals with Homozygous familial hypercholesterolemia exhibit extremely high low density lipoprotein cholesterol levels, usually above 400 mg/dL. They usually have xanthomas by early childhood. Planar xanthomas affecting the skin on the hands, elbows, buttocks and knees in a young child are diagnostic for this condition. Corneal arcus surrounding the entire inside edge of the cornea is often present. Most individuals with homozygous family hypercholesterolemia experience severe coronary artery disease by their mid-20 if not aggressively

treated. Narrowing of the heart valve leading to the aorta (aortic stenosis) often occurs, which may make it necessary to replace the aortic valve. Very aggressive therapy is needed to reduce the likelihood of vascular events. Most affected people will require filtering of their blood (low-density lipoprotein apheresis) and/or medications specifically approved by the FDA for Homozygous familial hypercholesterolemia (lomitapide, PCSK9 inhibitors or mipomersen). [10, Rank 4]

> **"Xanthomas, corneal arcus, heart and blood vessel disease are all physical characteristics of HoFH. A heart murmur may be the result of narrowing of the opening of the aortic valve by cholesterol buildup. A child with aortic valve disease and high LDL-C may have HoFH"**

Often the other medications that are the mainstay of treatment for heterozygous familial hypercholesterolemia (such as statins) are relatively ineffective in homozygous familial hypercholesterolemia. This is because the mechanism of action of statins normally "triggers" the liver to express additional low density lipoprotein receptive homozygous familial hypercholesterolemiators. In the most severe cases of homozygous familial hypercholesterolemia, the low-density lipoprotein receptors are completely inactive which makes this response futile. Statins can be effective in individuals Homozygous familial hypercholesterolemia if there is some residual low density lipoprotein receptor activity, or if they have causal DNA variants in the APOB or PCSK9 genes. [11, Rank 3]

Family History of Individuals with familial hypercholesterolemia

The family history of premature ischemic heart disease is very helpful to identify an autosomal dominant mode of inheritance and the patient's ancestry may suggest the molecular defect if there is a link to a population with a founder effect. Despite the high risk of heart disease in heterozygous familial hypercholesterolemia, the risk is significantly modified by other genes and environmental factors, so that the family history may occasionally be misleadingly benign. In such a setting, a recessive disorder should be considered, or a new mutation giving rise to a dominantly inherited pattern should be considered. [12, Rank 1]

Subclinical Artherosclerosis

Subclinical atherosclerosis is evident in young persons with familial hypercholesterolemia when sought by vascular imaging techniques. In homozygous familial hypercholesterolemia patients, aortic stenosis is a well-established complication as a result of lipid deposition in the aortic valve and root.

Other vessels may also have turbulent flow in homozygous familial hypercholesterolemia, especially the femoral arteries. [13, Rank 3]

Atherosclerosis is a condition in which fatty material collects along the walls of arteries. This fatty material thickens, hardens, and may eventually block the arteries. Atherosclerosis happens when fat and cholesterol and other substances build up in the arteries and form a hardened material called plaque. Atherosclerosis is imperfectly understood, but is clearly a multifactorial disease in which especially in familial hypercholesterolemia, low-density lipoprotein hypercholesterolemia plays a strong role. In familial hypercholesterolemia, the disease is more severe and results in clinical complications earlier. High concentrations of low-density lipoprotein, resident in the circulation for prolonged periods, permit more oxidative modification in the circulation and tissues [14, Rank 4]. These oxidised lipoproteins influence vascular endothelium adversely, promoting the attraction of monocytes that penetrate into or remain in the sub-endothelial space, where an indolent form of chronic inflammation takes place. Monocytes mature into macrophages that take up the lipid to become foam cells when ACAT1 esterifies cholesterol. Whilst the proportion of apoB that is glycated is normal in familial hypercholesterolemia, the absolute concentration is increased. This may contribute to atherosclerosis by the adverse effects of advanced glycation end products. Under relatively low rates of entrance of post-prandial and endogenous lipoproteins into the arterial wall and low oxidative stress on these lipoproteins, RCT may counter atherogenesis and its complications that include inflammation, plaque rupture and thrombosis. The pathological outcome in a high risk condition such as familial hypercholesterolemia may thus still be modulated by many additional factors to apoB-containing lipoproteins, including RCT and factors governing tissue responses suggested above. [15, Rank 5]

Signs &Symptoms

The major symptoms and signs of familial hypercholesterolemia are (as shown in figure 7):

- High levels of total cholesterol and low-density lipoprotein cholesterol.
- A strong family history of high levels of total and low-density lipoprotein cholesterol and/or early heart attack.
- Elevated and therapy-resistant levels of low-density lipoprotein in either or both parents.
- Xanthomas (waxy deposits of cholesterol in the skin or tendons).
- Xanthelasmas (cholesterol deposits in the eyelids).
- Corneal arcus (cholesterol deposit

around the cornea of the eye).

➤ If angina (chest pain) is present, it may be sign that heart disease is present.

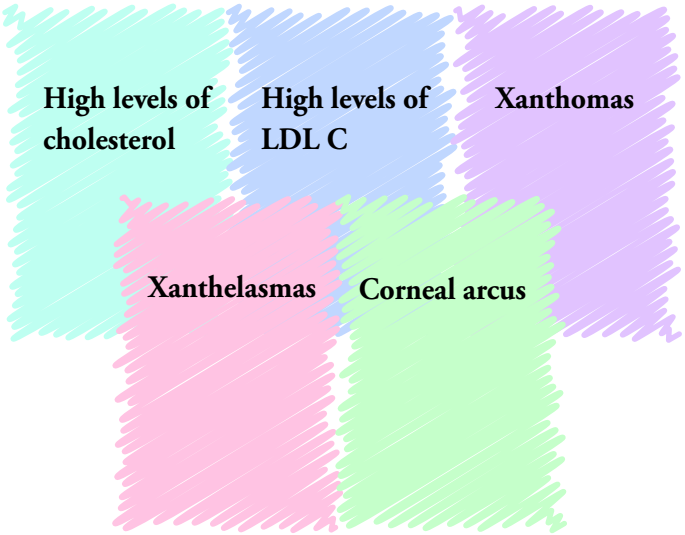

Figure 7: Major signs and symptoms of FH

Individuals who have homozygous familial hypercholesterolemia develop xanthomas beneath the skin over their elbows, knees and buttocks as well as in the tendons at a very early age, sometime in infancy. Heart attacks and death may occur before 30. [16, Rank 5]

Homozygous familial hypercholesterolemia

Signs and symptoms of homozygous familial hypercholesterolemia (as shown in figure 8) in children include the following:

➤ Symptoms consistent with ischemic heart disease, peripheral vascular disease, cerebrovascular disease, or aortic stenosis.

➤ Articular symptoms such as tendonitis or arthralgias.

➤ Unusual skin lesions, such as cutaneous xanthomas at birth or by early childhood (e.g. planar xanthomas, tuberous xanthomas; later, tendon xanthomas).

➤ Corneal arcus may be present and is sometimes circumferential.

➤ Murmur of aortic stenosis may be present.

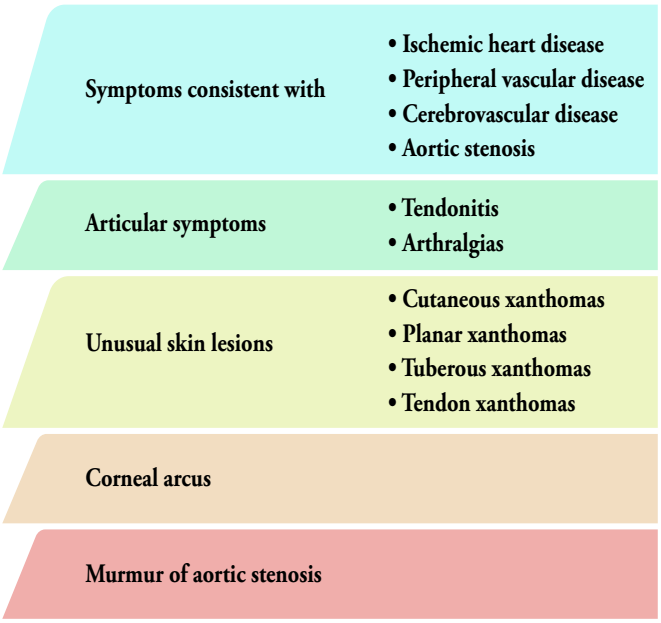

Figure 8: Signs and symptoms of HoFH

Most patients with homozygous familial hypercholesterolemia do not survive adulthood beyond age 30 years unless treated with unusual methods, such as liver transplantation, low-density lipoprotein apheresis or ileal bypass surgery to dramatically lower their low-density lipoprotein cholesterol levels. [17, Rank 4]

Physical Characteristics of homozygous familial hypercholesterolemia

➤ **Xanthomas**- These are collections of cholesterol under the skin or tendons. They are yellow bumps that can be small and hard

to see. These are often found in the folds of skin and buttocks in children. Also, there can be xanthomas on the tendons at the ankles and hands. Children often have xanthomas without any signs of heart problems in early childhood.

➤ **Corneal Arcus** - A corneal arcus is a greyish-white ring of cholesterol around the iris. A corneal arcus at a young age can mean that the child has homogenous familial hypercholesterolemia.

➤ **Heart and Blood Vessel Disease** - Cholesterol plaque builds up in the coronary arteries supplying blood to the heart, the carotids taking blood to the brain, the arteries to the kidneys, and other arteries. Blockage of the flow of blood to the heart may cause chest pain, shortness of breath, dizziness, or irregular heartbeats. A heart murmur may be the result of narrowing of the opening of the aortic valve by cholesterol build-up.

A child with aortic valve disease and high low-density lipoprotein cholesterol may have homogenous familial hypercholesterolemia. Special tests of the heart such as an EKG, echocardiogram, computerized tomographic angiogram or cardiac catheterization are recommended to check the aortic valve and coronary arteries at diagnosis and at least every 5 years. [47, Rank 3]

If both parents have very high low-density lipoprotein cholesterol (>190 mg/dL) and/or history of heart disease before age 55-65, this may suggest that they both have familial hypercholesterolemia and can each pass a mutated gene to their children. When each parent has heterozygous familial hypercholesterolemia, by chance, 1 of 4 children will have a normal cholesterol level, 2 of 4 children will have heterozygous familial hypercholesterolemia and 1 of 4 children will have homozygous familial hypercholesterolemia. Prenatal DNA testing may be available if the mutations are identified in the parents. [46, Rank 5]

If a person is living a healthy lifestyle and taking cholesterol-lowering medications like statins, and/or cholesterol absorption inhibitors and/or bile acid sequestrates and still has high cholesterol level (> 300 mg/dL), they may have homozygous familial hypercholesterolemia. [48, Rank 3]

It is important to remember that homozygous familial hypercholesterolemia is a serious medical condition and is life-threatening if not treated at a young age, preferably beginning in early childhood. A child or adult with homozygous familial hypercholesterolemia needs life-long medications and other specialized treatments to lower the low-density lipoprotein cholesterol and prevent heart attacks. This requires the expertise of a lipid specialist. [49, Rank 2]

Heterozygous familial hypercholesterolemia

Children with heterozygous familial hypercholesterolemia do not have symptoms related to coronary heart disease (CHD) and most do not develop tendon xanthomas or corneal arcus (as shown in figure 9). However, one parent will have severe hypercholesterolemia and will also probably have either a personal or family history for premature coronary artery disease.

Signs and symptoms of heterozygous familial hypercholesterolemia in adults include the following:

- Long-standing history of severe hypercholesterolemia dating back to childhood
- If no previous acute coronary event, symptoms consistent with ischemic heart disease, especially in the presence of other cardiovascular risk factors (especially smoking)
- Past or present symptoms of recurrent Achilles tendonitis or arthritic complaints
- If heterozygous familial hypercholesterolemia is left untreated, tendon xanthomas (Achilles tendons, metacarpophalangeal [MCP] extensor tendons) will occur by third decade of life in more than 60% of patients
- Xanthelasmas [18, Rank 5]

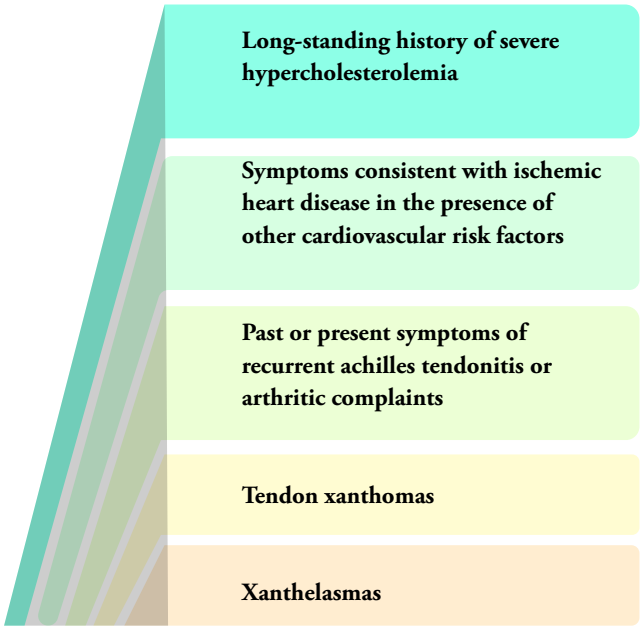

Figure 9: Signs and symptoms of HeFH

Diagnostic Criteria

The formal diagnostic criteria for familial hypercholesterolemia rely on a combination of the following:

- Extreme hypercholesterolemia
- History of premature coronary artery disease or other coronary artery disease
- Findings on physical examination
- Family history of premature coronary artery disease or other cardiovascular disease
- Identification of a pathogenic variant in a gene known to be associated with familial hypercholesterolemia

The diagnostic criteria most widely used in Western countries include (as shown in table 3): extreme hypercholesterolemia (untreated adults with low-density lipoprotein cholesterol >190 mg/dL or total choles-

terol levels >310 mg/dL; untreated children/adolescents with low-density lipoprotein cholesterol levels >160 mg/dL or total cholesterol levels >230 mg/dL); history of premature coronary artery disease or other cardiovascular disease, xanthomas, corneal arcus and a family history of features suggestive of familial hypercholesterolemia.

Diagnostic criteria			
1	Untreated adults	LDL-C > 190 mg/dl	TC>310 mg/dl
2	Untreated children/ adolescents	LDL-C > 160 mg/dl	TC>230 mg/dl)
3	History of premature CAD or other CVD		
4	Xanthomas		
5	Corneal arcus		
6	Family history of features suggestive of familial hypercholesterolemia		

Table 3: Diagnostic criteria of FH

The diagnosis of familial hypercholesterolemia can also be established by identification of a heterozygous pathogenic variant in one of the three genes (APOB, LDLR, and PCSK9) known to be associated with familial hypercholesterolemia. [19, Rank 3]

The diagnosis of Homozygous familial hypercholesterolemia (HoFH) can be established in a proband by identification of bial-

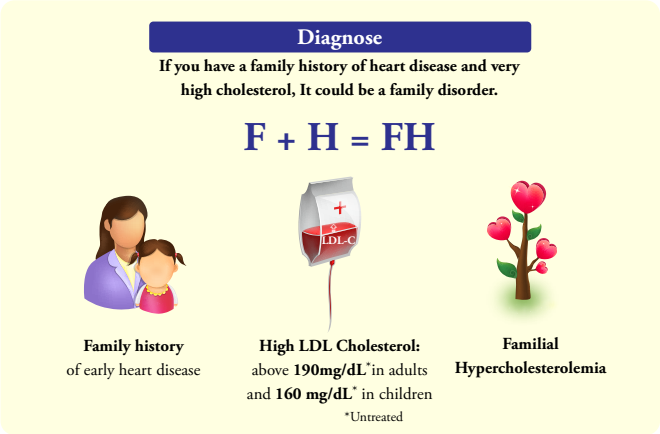

Figure 10: Diagnosis of FH

lelic pathogenic variants in one of the three genes (APOB, LDLR, and PCSK9) known to be associated with familial hypercholesterolemia. [20, Rank 2]

The diagnosis of both homozygous and heterozygous familial hypercholesterolemia is based primarily on the finding of severe low-density lipoprotein cholesterol elevations in the absence of secondary causes of hypercholesterolemia. A probable diagnosis of heterozygous familial hypercholesterolemia (as shown in figure 10) can be made if the low-density lipoprotein cholesterol level is greater than 330 mg/dL or if tendon xanthomas are present in a patient with a low-density lipoprotein cholesterol level above the 95th percentile. Definitive diagnosis can be made only with gene or receptor analysis. However, a substantial increase in serum triglyceride levels should raise the possibility of another lipid disorder. [21, Rank 2]

Findings on lipid analysis in patients with familial hypercholesterolemia (as shown in figure 11) include the following:

➤ ***Homozygous familial hypercholesterolemia:*** Severely elevated cholesterol levels (total cholesterol and low-density lipoprotein cholesterol levels >600 mg/dL); triglyceride levels within the reference range

➤ ***Heterozygous familial hypercholesterolemia:*** Elevated low-density lipoprotein cholesterol levels commonly greater than 250 mg/dL; in patients younger than 20 years, an low-density lipoprotein cholesterol level higher than 200 mg/dL is highly suggestive of heterozygous familial hypercholesterolemia or, possibly, familial ligand defective apoB-100; in adults, low-density lipoprotein cholesterol levels higher than 290-300 mg/dL suggest heterozygous familial hypercholesterolemia

Low-density lipoprotein receptor analysis can be used to identify the specific low-density lipoprotein receptor defect and low-density lipoprotein receptor or apoB-100 studies can help distinguish heterozygous familial hypercholesterolemia from the similar syndrome of familial defective apoB-100. [22, Rank 2]

The European Atherosclerosis Society (EAS) recommends screening for heterozygous familial hypercholesterolemia (as shown in figure 12)

Include patients with

➤ A family member presenting with diagnosed familial hypercholesterolemia

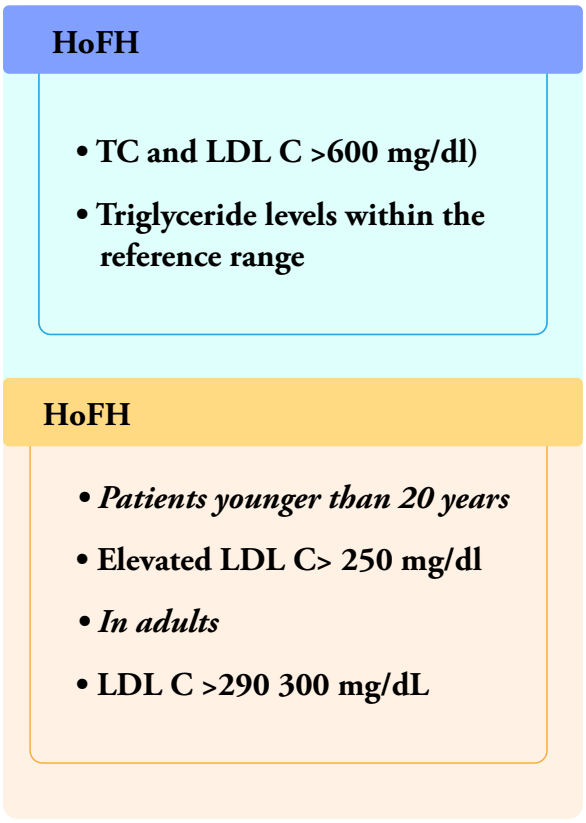

Figure 11: Lipid analysis for FCH

➤ Plasma cholesterol in an adult ≥ 8mmol/L (≥310 mg/dL)

➤ Plasma cholesterol in a child ≥ 6mmol/L (≥230 mg/dL)

➤ Premature CHD

➤ Tendon xanthomas; or

➤ Sudden premature cardiac death.

Treatment

Lifestyle changes, such as exercising and eating a healthy low-fat diet, are the first line of defence against high cholesterol (as shown in figure 13). Specific recommendations include:

➤ Reducing the amount of saturated fat in your diet to less than 30 percent of your

daily calories.

- Consuming 10 to 20 grams of soluble fibre a day. Good sources include oats, peas, beans, apples, citrus fruits and carrots.
- Increasing physical activity.
- Maintaining a healthy body weight.

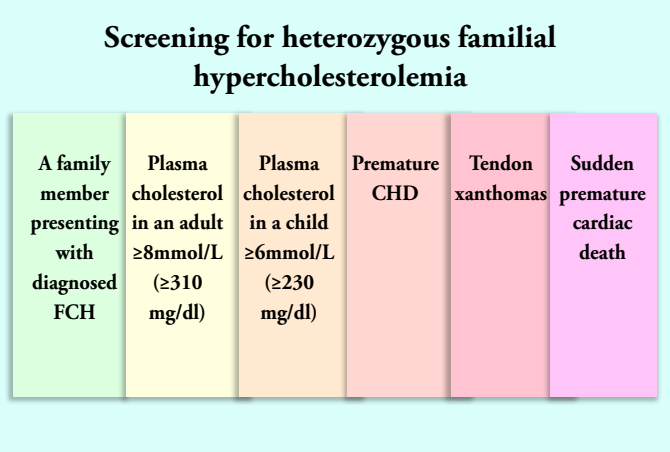

Figure 12: Screening for HeFH

People with familial hypercholesterolemia have an excellent prognosis - when they're identified early enough and treated aggressively enough. [24, Rank 5] Familial hypercholesterolemia can't be treated by diet and exercise alone. These lifestyle changes will lower low-density lipoprotein, but when levels must be lowered by 50 or 75 percent, medication is needed. Treatment usually involves a statin drug. Often familial hypercholesterolemia patients require more than one medication and sometimes more than two. When statins don't lower cholesterol enough, more cholesterol-lowering medications like ezetimibe are used. People with extremely high low-density lipoprotein, like those with the homozygous form, may undergo low-density lipoprotein aphaeresis. This is a dialysis-like procedure that's done every few weeks to remove cholesterol from the blood. [25, Rank 3]

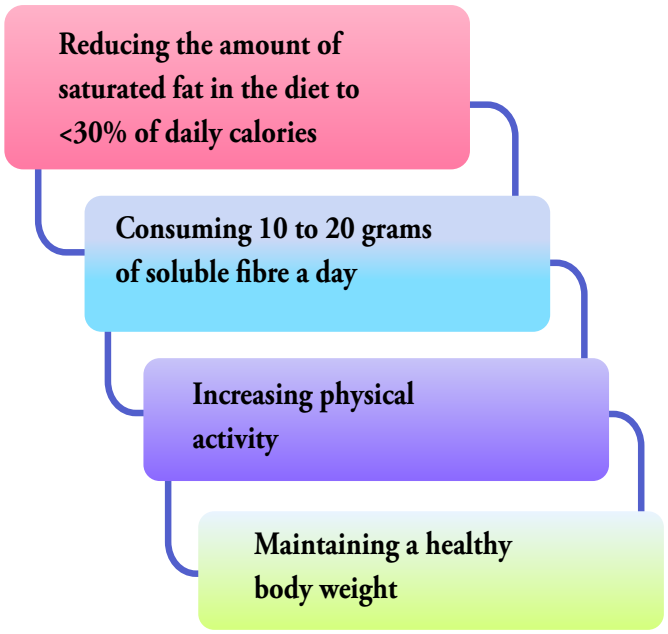

Figure 13: Lifestyle changes to achieve low LDL

Another class of lipid-lowering medications (bile acid sequestrates) like cholestyramine or colesevelam may also be used. They reduce the amount of cholesterol absorbed by the intestines. This lowers the amount of cholesterol that gets into the blood. [26, Rank 1]

Two PCSK9 inhibitors are newly developed injectable antibodies that lower cholesterol levels. They target and block the PCSK9 protein. This makes more receptors on the liver available to remove low-density lipoprotein cholesterol from blood. Although FDA-approved, they're still a new, costly

treatment with limited use (as shown in figure 14). [27, Rank 3]

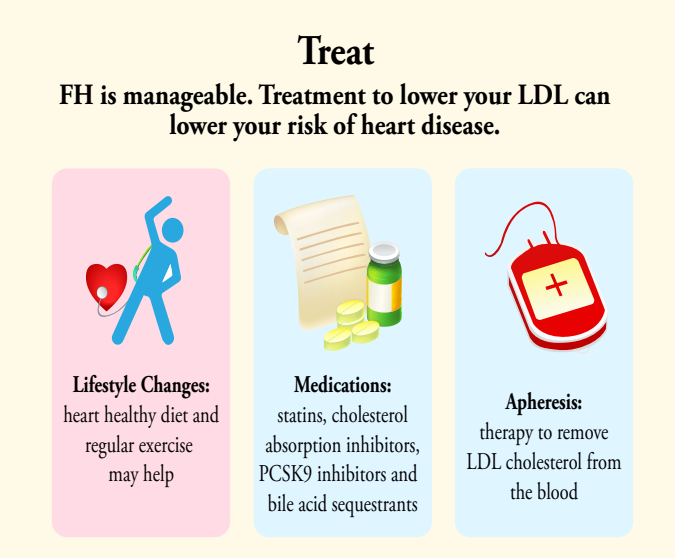

Figure 14: Management of FH

Differential Diagnosis

Conditions with **clinical findings** similar to those of familial hypercholesterolemia (FH) include the following (as shown in figure 15):

➤ 27-hydroxylase deficiency (cerebrotendonousxanthomatosis): this is characterized by xanthomas. Distinguishing features are normal low-density lipoprotein cholesterol (LDL-C) levels and the presence of dementia, ataxia, and cataracts. Biallelic pathogenic variants in CYP27A1 are causative; inheritance is autosomal recessive.

➤ ***Hyperlipoproteinemia type III (familial dysbetalipoproteinemia):*** Clinical features may include xanthomas. Hyperlipoproteinemia type III is caused by biallelic pathogenic variants in APOE. Inheritance is autosomal recessive

> **" Extremely elevated lipoprotein a (Lpa) and Familial combined hyperlipidemia (FCHL) are inherited in an autosomal dominant manner.**
>
> **Familial dysbetalipoproteinemia and cerebrotendonousxanthomatosis are inherited in an autosomal recessive manner "**

➤ ***Sitosterolemia (phytosterolemia):*** Which is distinguished by normal or only mildly elevated low-density lipoprotein cholesterol levels? Biallelic pathogenic variants in either ABCG5 or ABCG8 are causative; inheritance is autosomal recessive.

➤ ***Polygenic hypercholesterolemia:*** Individuals with features suggestive of familial hypercholesterolemia in which an LDLR, PCSK9, or APOB pathogenic variant was not identified are in fact likely to have polygenic hypercholesterolemia. In this case, individuals have a high genetic risk score for more common low-density lipoprotein cholesterol raising alleles.

➤ ***Extremely elevated lipoprotein A (Lpa):*** Individuals with very high Lpa often have a personal and family history of early-onset coronary artery disease and very

elevated low-density lipoprotein cholesterol levels. High lipoprotein A levels are also widely appreciated to synergistically increase risk in individuals with familial hypercholesterolemia. The disorder is inherited in an autosomal dominant manner and caused by variants in the number of kringle IV type 2 repeats in lipoprotein lipase. [28, Rank 5]

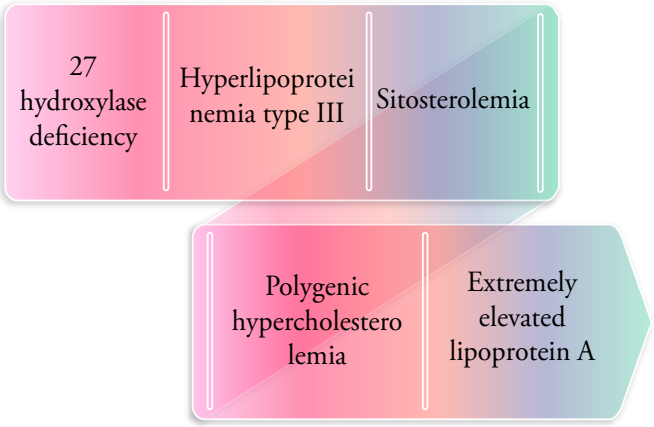

Figure 15: Conditions similar to FH based on clinical findings

Conditions with laboratory findings similar to those of familial hypercholestrolemia include the following (as shown in figure 16):

➤ Hypercholesterolemia secondary to obesity, diabetes mellitus, hypothyroidism, drugs (e.g., steroids), or kidney disease. Inheritance follows a non-Mendelian pattern.

➤ Autosomal recessive hypercholesterolemia caused by biallelic pathogenic variants in low density lipoprotein receptor AP1. Persons with biallelic pathogenic variants have low-density lipoprotein cholesterol >400 mg/dL (>10 mmol/L), whereas heterozygotes have normal low-density lipoprotein cholesterol levels.

➤ ***Familial combined*** hyperlipidemia (FCHL), associated with elevated low-density lipoprotein cholesterol and triglycerides. Familial combined hyperlipidemia is genetically heterogeneous. Only 10%-20% of individuals show elevated levels in childhood (usually in the form of hypertriglyceridemia). Familial combined hyperlipidemia is inherited in an autosomal dominant manner and caused by pathogenic variants in lipoprotein lipase. [29, Rank 5]

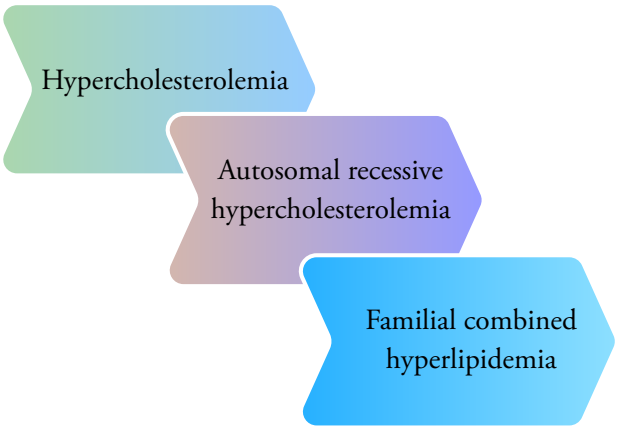

Figure 16: Conditions with laboratory findings similar to those of FH

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs of an individual diagnosed with familial hypercholesterolemia (FH) the following evaluations are recommended in adults and children (as shown in figure 17):

➤ Measurement of pre-treatment lipid values and lipoprotein (A) levels when possi-

ble. Exclusion of concurrent illnesses (kidney disease, acute myocardial infarction, infection) that can affect lipid values

➤ Lipid panel including total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and triglycerides

➤ ***Consultation with a lipid specialist or clinician*** with expertise in familial hypercholesterolemia

➤ Recommended in some guidelines: ***non-invasive imaging modalities*** in children (e.g., measurement of carotid intima-media thickness) to help inform treatment decisions

➤ ***Consultation with a clinical geneticist and/or genetic counsellor*** [30, Rank 5]

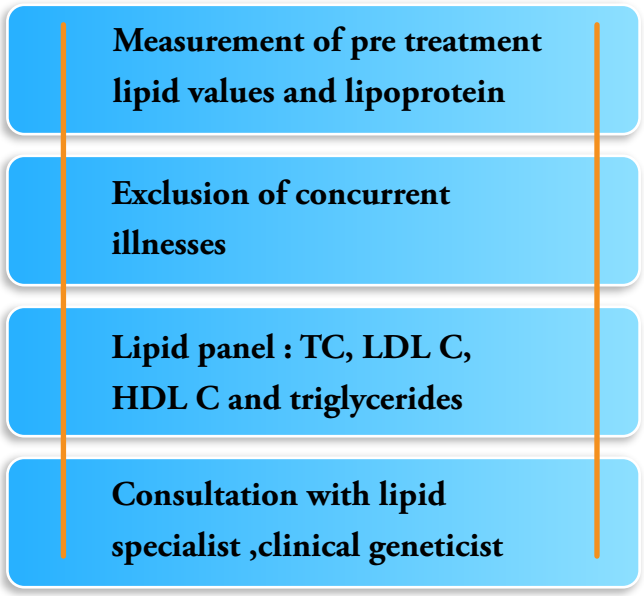

Figure 17: Evaluations following initial diagnosis of FH

Treatment

For adults, treatment should begin as soon as possible after diagnosis. All adults with familial hypercholesterolemia require diet/ lifestyle management and almost without exception will also require cholesterol-lowering drug therapy.

Risk factors (e.g., smoking, diabetes mellitus, and hypertension) are the same in familial hypercholesterolemia as in the general population; aggressive management is required to reduce coronary artery disease risk, with special attention to smoking cessation. Regular physical activity, a healthy diet (reduce saturated fat intake, increase intake of soluble fiber to 10-20 g/day), and weight control should be emphasized. Blood pressure should be treated to 140/90mm Hg (or 130/80 mm Hg in those with diabetes mellitus). Low-dose aspirin (75-81 mg/day) should be considered in those at high risk for coronary artery disease or stroke.

Consider referral to a lipid specialist with expertise in familial hypercholesterolemia if low-density lipoprotein cholesterol concentrations are not reduced with maximal medical therapy. Although it has not been specified, this recommendation generally pertains to low-density lipoprotein cholesterol levels that cannot be reduced by ≥50% with maximal medical therapy over a 6-month period

Testing of first-degree and second-degree relatives should be recommended to all individuals with familial hypercholesterolemia. For adults with familial hypercholesterolemia age 20 years or older, treatment with statins should be initiated to reduce the low-density lipoprotein cholesterol level ≥ 50% or to <100 mg/dL (<2.6 mmol/L). Many guidelines suggest a target low-density lipoprotein cholesterol of <100 mg/dL even in those without known coronary artery disease as individuals with familial hypercholesterolemia have had a lifelong burden of high low-density lipoprotein cholesterol [31, Rank 1]

For persons with familial hypercholesterolemia with any of the following coronary artery disease risk factors, drug treatment may need to be intensified to achieve more aggressive treatment goals (low-density lipoprotein cholesterol <100 mg/dL [<2.6 mmol/L] and non- low-density lipoprotein cholesterol<130 mg/dL [<3.4 mmol/L]).

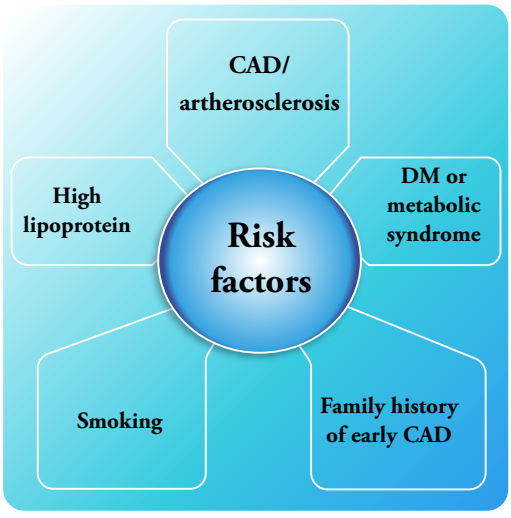

Figure 18: Risk factors of FH

Risk factors (as shown in figure 18):

- Clinically evident coronary artery disease or other atherosclerotic cardiovascular disease; the goal is low-density lipoprotein cholesterol level of <70 mg/dL (<1.8 mmol/L)
- Diabetes mellitus or metabolic syndrome
- Family history of very early CAD (men age <45 years; women age <55 years)
- Current smoking
- High lipoprotein(a) (≥50 mg/dL [≥1.3 mmol/L] using an isoform insensitive assay)

The second-line agent for individuals with familial hypercholesterolemia who do not achieve acceptable low-density lipoprotein cholesterol levels is generally ezetimibe. Treatment options for intensification of therapy after ezetimibe or for those intolerant of statins include: bile acid sequestrants and/or PCSK9 inhibitors. Although niacin has been used as an adjunctive therapy in individuals with familial hypercholesterolemia, given recent data, niacin is generally not favoured before the other options have been exhausted [32, Rank 4]

" The second-line agent for individuals with familial hypercholesterolemia who do not achieve acceptable low-density lipoprotein cholesterol levels is generally ezetimibe. "

Children with Familial hypercholesterolemia

Children should be considered for drug treatment with statin-based regimens when low-density lipoprotein cholesterol levels are ≥190 mg/dL (≥4.9 mmol/L) and Low-density lipoprotein cholesterol levels are ≥160 mg/dL (≥4.1 mmol/L) and at least two other risk factors are present (as shown in figure 19).

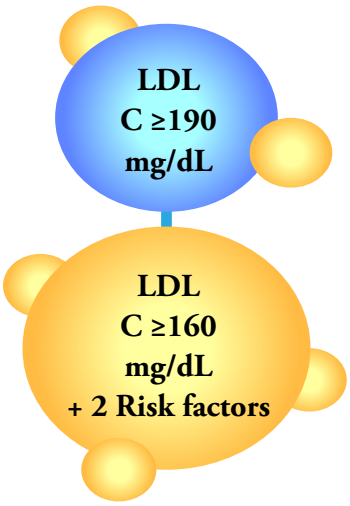

Figure 19: Initiation of Drug therapy for FH based on LDL-C levels

Consultation or referral to a lipid specialist is recommended. Management of diet and physical activity is recommended at an early age. Statins are the preferred initial pharmacologic treatment in children. Consideration should be given to starting statin treatment at age eight years or older. In special cases, such as children with homozygous familial hypercholesterolemia, drug treatment needs to be initiated prior to age of 8 years. The goal of lipid-lowering therapy in children with familial hypercholesterolemia is a ≥50% reduction in low density lipoprotein cholesterol or low density lipoprotein cholesterol <130 mg/dL (<3.4 mmol/L). More aggressive lowering of low-density lipoprotein cholesterol levels should be considered for children with additional coronary artery disease risk factors (e.g., family history of coronary artery disease high blood pressure, unhealthy diet or exercise behaviours, obesity). [33, Rank 5]

Children and adults with homozygous familial hypercholesterolemia (HoFH)

The following are the NLA guidelines (as shown in figure 20) for homozygous familial hypercholesterolemia

- Referral to a lipid specialist is indicated.
- Early initiation of therapy and monitoring are recommended.
- Multiple drug therapy is usually needed. Several different classes of medications are currently being used to treat homozygous familial hypercholesterolemia.

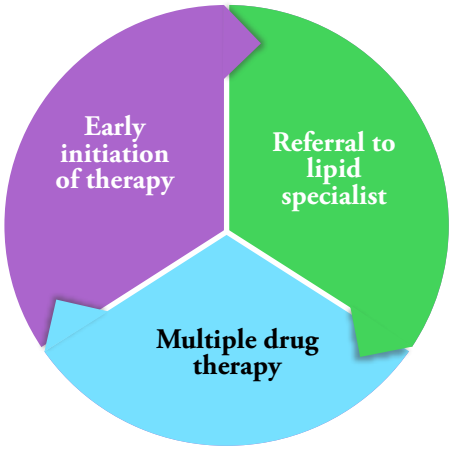

Figure 20: NLA guidelines for HoFH

Since many cholesterol-lowering medications target the low-density lipoprotein receptor, effectiveness in persons with familial hypercholesterolemia with biallelic loss-of function low density lipoprotein receptor pathogenic variants can be limited. Statins are often relatively ineffective in the treatment of homozygous familial hypercholesterolemia because their efficacy largely depends on the upregulation of functional low-density lipoprotein receptors in the liver. In homozygous familial hypercholesterolemia, both copies of the low density lipoprotein receptor have absent or greatly reduced activity.

High-dose statins, ezetimibe, and bile-acid binding resins may be effective in some persons with homozygous familial hypercholesterolemia, especially those with some residual low density lipoprotein receptor activity. For homozygous familial hypercholesterolemia, evolocumab is a PCSK9 inhibitor that showed a 40% mean reduction in low-density lipoprotein cholesterol compared with placebo; however, individuals with two loss-of-function variants saw no response. PCSK9 inhibitors have not been formally approved in children with familial hypercholesterolemia.

Homozygous familial hypercholesterolemia -specific medications (lomitapide and mipomersen) are effective even with complete loss of low-density lipoprotein receptor function and – though not formally FDA approved for children – should strongly be considered. Despite these options, many individuals with homozygous familial hypercholesterolemia (especially those with complete loss of low-density lipoprotein receptor function) will require ongoing low-density lipoprotein aphaeresis. Low-density lipoprotein apheresis (≤2x/week) is often required starting from a young age. Apheresis can lower low-density lipoprotein cholesterol levels by 80% acutely and 30% chronically (weekly or biweekly). Apheresis is offered at a limited number (~40-50) of centers in the United States; many states do not have an apheresis center. Liver transplantation is also being used in rare circumstances in some centers [34, Rank 1]

Children and adults with hetrozygous familial hypercholesterolemia (HeFH)

Heterozygous familial hypercholesterolemia is an autosomal dominant disorder of lipid metabolism that results in lifelong elevated levels of low density lipoprotein cholesterol. Untreated heterozygous familial hypercholesterolemia leads to early onset atherosclerosis and increases the risk of future cardiovascular events. Heterozygous familial hypercholesterolemia is generally a silent disease making under diagnosis and under treatment common (as shown in figure 21).

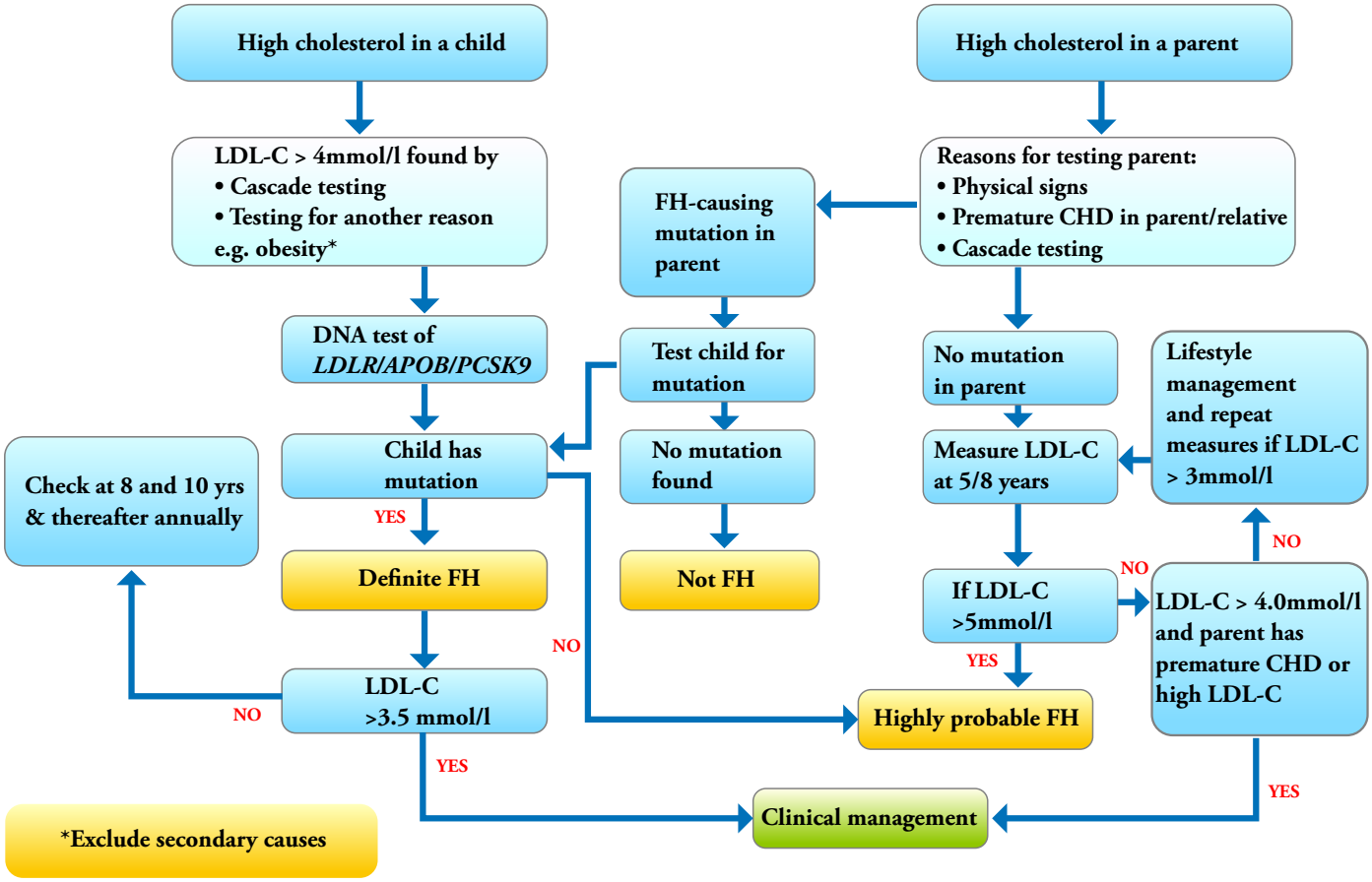

Figure 21: Identification of childhood HeFH

Diagnostic Workup of Familial hypercholesterolemia

A thorough clinical assessment and the results from routine chemical assays deriving low-density lipoprotein cholesterol concentration by the Friedewald calculation [low-density lipoprotein cholesterol = total cholesterol – high density lipoprotein cholesterol – (TG/2.2) in mmol/L] (as shown in figure 22) or directly, can identify the heterozygous phenotype, and could even discriminate the rare sterol defects within the homozygous phenotype. [35, Rank 3]

The clinical diagnosis of the heterozygous familial hypercholesterolemia phenotype is adequate for risk stratification and appropriate pharmaceutical management by general practitioners and specialists. Precision in the diagnosis of familial hypercholesterolemia could be of value for discriminating between polygenic or secondary dyslipidemias and familial hypercholesterolemia in

Friedewald Formula

•LDLC = TC HDLC – (TG/2.2)

Figure 22: Friedewald formula

family studies. Genetic counselling is similar as all three disorders are inherited in an autosomal dominant fashion, but for affected couples accurate diagnosis may be of value in counselling about disease in offspring. When both parents are heterozygous for low-density lipoprotein receptor defects, there is a 25% chance of producing a homozygote. However, in counselling the inheritance of dyslipidemia in couples who have different genes for the heterozygous phenotype, it is known that co-inheritance of Low-density lipoprotein receptor mutation and FDB results in an intermediate phenotype. The co-inheritance of Low-density lipoprotein receptor defects and NARC1 has not yet been reported, but is likely similar to FDB and Low-density lipoprotein receptor co-inheritance. [36, Rank 2]

Although investigations with radio-iodinated low-density lipoprotein can demonstrate deficient clearance of normal low-density lipoprotein in familial hypercholesterolemia subjects with low-density lipoprotein receptor defects, and abnormal clearance of binding defective low-density lipoprotein in normal subjects, these procedures are labour intensive, expensive and not used in practice. Analysis of peripheral blood mononuclear cells101 or cultured cells after up-regulation of low-density lipoprotein receptors with lipoprotein deficient media by means of radio-iodinated or fluorescent low-density lipoprotein or by fluorescently-tagged antibodies in flow cytometry may discriminate normal from heterozygous familial hypercholesterolemia subjects, but remains experimental. [37, Rank 1]

The genetic diagnosis by polymerase chain reaction for low-density lipoprotein and apoB defects is now available in many laboratories. Only a few mutations are known in apoB, but there are more than 750 low-density lipoprotein receptor mutations. In populations with founder effects, genetic diagnosis is easier. In other populations, where research centres can sequence the genes in affected families, molecular diagnosis can be made in family members. In the future, micro-array chips may provide simultaneous evaluation for many mutations. [38, Rank 3]

Patients with a homozygous familial hypercholesterolemia phenotype should be referred to specialised centres for diagnostic work-up and management. Cell culture is more reliable to identify low-density lipoprotein receptor defects. In fibroblast cultures, low-density lipoprotein receptor mutations will result in low binding, whereas adaptor protein mutations will not. It is worth considering measurement of plasma phytosterols for phytosterolaemia and cholestanol for CTX and investigating the genes influencing the concentration of these products. [39, Rank 3]

Medication Choices

(as shown in table 4)

Statins: are among the most commonly prescribed medications for lowering cholesterol — block a substance your liver needs to make cholesterol. This causes your liver to remove cholesterol from your blood. Statins may also help your body reabsorb cholesterol from built-up deposits on your artery walls, potentially reversing coronary artery disease. Choices include atorvastatin (Lipitor), fluvastatin (Lescol), lovastatin (Altoprev,), pitavastatin (Livalo), pravastatin (Pravachol), rosuvastatin (Crestor) and simvastatin (Zocor). Major recommendations for statin therapy for atherosclerotic cardiovascular disease prevention is followed based on ACC/AHA guidelines (as shown in figure 23)

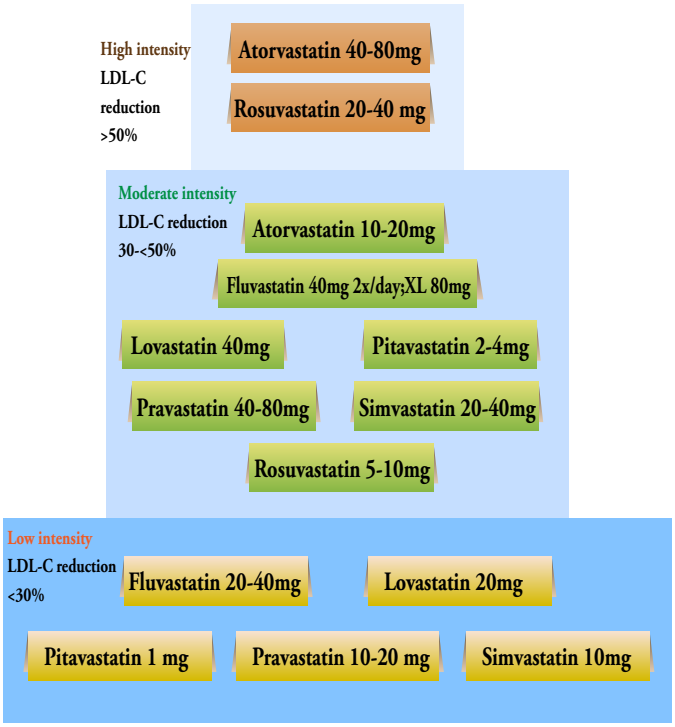

Figure 23: Medications to reduce LDL-C

> **" It is important to find familial hypercholesterolemia and take action at any age, because when treated, the risk of heart disease can be reduced to levels similar to those of the general population. "**

Bile-acid-binding resins: Your liver uses cholesterol to make bile acids, a substance needed for digestion. The medications cholestyramine (Prevalite), colesevelam (Welchol) and colestipol (Colestid) lower cholesterol indirectly by binding to bile acids. This prompts your liver to use excess cholesterol to make more bile acids, which reduces the level of cholesterol in your blood.

	Classification	Drugs
1	Statins	Atorvastatin Fluvastatin Lovastatin Pitavastatin Pravastatin Rosuvastatin Simvastatin
2	Bile-acid-binding resins	Cholestyramine Colesevelam Colestipol
3	Cholesterol absorption inhibitors	Ezetimibe
4	Combination cholesterol absorption inhibitor and statin	Ezetimibe
5	Injectable medications	Alirocumab Evolocumab

Table 4: Drugs used to treat FH

Cholesterol absorption inhibitors: Your small intestine absorbs the cholesterol from your diet and releases it into your bloodstream. The drug ezetimibe (Zetia) helps reduce blood cholesterol by limiting the absorption of dietary cholesterol. Zetia can be used in combination with any of the statin drugs.

Combination cholesterol absorption inhibitor and statin: The combination drug ezetimibe-simvastatin (Vytorin) decreases both absorption of dietary cholesterol in your small intestine and production of cholesterol in your liver. It's unknown whether Vytorin is more effective in reducing heart disease risk than taking simvastatin by itself.

Injectable medications: A new class of drugs can help the liver absorb more low-density lipoprotein cholesterol — which lowers the amount of cholesterol circulating in your blood. The Food and Drug Administration recently approved alirocumab (Praluent) and evolocumab (Repatha) for people who have a genetic condition that causes very high levels of low density lipoprotein. These drugs may also be used for people who have had heart attacks or strokes and need additional lowering of their low density lipoprotein levels. These injectable drugs are administered at home one or two times a month. [50, Rank 3]

Medications for High Triglycerides

If you also have high triglycerides, your doctor may prescribe (as shown in figure 24):

➤ ***Fibrates:*** The medications fenofibrate (Tricor) and gemfibrozil (Lopid) decrease triglycerides by reducing your liver's production of very-low-density lipoprotein (VLDL) cholesterol and by speeding up the removal of triglycerides from your blood. Very-low-density lipoprotein cholesterol contains mostly triglycerides.

> **"Niacin and Statin decreases triglycerides by limiting liver's ability to produce LDL and VLDL cholesterol.**
> **Fibrates decrease triglycerides by reducing liver's production of VLDL"**

➤ ***Niacin:*** Niacin (Niaspan) decreases triglycerides by limiting your liver's ability to produce low density lipoprotein and very-low-density lipoprotein cholesterol. But niacin doesn't usually provide any additional benefit than using statins alone. Niacin has also been linked to liver damage and stroke, so most doctors now recommend it only for people who can't take statins.

➤ ***Omega-3 fatty acid supplements:*** Omega-3 fatty acid supplements can help lower your triglycerides. They are available by

prescription or over-the-counter. If you choose to take over-the-counter supplements, get your doctor's OK first. Omega-3 fatty acid supplements could affect other medications you're taking. [51, Rank 1]

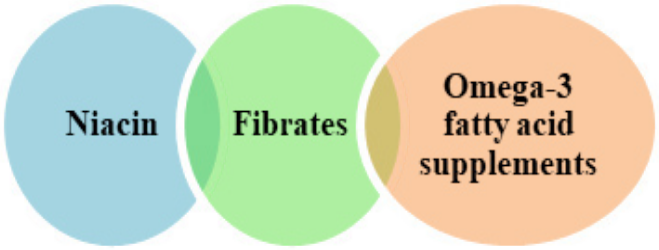

Figure 24: Medications for high triglycerides

Founder Effects in familial hypercholesterolemia

The frequency of familial hypercholesterolemia has been established at approximately 0.002 in the general population at large. There is a very low mutation rate in genes that result in familial hypercholesterolemia and heterozygous familial hypercholesterolemia seldom if ever results in death before reproduction, so that the mutated genes are retained. A variety of mutations in the low-density lipoprotein receptor can be demonstrated in populations that have been isolated for long periods of time and have grown to large numbers. [40, Rank 1]

The founder effect refers to the occurrence of familial hypercholesterolemia at a higher frequency than 0.002 and/or the predominance of one or a few mutations in a population. This phenomenon is typically found in more recently established populations that have migrated in small groups and expanded into a geographically and/or culturally isolated setting. Examples are the Afrikaners in South Africa, French Canadians, Christian Lebanese and the Finns. Such a founder effect may undergo genetic drift according to selection or may become diluted by admixture. [41, Rank 3]

South Africa is well known for its high prevalence of familial hypercholesterolemia in Afrikaners, due to three founder mutations. The prevalence of familial hypercholesterolemia was estimated at 1 in 83 in a rural community. Although it is generally true that three founder mutations explain 95% of familial hypercholesterolemia, the extent to which these three founder mutations account for familial hypercholesterolemia in the Afrikaner varies. A lower proportion of familial hypercholesterolemia is attributable to the founder mutations in the Cape, the portal of entry into South Africa. The V408M mutation that ranks second in frequency in the Afrikaner has been described from the Netherlands and there was evidence that it came from northern Germany. Ancestral linkage of these populations was indicated by the presence of a specific haplotype, which included the Dutch immigrants to Canada. [41, Rank 4]A recurrent mutation of V408M has been

reported in a different population group in South Africa and Cuba. The prevalence of familial hypercholesterolemia is estimated to be high in the South African Jews, with the common mutation being the deletion of codon 197 that is believed to be from Lithuania and also accounts for about a third of familial hypercholesterolemia in St Petersburg and appears limited to Jews in this region. The occurrence of the same haplotype on samples from Jews with familial hypercholesterolemia in many countries also indicated an ancestral link. In South Africa, familial hypercholesterolemia in the Jewish community is also accounted for by local mutations. [42, Rank 3]

In French Canadians, 11 mutations in the low-density lipoprotein receptor describe approximately 90% of subjects with familial hypercholesterolemia, and regional variation in the prevalence of different mutations is striking. A recently identified founder effect has been described from Tunisia which, at 1 in 165, is less common than in French Canada. In most countries, a wider range of mutations has been reported in the low-density lipoprotein receptor. In the Danish population about 5 of the 29 documented mutations occurred in 50% of the population. Germany also lacks a founder effect: 37 mutations have been described in 56 individuals with familial hypercholesterolemia. At least 29 mutations have been identified in the Chinese, with no apparent founder effect [43, Rank 1]

Familial hypercholesterolemia Concepts

Familial hypercholesterolemia is treatable. If familial hypercholesterolemia is found early, serious problems of the heart and blood vessels may be prevented or dramatically delayed by taking steps to protect one. These include:

- Not smoking.
- Exercising regularly.
- Eating a healthy diet low in saturated and transfats.
- Taking medications.
- Going on LDL-apheresis.

Nearly 100% of people with familial hypercholesterolemia will require cholesterol-lowering medications. For some people with familial hypercholesterolemia, more aggressive measures are needed, including low-density lipoprotein -apheresis (a very simple procedure in which low-density lipoprotein cholesterol cholesterol is removed from the blood on a weekly or biweekly basis.) [44, Rank 4]

The American Academy of Pediatrics recommends that if a family has a pattern of early heart attacks or heart disease defined as before age 55 for men and 65 for women,

children in that family should have cholesterol testing after the age of 2 years and before age 10.

There are three different genes that may be mutated in homogenous familial hypercholesterolemia. The most common gene codes for a protein called the low-density lipoprotein receptor. Low-density lipoprotein receptors in the liver remove low-density lipoprotein cholesterol from the blood. If a person has a mutated gene for the low-density lipoprotein receptor, the level of low-density lipoprotein cholesterol in his or her blood will increase. Genes that make other proteins, such as PCSK9 and apolipoprotein B (ApoB), may also be mutated and decrease the removal of low-density lipoprotein cholesterol from the blood. [45, Rank3]

If a person has a mutated gene for any of these proteins, the level of cholesterol in her or her blood will increase. People can have one or two of these mutated genes. When a person has one of these mutated genes (either for the low-density lipoprotein receptor, PCSK9, or ApoB), he or she has heterozygous familial hypercholesterolemia. So, the difference between heterozygous familial hypercholesterolemia and homozygous familial hypercholesterolemia is that a person with homogenous familial hypercholesterolemia has two mutated genes. Two mutated genes greatly increase a person's blood cholesterol level and the risk of a heart attack. [46, Rank 3]

Prevention of Primary Manifestations

Preventive measures include the following:

- Statin-based therapy with addition of other medications as needed
- Reduced intake of saturated fat
- Increased intake of soluble fiber to 10-20 g/day
- Increased physical activity
- Not smoking [52, Rank 5]

Surveillance

A child who has a family history of familial hypercholesterolemia or of premature coronary artery disease, who is heterozygous for the familial hypercholesterolemia pathogenic variant in his or her family or who has an elevated serum cholesterol concentration should have lipid levels checked starting as early as age two years. It is reasonable to check a non-fasting lipid level first and, if borderline, to follow with measurement of low-density lipoprotein cholesterol. Some guidelines state that elevation of two consecutive measures of low-density lipoprotein cholesterol is needed to confirm a diagnosis of familial hypercholestrolemia. [53, Rank 4]

A low-density lipoprotein cholesterol level of >130 mg/dL (>3.4 mmol/L) in a

child is suspicious for Familial hypercholesterolemia and a low-density lipoprotein of >160 mg/dL (>4.1 mmol/L) is relatively specific for familial hypercholesterolemia. [54]

During treatment, individuals of any age with: Familial hypercholesterolemia should have lipid levels monitored as recommended and homozygous familial hypercholesterolemia should be monitored with various imaging modalities (including echocardiogram, CT angiogram, and cardiac catheterization) as recommended [55, Rank 4]

Treatment Goals

The overall goal of treatment is to lower the risk for atherosclerotic heart disease by lowering the low-density lipoprotein cholesterol levels in the blood stream. Atherosclerosis is a condition in which fatty material collects along the walls of arteries. This fatty material thickens, hardens and may eventually block the arteries. Atherosclerosis happens when fat and cholesterol and other substances build up in the arteries and form a hardened material called plaque. The plaque deposits make the arteries less flexible and more difficult for blood to flow leading to heart attack and stroke. [56, Rank 1]

The first step in treatment for an individual who has heterozygous familial hypercholesterolemia is changing the diet to reduce the total amount of fat eaten to 30 percent of the total daily calories. This can be done by limiting the amount of beef, pork, and lamb in the diet; cutting out butter, whole milk and fatty cheeses as well as some oils like coconut and palm oils; and eliminating egg yolks, organ meats and other sources of saturated fat from animals. Dietary counselling is often recommended to help people to make these changes in their eating habits. [57, Rank 5]

Exercise, especially to lose weight, may also help in lowering cholesterol levels. Drug therapy is usually necessary in combination with diet, weight loss, and exercise, as these interventions may not be able to lower cholesterol levels alone. There are a number of cholesterol-lowering medications that are currently used. The first and more effective choice are drugs called "statins." Other drugs that may be used in combination with or instead of the statins are: bile acid sequestrant resins (for example, cholestyramine), ezetemibe, nicotinic acid (niacin), gemfibrozil, and fenofibrate. [58, Rank 3]

Individuals who have homozygous familial hypercholesterolemia need more aggressive therapies to treat their significantly elevated levels of cholesterol. Often drug therapies are not sufficient to lower low-density lipoprotein cholesterol levels at

the desiderated goal and these individuals may require periodical low-density lipoprotein apheresis, a procedure to "clean up" low-density lipoprotein from the blood stream, or highly invasive surgery such as a liver transplant. [59, Rank 5]

Challenges in Counselling Patients about familial hypercholesterolemia

According to cardiovascular nurses who participated in the roundtable discussion, the challenges in providing proper care often begin with the term "familial hypercholesterolemia" itself. Many nurses reported that they seldom use this term in discussions with patients because it can be confusing and intimidating. Instead, they often refer to familial hypercholesterolemia using more conversational phrasing, such as "high cholesterol in the family," "genetic high cholesterol," or "something they inherited." While this phrasing may be more comforting to patients, nurses also note that it could imply that the disease is not serious. As a result, patients may not understand the severity of the risk and consequently avoid seeking specialized treatment. Some nurses also noted that colleagues often are not aware that familial hypercholesterolemia can cause dangerously high cholesterol levels in children as young as age two, and consequently do not raise the issue of familial hypercholesterolemia with parents. [52, Rank 4] To address the problem, many healthcare providers call for broader access to information about familial hypercholesterolemia overall and in children specifically. Nurses indicate that this information should be available to colleagues in primary care as well as multiple specialty areas including pediatrics, gynecology, obstetrics and cardiovascular health. In the discussion, some called for resources that highlight the prevalence of familial hypercholesterolemia, the benefits of screening for high cholesterol beginning in childhood, and the importance of screening family members of those who have been diagnosed. One positive note is that some nurses reported that support for screening in children may be increasing. This could be attributed to the American Academy of Pediatrics (AAP), which now encourages cholesterol testing after the age of two for all children from families where a pattern of premature heart disease or familial hypercholesterolemia are identified (as shown in figure 25). Additionally, AAP recently endorsed guidelines calling for universal cholesterol screening in children beginning at age 9. [47, Rank 5]

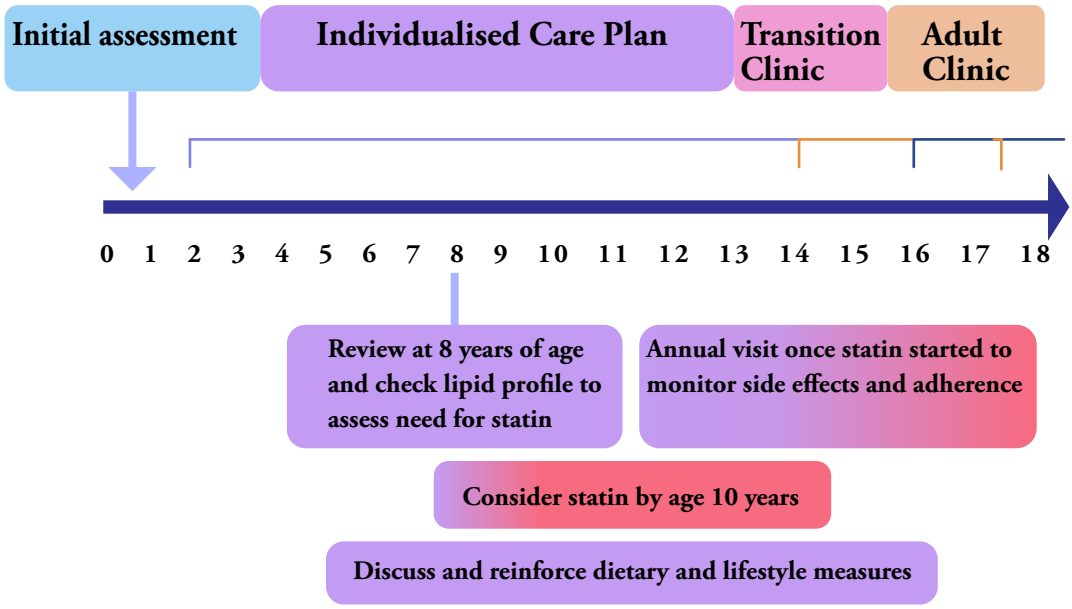

Figure 25: AAP guidelines for screening cholesterol levels in children

High Cholesterol and Familial hypercholesterolemia

High cholesterol is among the most common global health issues, affecting 71 million people in the U.S. alone. Familial hypercholesterolemia is a genetic condition that often causes dangerously high levels of low-density lipoprotein cholesterol to build up in the blood, due to inherited genes that impair the liver's ability to clear cholesterol. It affects about one in 500 people, making it four times more common than sickle cell disease, and five times more common than cystic fibrosis. Familial hypercholesterolemia is an autosomal dominant disorder, meaning that all first degree relatives of people with familial hypercholesterolemia have a 50 percent chance of also having the disorder. More than 1.6 million people in the U.S. and Europe are living with familial hypercholestrolemiatoday. But despite its prevalence, familial hypercholesterolemia remains relatively unknown both within the population as a whole and among healthcare professionals. [60, Rank 3]

Many people with familial hypercholesterolemia do not exhibit visible symptoms and usually do not conform to the typical image of someone at high risk for cardiovascular disease. Additionally, children and younger adults are not typically screened for high cholesterol in routine health maintenance. Without treatment, the risk of developing premature cardiovascular disease is 20 times higher in people with familial hypercholesterolemia than that of the general population. People with familial hypercholesterolemia in their 40s often have narrowing of the arteries similar to that found in a 70-year old. While treatment can help many people with familial hypercholesterolemia to balance cholesterol levels, others may develop a more

severe form of the disease in which cholesterol levels remain dangerously high, even following treatment. [60, Rank 3]

How to tell if a Person Has Familial Hypercholesterolemia

Familial hypercholesterolemia is a serious disorder. If left untreated familial hypercholesterolemia leads to premature heart disease. Yet for most people with familial hypercholesterolemia, until they experience a heart attack, there are few physical signs or symptoms. Some people will develop cholesterol deposits in specific locations including: the Achilles tendons (the back of the ankle) and the tendons of the hands. These are called tendon xanthomas and can sometimes be hard to recognize. [23, Rank 1]

Some people develop orange or yellow fatty deposits around the eyes called xanthelasmas. Cholesterol may also deposit in the periphery of the clear outer covering (cornea) of the eye. This usually occurs in the shape of a half moon (arcus) but can also wrap all the way around the eye. It is generally a whitish grey hue. [20, Rank 2]

Unfortunately, these are not always recognized by treating clinicians as signs of familial hypercholesterolemia. It is also quite possible for a person to have familial hypercholesterolemia without any of the aforementioned physical findings. In general, the older a person, the more likely he or she is to manifest some signs. [17, Rank 1]

Many individuals with familial hypercholesterolemia feel and look healthy, yet their arteries may be significantly diseased. If you have a family history of early heart disease or death from cardiac events, as well as a low-density lipoprotein cholesterol level over 190 mg/dL, then you need to work with your clinician to rule out familial hypercholesterolemia as the cause. In the United States it is estimated that fewer than 10% of individuals with familial hypercholesterolemia have properly diagnosed. This means that sometimes patients have to help educate their doctors about familial hypercholesterolemia. This is okay though, as healthy patient-doctor relationships require shared openness and honesty. [8, Rank 5]

Risks Associated With Familial hypercholesterolemia

If an individual has familial hypercholesterolemia, the low-density lipoprotein cholesterol levels will be very high, leading to narrowing or blockage of blood vessels (atherosclerosis). This process starts prior to birth and can ultimately result in heart disease, heart attack, or stroke. Because people with familial hypercholesterolemia have excessive cholesterol levels since before their birth, their risk of heart disease is 20 times greater than that of the general population. If a child has Homozygous familial

hypercholesterolemia (inherited the familial hypercholesterolemia gene from both parents), she is exposed to an even higher risk, because her low density lipoprotein cholesterol levels are extraordinarily elevated and lead to progressive heart disease very early in life (often in the teens). Other cardiovascular disease risk factors include smoking, over-weight, high blood pressure, and a sedentary life. A patient with familial hypercholesterolemia is advised to eliminate smoking, control your weight and blood pressure and lead a physically active lifestyle. All these are important factors, together with medical therapy and a healthful diet, in lowering the risk of an early heart attack. [44, Rank 4]

Therapeutic Strategies in Familial hypercholesterolemia

Modern pharmacotherapy can achieve desirable concentrations of low-density lipoprotein in heterozygotes, but treatment for homozygotes remains problematic. Heterozygous familial hypercholesterolemia responds like normal subjects to lipid-modifying treatment, as there is a functional low-density lipoprotein receptor that will clear low-density lipoprotein from plasma. Dietary cholesterol and saturated fat restriction will have a modest low-density lipoprotein -lowering effect owing to an up-regulation of low-density lipoprotein receptors when the liver receives less cholesterol through chylomicron remnants. The reduction achieved in plasma low-density lipoprotein cholesterol is approximately 10%, but is variable. A low-fat and low-cholesterol diet may not only up-regulate low-density lipoprotein receptor activity, but may also decrease the endogenous synthesis of cholesterol as suggested by decreased lathosterol concentration in a study of high- and low- fat diets together with statin treatment.[34, Rank 4]

Bile acid sequestrants that waste more bile acids for the patient result in a reduction of the cholesterol pool in cells, and there is a consequent increase in de novo cholesterol synthesis, as well as in low-density lipoprotein receptor synthesis. Low-density lipoprotein cholesterol concentration decreases by 25% at maximal doses. Cholesterol absorption is reduced by phytosterols and phytostanols. Low-density lipoprotein concentrations decrease by about 6 to 10%. [55, Rank 3]

The most powerful cholesterol-lowering agents for familial hypercholesterolemia are the statins. By inhibiting de novo cholesterol synthesis at HMG-CoA reductase, compensatory upregulation of low-density lipoprotein receptors lowers plasma low-density lipoprotein concentration. Familial hypercholesterolemia subjects who achieved steady states of sterol and lipoprotein metabolism with higher de novo cholesterol synthetic rates have higher fasting early morning plasma mevalonic acid concentration and

respond better to statins than those with lower plasma mevalonic acid concentration. [50, Rank 4]

> **" The most powerful cholesterol-lowering agents for familial hypercholesterolemia are the statins. "**

There is no clarity about residual activity of low density lipoprotein receptors and response to treatment in heterozygous familial hypercholesterolemia. A greater percentage decrease of low-density lipoprotein cholesterol was reported in receptor-negative subjects. One study that examined low-density lipoprotein responses in heterozygous familial hypercholesterolemia subjects treated with pravastatin, found some correlation (r = 0.68) between maximal fibroblast low density lipoprotein receptor activity and low-density lipoprotein reduction that ranged from 30 to 70%. A comparison of responses of cohorts with different mutations revealed that the low-density lipoprotein receptor mutation explained 41% of the response in low-density lipoprotein cholesterol to fluvastatin. Two mutations with detectable differences in their phenotype responded similarly to statins. FDB responds well to statins as the low-density lipoprotein receptor up-regulation increases the clearance of both remnants and low-density lipoprotein. It is also likely that statins reduce the production of lipoproteins. [13, Rank 2]

If up-regulation of low-density lipoprotein receptors were the only mechanism by which statins lowered low-density lipoprotein, subjects with homozygous familial hypercholesterolemia due to complete absence of low-density lipoprotein receptor activity will not respond. A decreased production rate of low-density lipoprotein was described in a small cohort of homozygous familial hypercholesterolemia subjects on statins whose rebounds in plasma low-density lipoprotein were analysed. Clearance constants for low-density lipoprotein did not change significantly. One subject had receptor-negative status. These findings indicated that lipoprotein production must be limited, but it is not clear how this happens. Research synthesised cholesterol or a regulatory response to cholesterol depletion may play an important role in lipoprotein assembly and secretion. It appeared unlikely that delivery of lipoproteins to the liver plays a strong modulatory role in production and clearance rates for apo B-containing lipoproteins in the plasma as regular apheresis resulted in no change of these parameters. [29, Rank 5]

Ezetimibe, a recently developed drug that limits cholesterol absorption, lowers low-density lipoprotein cholesterol by about 15%. Interestingly, the impact is similar in heterozygous and homozygous familial

hypercholesterolemia. The mechanism of its action is presumably by limiting lipoprotein production through a poorly understood disruption of cholesterol supply to the liver by lipoprotein remnants. [33, Rank 5]

The inhibition of MTP disrupts lipoprotein assembly and is highly successful at controlling hypercholesterolaemia in the Watanabe rabbit, an animal model of homozygous familial hypercholesterolemia. However, the accumulation of fat in the liver as a result of decreased export may be detrimental. [30, Rank 3]

Plasmapheresis is a well-established procedure that, together with statin and ezetimibe therapy is the treatment of choice for homozygous familial hypercholesterolemia. The original procedure of plasma exchange in which albumin in sterile physiologic saline is used has been replaced by more specific adsorption of lipoproteins onto dextran sulphate or anti-apoB immunoglobulin columns, extracorporeal precipitation with heparin, or double filtration. Liver transplantation, by correcting the function of the most important organ in cholesterol homeostasis, is probably reserved for subjects requiring heart transplant. Gene therapy will hopefully permit effective treatment of this severe disorder in the future. [27, Rank 1]

Dyslipidemias Which Are Coexistent with familial hypercholesterolemia

Low-density lipoprotein particle size and density vary according to the properties of the secreted form of the lipoprotein and the modulation of low-density lipoprotein particle size by hypertriglyceridaemia, cholesteryl ester transfer protein (CETP) and hepatic lipase. The metabolic syndrome (atherogenic lipoprotein phenotype) in subjects with insulin resistance is characterised by mild hypertriglyceridaemia, low high density lipoprotein -cholesterol and small low-density lipoprotein particles. This lipoprotein phenotype is due to environmental and likely multiple genetic factors. In diabetes, the lack of suppression of hormone-sensitive lipase in adipocytes leads to increased release of fatty acids. After re-assembly of fatty acids into triglycerides in the liver, the increased secretion of very-low-density lipoprotein, as well as a modest reduction in the expression of lipoprotein lipase in the diabetic state, leads to hypertriglyceridaemia, low high density lipoprotein -cholesterol concentrations and small dense low-density lipoprotein, as well as increased glycation of plasma proteins. To date, there has been little information on the interaction of diabetes and familial hypercholesterolemia, although it is known that remnants are increased even further in diabetics or in subjects who have impaired glucose tolerance. Low-density lipoprotein particle size was described as being large in 16 of 26 familial hypercholesterolemia subjects and

was influenced by triglycerides concentration. More studies are required to establish whether low-density lipoprotein in familial hypercholesterolemia has the same sensitivity to modulation and whether small low-density lipoprotein has a significant impact on the pathogenesis of atherosclerosis. [29, Rank 4]

The co-existence of familial hypercholesterolemia and FDB has been described. The clinical features of the complex heterozygote for low-density lipoprotein receptor and apoB mutations was no different to heterozygous familial hypercholesterolemia in one case, and intermediate between heterozygous and homozygous familial hypercholesterolemia in the other 2 cases. [40, Rank 3]

Until there is a specific marker for familial combined hyperlipidaemia (FCH), its co-existence with familial hypercholesterolemia cannot be studied properly. Since familial combined hyperlipidaemia is believed to be due to an overproduction of very-low-density lipoprotein, it is possible that it may account for hypertriglyceridaemia occasionally seen in familial hypercholesterolemia. More severe hypertriglyceridaemia may also be seen with concurrent dysbetalipoproteinaemia and familial hypercholesterolemia. [33, Rank 1]

ApoE plays an important role in the clearance of apoB-containing lipoproteins larger than low-density lipoprotein. The apoE2isoform is homozygous in approximately 1% of the population. Under conditions that increase lipoprotein production and/or decrease clearance, remnants of triglyceride-rich lipoproteins accumulate to produce a mixed hyperlipidaemia (dysbetal-ipoproteinaemia). The phenotype in familial hypercholesterolemia subjects also homozygous for apoE2could is similarly affected to normal subjects. An initial amelioration in childhood could reverse after changes in metabolism with age and disease to produce significant hypertriglyceridaemia and cutaneous xanthomata. The presence of significant concentrations of low-density lipoprotein in subjects with dysbetalipoproteinaemia should suggest the co-existence of familial hypercholesterolemia. A study of a relatively small cohort of co-existent dysbetalipoproteinaemia and familial hypercholesterolemia revealed no aggravation of the atherosclerosis complications. Cutaneous xanthomata, rare in heterozygous familial hypercholesterolemia may be prominent in coexisting dysbetalipoproteinaemia and familial hypercholesterolemia. [16, Rank 5]

> **" Conditions with clinical findings similar to those of familial hypercholesterolemia (FH) are cerebrotendonous xanthomatosis, familial dysbetalipoproteinemia, phytosterolemia and Polygenic hypercholesterolemia "**

Familial hypercholesterolemia subjects with lipoprotein lipase deficiency have no low-density lipoprotein. The co-inheritance of hypobetalipoproteinaemia and a heterozygous familial hypercholesterolemia condition would render the low-density lipoprotein cholesterol low. [12, Rank 3]

Evaluation of At-Risk Relatives

There is a significant benefit from performing family-based cascade screening using cholesterol testing with or without DNA analysis on relatives of affected persons with familial hypercholesterolemia in order to identify previously unknown cases of familial hypercholesterolemia and provide those people with life-saving treatment. Early diagnosis and treatment of relatives at risk for familial hypercholesterolemia can reduce morbidity and mortality. [15, Rank 3]

> **" Molecular genetic methods contribute to higher specificity of diagnosis, justification of intensity of treatment and simpler screening for patient relatives. "**

The genetic status of at-risk family members can be clarified by either of the following (as shown in figure 26):

- Molecular genetic testing if the pathogenic variant has been identified in an affected family member
- Measurement of low-density lipoprotein cholesterol level. The following table provides age-specific total cholesterol and low-density lipoprotein cholesterol levels [10, Rank 4]

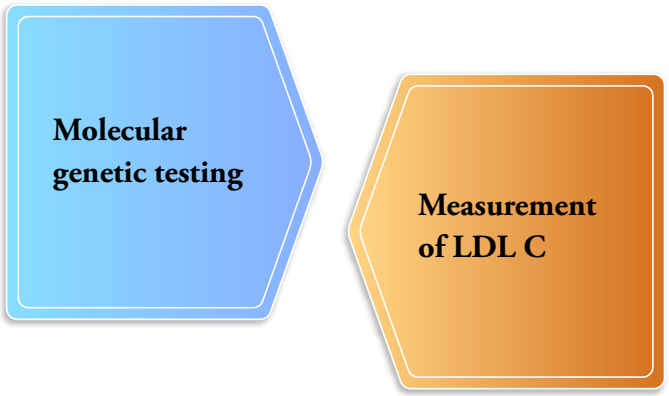

Figure 26: Determinants of genetic predisposition of FH

Total and low-density lipoprotein cholesterol Levels in Heterozygotes for familial hypercholesterolemia based on Degree of Relatedness (as shown in table 5) to an Individual with familial hypercholesterolemia

TC & LDL-C Levels (mg/dL)			
Age	First Degree Relative	Second Degree Relative	Third Degree Relative
< 20	220 (155)	230 (165)	240 (170)
20 – 29	240 (170)	250 (180)	260(185)
30 – 39	270 (190)	280 (200)	290(210)
> 40	290 (205)	300 (215)	310 (225)

Table 5: TC and LDL-C levels in HeFH

First Degree Relative – A parent, sib, or child. First-degree relatives share about half of their genes.

Second Degree Relative – An uncle, aunt, nephew, niece, grandparent, grandchild, or half-sib. Second-degree relatives share about one quarter of their genes.

Third Degree Relative – A first cousin, great-grandparent, or great-grandchild. Third-degree relatives share about one eighth of their genes

Diagnosis Dilemmas

Among nurses who treat familial hypercholesterolemia patients, there is a concern that lack of awareness of familial hypercholesterolemia among healthcare providers increases the risk of non-diagnosis or misdiagnosis. They report that many families are tested only after a relatively young family member experiences an ischemic event. Leading up to such an episode, some people with familial hypercholesterolemia are diagnosed with "high cholesterol" and treated with lifestyle modifications including diet and exercise which are not sufficient to reduce extremely high cholesterol levels caused by familial hypercholesterolemia related to the nature of the genetic defect. In addition to ongoing lifestyle management of diet, exercise and non-smoking, statin therapy is the pharmaceutical intervention of choice, which up-regulates low density lipoprotein receptors and influences the cholesterol that the body is making by interrupting an essential step in its production. As noted by the National Lipid Association in their recommendations for the identification and treatment of familial hypercholesterolemia, those with this genetic disorder that are diagnosed early and treated aggressively have the same lifetime risk of heart disease than another person without familial hypercholesterolemia. [57, Rank 3]

The possibility of non-diagnosis is particularly hazardous in the case of familial hypercholesterolemia because the disease is hereditary and essentially invisible. Some nurses express doubt that healthcare providers are taking the proper steps to reach all first-degree family members following a diagnosis of familial hypercholesterolemia. They stressed that nurses can play a key role in getting more at-risk patients screened for familial hypercholesterolemia by identifying and reaching out to first-degree family members following a diagnosis. [52, Rank 3]

To improve strategies in screening and diagnosis, some nurses conclude that streamlining the current patient advocacy framework is paramount. Primary care providers (PCP) should be on the frontline in primary prevention of familial hypercholesterolemia, but there is a lack of effective referral protocols when low density lipoprotein cholesterol levels are unmanageable. Familial hypercho-

lesterolemia patients who require more intensive management and monitoring should be treated by a lipidologist in collaboration with a primary care provider. The scarcity of experienced lipidology practices in the U.S. continues to present challenges in patient access to appropriate treatment and coordination of care. [50, Rank 3]

Pregnancy Management

Women with familial hypercholesterolemia face unique life time risks given that they are unable to remain on cholesterol reduction therapy with statins during pregnancy. Statins are contraindicated during pregnancy; women with familial hypercholesterolemia who are considering a pregnancy should be counselled of this risk and statins should be discontinued prior to conception. Pregnant women should incorporate all the other recommended lifestyle changes including low saturated and Tran's unsaturated fat intake, no smoking, and high dietary soluble fiber intake. [11, Rank 3]

> **" Statins are contraindicated in pregnancy due to concerns for teratogenicity. "**

Pharmacologic Treatment During Pregnancy

➤ Statins are contraindicated in pregnancy due to concerns for teratogenicity. The use of statins during human pregnancy has not definitively been associated with adverse foetal outcome; however, the role of cholesterol in embryologic development has led to theoretic concerns about the effect of these medications on a developing foetus and a recommendation that alternative medications be considered during pregnancy and lactation. Nursing mothers should not take statins. [5, Rank 3]

➤ ***Bile acid binding resins*** (colesevelam, cholestyramine) are generally considered safe (Class B for pregnancy). Based primarily on animal studies, cholestyramine use during pregnancy has not been associated with an increased risk of fetal anomalies. However, use of cholestyramine could theoretically cause depletion of maternal fat-soluble vitamins, including vitamin K. [1, Rank 1]

➤ ***Low-density lipoprotein aphaeresis*** is also occasionally used.

Regarding other agents:

➤ ***PCSK9 inhibitors:*** Use during pregnancy has not been well studied.

➤ ***Ezetimibe:*** Use during human pregnancy has not been well studied.

➤ ***Niacin:*** The use of pharmacologic doses of niacin, an essential vitamin, has not been studied in human pregnancy. The recommended upper limit of niacin intake during pregnancy is 30-35 mgs/day; higher doses have been associated with toxicity. [51, Rank 4]

Opportunities for Nurses

Nurses at the forum indicated that there may be significant opportunities for both cardiac and primary care nurses to play major roles in expanding awareness of familial hypercholesterolemia and in managing familial hypercholesterolemia patients. They are often well positioned to lead family outreach and education initiatives, which are especially important relative to genetic diseases. Nurses can also play a key role directing patients and families to appropriate care resources. PCNA stands at the forefront leading the way for education in the nursing community. [25, Rank 2]

In efforts to expand awareness of familial hypercholesterolemia and access to care for patients, nurses said they can help push for more clarity in the division of responsibilities related to patient care involving Primary care providers, nurses, lipidologists, dieticians, and others. They also called for more efficient coordination of care while sharing patient information with other members of the care team. Cardiac nurses also saw an essential need to create a greater sense of urgency about familial hypercholesterolemia and to determine terminology and broader messaging about the disease that will resonate with other clinicians, patients, and at-risk populations. [22, Rank 3]

The insights presented in these discussions show clearly that all nurses and specifically cardiovascular nurses can take an active and leadership role in educating people about familial hypercholesterolemia. But they also highlight a critical need to help more healthcare providers to learn about FH and the best strategies to counsel patients and families. [26, Rank 3]

Image Problem of familial hypercholesterolemia

The focus on familial hypercholesterolemia in the healthcare community may be further limited by the fact that patients often show no visible symptoms of disease and appear healthy. For this reason, some nurses report that familial hypercholesterolemia lacks the "fear factor" associated with some less common diseases that are equally dangerous, but where patients present with visible symptoms that inspire them to seek appropriate medical care. [29, Rank 3]

According to one nurse who treats familial hypercholesterolemia patients, "It's an ongoing challenge to alert patients with familial hypercholesterolemia that their health may be at risk and that they may require lifelong health management strategies." Some nurses also find that diagnosed familial hypercholesterolemia patients who have experienced cardiac events wrongly con-

clude they are "cured" following treatment with stents or even bypass surgeries. [28, Rank 4]

Historically, treatment for familial hypercholesterolemia has largely been based on NIH guidelines, which recommend aggressive intervention to treat high cholesterol only when there is evidence of heart disease and a risk of atherosclerosis, heart attack, or stroke. But nurses familiar with familial hypercholesterolemia also call for early intervention including proper screening, diagnosis, and treatment to help patients reduce the risk of cardiovascular disease and manage cholesterol levels over the long term. Many nurses saw an advantage in creating a stronger sense of urgency regarding the dangers of high cholesterol to encourage more patients and healthcare providers to appreciate the risks and take action. But they concede that efforts to build awareness of familial hypercholesterolemia that can result in more pre-emptive action by patients and healthcare providers will continue to be a challenge. [34, Rank 4]

Management of Patients with familial hypercholesterolemia

The goal of familial hypercholesterolemia treatment is to reduce the risk of coronary heart disease or risk of a coronary heart disease-equivalent condition (eg, carotid artery disease, diabetes, peripheral arterial disease). [33, Rank 5]

Risk categories for developing coronary heart disease are as follows (as shown in figure 27):

- ***High risk:*** coronary heart disease or coronary heart disease risk equivalent (10-year risk >20%)
- ***Moderately high risk:*** More than 2 risk factors (10-year risk 10-20%)
- ***Moderate risk:*** More than 2 risk factors (10-year risk 10%)
- ***Lower risk:*** 0-1 risk factor [21, Rank 1]

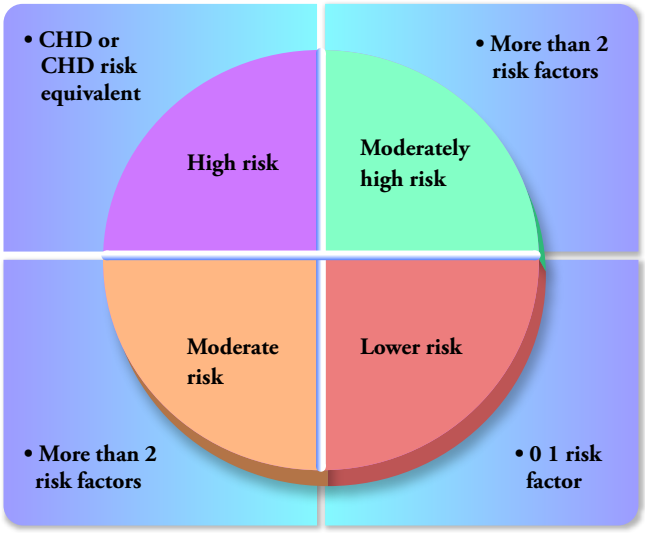

Figure 27: Risk categories for developing CHD

Management of Patients with familial hypercholesterolemia

The following are used in the management of homozygous familial hypercholesterolemia:

- ***Lifestyle changes:*** Recommended for cardiovascular benefits
- ***High doses of HMG-CoA reductase inhibitors*** (statins) combined with bile acid sequestrants, ezetimibe, and niacin

- ***Anti–proprotein convertase subtilisin/kexin type 9 (anti-PCSK9) monoclonal antibodies*** (specifically, evolocumab and alirocumab) can be used as an adjunct to diet and maximally tolerated statin therapy or Mipomersen, or Lomitapide
- ***Estrogen replacement therapy*** in postmenopausal women
- ***Low-density lipoprotein apheresis*** for selective removal of lipoproteins that contain apo-B (when the low-density lipoprotein receptors are absent or nonfunctional) [30, Rank 1]

The following are procedures used in the treatment of homozygous familial hypercholesterolemia:

- Portacaval anastomosis
- Liver transplantation (rarely)

Investigative therapies for homozygous and heterozygous familial hypercholesterolemia include probucol, which causes regression of cutaneous and tendon xanthomas in patients with both homozygous and heterozygous familial hypercholesterolemia but no long-term benefits for reduced coronary atherosclerosis, and gene therapy. [28, Rank 4]

Homozygous Familial Hypercholesterolemia (HoFH) - Risk to Family Members

Parents of a Proband

The parents of an affected individual are obligate heterozygotes and thus have one familial hypercholesterolemia-related pathogenic variant. Individuals with one pathogenic variant have familial hypercholesterolemia. [47, Rank 3]

Siblings of a Proband.

The risk to sibs of having familial hypercholesterolemia is 50%; the risk to sibs of having homozygous familial hypercholesterolemia is 25%. [39, Rank 1]

Offspring of a Proband.

The offspring of an individual with homozygous familial hypercholesterolemia are obligate heterozygotes for a pathogenic variant; thus, all will have familial hypercholesterolemia. [30, Rank 2]

Other Family Members.

Sibs of the proband's parents are at 50% risk of having a pathogenic variant and, thus, familial hypercholesterolemia. [29, Rank 2]

Specific Risk Issues.

Individuals inheriting pathogenic variants from both parents will develop a severe form of homozygous familial hypercholesterolemia (HoFH). [22, Rank 1]

Predictive Genetic Testing for asymptomatic adult family members at risk for familial hypercholesterolemia requires prior identification of the pathogenic variant in the family. [11, Rank 2]

Family planning

The optimal time for determination of genet-

ic risk and discussion of the availability of prenatal testing is before pregnancy. It is appropriate to offer genetic counselling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk. [9, Rank 1]

DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. [6, Rank 3]

> **" If a child has Homozygous FH (inherited the FH gene from both parents), she is exposed to an even higher risk, because her LDL-cholesterol levels are extraordinarily elevated and lead to progressive heart disease very early in life "**

Prenatal Testing and Pre-implantation Genetic Diagnosis

Once the pathogenic variant has been identified in a family member with familial hypercholesterolemia (or if both pathogenic variants have been identified in a family member with homozygous familial hypercholesterolemia), prenatal testing for a pregnancy at increased risk or pre-implantation genetic diagnosis are possible. [50, Rank 4]

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. Although most centres would consider decisions about prenatal testing to be the choice of the parents, discussion of these issues is appropriate. [39, Rank 3]

Other Risk Categories – coronary heart disease or coronary heart disease risk equivalent

- Clinical coronary heart disease
- Symptomatic carotid artery disease or carotid stenosis greater than 70%
- Peripheral artery disease
- Abdominal aortic aneurysm
- Diabetes
- Global 10-year risk of major coronary heart disease event (ie, fatal or nonfatal myocardial infarction) greater than 20% [37,Rank 2]

Risk Determination

Treatment of elevated low-density lipoprotein cholesterol levels is based upon the risk for a coronary heart disease (CHD) event. The 2001 National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATPIII) defined target low-density lipoprotein cholesterol levels and levels based on risk for coronary heart disease. The 2004

update added optional lower low-density lipoprotein cholesterol goals to reflect the findings of several interventional trials demonstrating that more aggressive low-density lipoprotein cholesterol lowering further reduced coronary event rate. [21, Rank 5]

In patients without atherosclerotic disease, the risk for developing coronary heart disease is defined by the number of major risk factors for coronary heart disease and by the following:

- Hypertension (blood pressure ≥ 140/90 mm Hg or treatment for hypertension)
- Cigarette smoking (any within the past month)
- Low-density lipoprotein cholesterol level below 40 mg/dL
- Male sex and age 45 years or older
- Female sex and age 55 years or older
- Family history of premature coronary heart disease:

Clinical coronary heart disease or sudden death in first-degree male relative younger than 55 years or first-degree female relative younger than 65 years [26, Rank 3] a low-density lipoprotein cholesterol level of 60 mg/dL or greater is a negative risk factor for coronary heart disease and its presence removes one risk factor from the total. [53, Rank 1]

Optional low-density lipoprotein cholesterol goal less than 70 mg/dL, especially for very high risk patients include the following:

- Patients with coronary heart disease and multiple other major risk factors for coronary heart disease, especially diabetes
- Severe, poorly controlled risk factors, especially continued cigarette smoking
- Multiple risk factors of the metabolic syndrome
- Patients admitted with an acute coronary syndrome [44,Rank 4]

Moderately high risk - more than 2 risk factors

- Global risk 10-20% - low-density lipoprotein cholesterol goal less than 130 mg/dL, optional low-density lipoprotein cholesterol goal less than 100 mg/dL
- Consider medical therapy for low-density lipoprotein 100-129 [50, Rank 3]

Moderate risk - 2 risk factors or more

- Global risk less than 10% - low-density lipoprotein cholesterol goal less than 130 mg/dL [49, Rank 5]

Low risk

- None to 1 major risk factor for coronary heart disease
- Low-density lipoprotein cholesterol goal less than 160 mg/dL
- Low-risk patients have fewer than 2

risk factors and a 10-year risk for a major coronary heart disease event that is almost always less than 10%. The goal low-density lipoprotein cholesterol is less than 160 mg/dL.

- Moderate risk patients have 2 or more factors and a 10-year risk for coronary heart disease of less than 10%. The goal low-density lipoprotein cholesterol is less than 130 mg/dL.
- Moderately high risk patients have 2 or more risk factors and a 10-year risk of 10-20%. The goal low-density lipoprotein cholesterol is less than 130 mg/dL and the update suggested optional goal low-density lipoprotein cholesterol of less than 100 mg/dL. [40, Rank 3]

The highest category of risk includes coronary heart disease and coronary heart disease risk equivalents include the following:

- Clinical coronary heart disease
- Symptomatic carotid artery disease (transient ischemic attack or stroke of carotid origin)
- Peripheral artery disease
- Abdominal aortic aneurysm
- Diabetes
- 10-year risk less than 20% [38, Rank 1]

The low-density lipoprotein cholesterol goal for high-risk patients is less than 100 mg/dL and the 10-year risk is greater than 20%. In addition to lifestyle changes, institution of medication is recommended if low-density lipoprotein cholesterol level is greater than 100 mg/dL. Patients at high or very high risk have an optional low-density lipoprotein cholesterol goal of less than 70 mg/dL. [27 Rank 3]. Patients with cardiovascular disease who are at very high risk have an optional low-density lipoprotein cholesterol goal of less than 70 mg/dL.

Very high risk is defined as the presence of the following:

- Multiple other major risk factors for coronary heart disease, especially diabetes
- Severe, poorly controlled risk factors, especially continued cigarette smoking
- Multiple risk factors for the metabolic syndrome (especially triglycerides >200 mg/dL, non- low-density lipoprotein cholesterol>130 mg/dL, and low-density lipoprotein cholesterol< 40 mg/dL)
- Patients with acute coronary syndromes [18, Rank 5]

Treatment Recommendations for Homozygous FH

In July, 2014, the EAS published a consensus statement for the screening and treatment of homozygous familial hypercholesterolemia. The treatment recommenda-

tions are summarized as follows:

- Treatment of homozygous familial hypercholesterolemia involves a combination of lifestyle changes, statin therapy, and lipoprotein apheresis, if available, and should be started as early as possible.
- Low-density lipoprotein aphaeresis should begin as early as age 5 years and no later than age 8 years.
- For homozygous familial hypercholesterolemia patients, the low-density lipoprotein cholesterol targets are <100 mg/dL for adults, <70 mg/dL for adults with clinical cardiovascular disease, and <135 mg/dL for children.
- Two novel agents for low-density lipoprotein cholesterol lowering, lomitapide and mipomersen, can be considered as adjunctive treatments for patients who do not achieve the recommended low-density lipoprotein cholesterol targets and remain at high cardiovascular risk. [40, Rank 3]

Because of improved diet normally results in up regulation of low-density lipoprotein receptors, the impact of diet changes on low-density lipoprotein cholesterol levels in homozygous patients is negligible (there are no receptors to up regulate), but lifestyle changes have other cardiovascular benefits and should be strongly encouraged. [33, Rank 4]

Because of the severity of coronary heart disease and lack of response, homozygous familial hypercholesterolemia patients require heroic intervention. [28, Rank 5]. Occasionally, the low-density lipoprotein receptors retain some degree of function and diet control and high doses of HMG-CoA reductase inhibitors combined with bile acid sequestrants, ezetimibe, and niacin can be effective. Estrogen replacement therapy in postmenopausal women is also effective, but this therapy is not recommended because of its adverse effects in older women. However, in some women the benefits may outweigh risks. [22, Rank 4]

The FDA approved Liptruzet (Merck)–a combination of ezetimibe and atorvastatin–for the reduction of cholesterol levels in patients with homozygous familial hypercholesterolemia and as an adjunct to dietary changes in the treatment of elevated low-density lipoprotein cholesterol levels in patients with primary or mixed hyperlipidemia. A once-daily tablet, Liptruzet contains 10 mg of ezetimibe combined with 10, 20, 40, or 80 mg of atorvastatin. [37, Rank 4] When the low-density lipoprotein receptors are absent or non-functional, one of the following is necessary: Low-density lipoprotein apheresis for homozygous familial hypercholesterolemia involves selective removal of lipoproteins that contain apo-B by heparin precipitation, dextran sulfate cellulose columns, or immunoadsorption columns. All

methods reduce low-density lipoprotein cholesterol levels more than 50% and also lower lipoprotein (a), very low density lipoprotein, and triglyceride levels. Low-density lipoprotein is spared. The procedure takes 3 or more hours and is performed at 1- to 2-week intervals. Few adverse events are experienced, most of which are noncritical episodes of hypotension. LDL apheresis is an extremely expensive procedure and is not readily available. [51, Rank 3]

Portacaval Anastomosis

Compared to liver transplantation, this procedure is less hazardous and requires no immunosuppressant. Although cholesterol levels are not reduced as dramatically when compared with transplantation or apheresis, the clinical benefits appear comparable. Low-density lipoprotein cholesterol reductions 50% have been reported; regressions of coronary lesions, aortic lesions, and xanthomas have been documented. The exact mechanism by which low-density lipoprotein cholesterol is lowered is unclear. [41, Rank 1]

Other treatments for homozygous Familial hypercholesterolemia (as shown in figure 28)

- **Evolocumab: Evolocumab** (Repatha) was approved in August 2015. It is indicated as an adjunct to diet and other low-density lipoprotein -lowering therapies (eg, statins, ezetimibe, low-density lipoprotein apheresis) for the treatment of patients with homozygous familial hypercholesterolemia who require additional lowering of low-density lipoprotein cholesterol in adults and adolescents aged 13-17 years. It is also indicated for heterozygous familial hypercholestrolemia in adults. [39, Rank 3]

- **Lomitapide:** Lomitapide (Juxtapid) is a first-in-class microsomal triglyceride transfer protein (MTP) inhibitor. It was approved by the FDA in December 2012 as an adjunct to a low-fat diet and other lipid-lowering treatments, including low-density lipoprotein apheresis where available, to reduce low-density lipoprotein cholesterol, TC, apoB, and non- low-density lipoprotein cholesterol in patients with homozygous familial hypercholesterolemia.

  Because lomitapide increases risk of hepatotoxicity, it is only available through a restricted access program. Approval was based on a small trial of 29 patients exposed to lomitapide, with 23 patients exposed to the drug for 1 year, 15 patients exposed for 2 years, and 5 patients exposed for 3 years. At baseline, the mean low-density lipoprotein cholesterol in the homozygous familial hypercholestrolemia patients was 336 mg/dL, and this was reduced 50% after 26 weeks of treatment ($P < 0.0001$) [33, Rank 2]

- Mipomersen: Mipomersen (Kynamro) is an antisense oligonucleotide inhibitor

targeting mRNA for apolipoprotein B-100. It was approved by the FDA in January 2013 as an adjunct to lipid-lowering medications and diet to reduce low-density lipoprotein cholesterol, apoB, total cholesterol and non-low-density lipoprotein cholesterol in patients with homozygous familial hypercholesterolemia. Safety and effectiveness as an adjunct to low density lipoprotein apheresis have not been established. [26, Rank 3]

➤ **Probucol:** Probucol, a medication with only mild low-density lipoprotein lowering effects and an undesirable high density lipoprotein lowering impact, has been shown to cause regression of cutaneous and tendon xanthomas in patients with both homozygous and heterozygous familial hypercholesterolemia. An animal model has demonstrated reduced coronary atherosclerosis. No long-term benefits have been documented for patients with familial hypercholesterolemia. [16, Rank 5]

➤ **Gene therapy:** Gene therapy is still at the investigational stage. Initially, expectations were high that genetic manipulation would be a less hazardous method for providing functional low-density lipoprotein receptors compared with liver transplantation; however, advances have been slow. [6, Rank 1]

Evolocumab

Lomitapide

Mipomersen

Probucol

Gene therapy

Figure 28: Other treatments for HoFH

Heterozygous familial hypercholesterolemia

The following are used in the management of heterozygous familial hypercholesterolemia:

➤ Lifestyle modification, including diet (limited saturated fats, trans fats, and cholesterol); weight management; aerobic/toning exercises

➤ HMG-CoA reductase inhibitors (statins) (eg, simvastatin, atorvastatin, or rosuvastatin), and one or more other low-density lipoprotein lowering medications (as shown in figure 29), or

➤ Bile acid sequestrants, or Ezetimibe, or Niacin or Estrogen replacement therapy in postmenopausal women

Consider low-density lipoprotein apheresis for the following patients:

➤ Those with documented coronary heart disease whose low-density lipoprotein

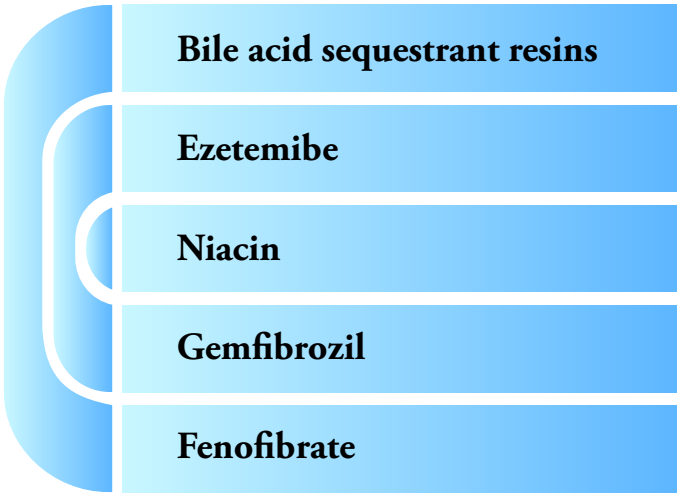

Figure 29: Drugs used in combination with or alternative to statins

cholesterol level cannot be lowered below 200 mg/dL by conventional therapy

➤ Those without coronary heart disease but who have an low-density lipoprotein cholesterol level greater than 300 mg/dL

> **"A healthy lifestyle is the therapeutic cornerstone for all children with HeFH"**

The EAS consensus statement for treatment of heterozygous familial hypercholesterolemia includes the following recommendations (as shown in figure 30):

➤ A low-density lipoprotein target of < 3.5 mmol/L (< 135 mg/dL) for children with Familial hypercholestrolemia (age 8–10)

➤ A low-density lipoprotein target of < 2.5 mmol/L (< 100 mg/dL) for adults with familial hypercholesterolemia

➤ A low-density lipoprotein target of < 1.8 mmol/L (< 70 mg/dL) for adults with known coronary heart disease or diabetes. [48, Rank 4]

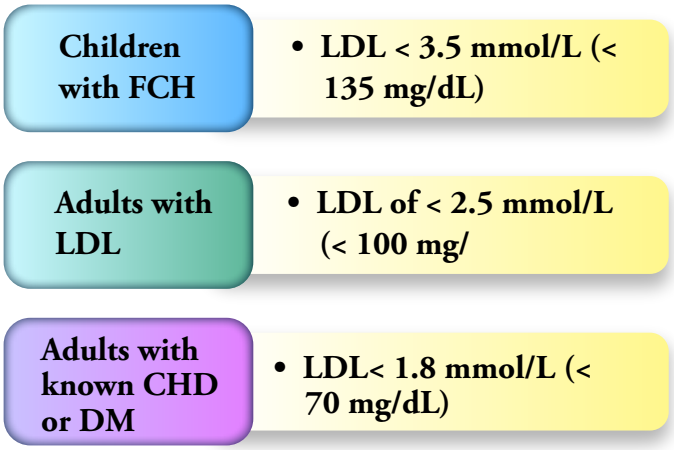

Figure 30: EAS consensus statement for treatment of HeFH

Heterozygous familial hypercholesterolemia – Risk to Family Members

Parents of a proband

Almost all individuals diagnosed with familial hypercholesterolemia have an affected parent. A proband with familial hypercholesterolemia may have the disorder as the result of a de novo pathogenic variant. Because simplex cases (i.e., a single occurrence in a family) have not yet been evaluated sufficiently to determine if the pathogenic variant occurred de novo, the proportion of familial hypercholesterolemia caused by de novo pathogenic variants is unknown but appears to be very low. [50, Rank 3]

If the pathogenic variant found in the

proband cannot be detected in leukocyte DNA of either parent, two possible explanations are germline mosaicism in a parent or a de novo pathogenic variant in the proband. Although no instances of germline mosaicism have been reported, it remains a possibility. [57, Rank 3]

Recommendations for the evaluation of parents of a proband with an apparent de novo pathogenic variantinclude molecular genetic testing if the pathogenic variant has been identified in the proband, or cholesterol testing if the pathogenic variant has not been identified in the proband. Evaluation of parents may determine that one is affected but has escaped previous diagnosis because of a milder phenotypic presentation. Therefore, an apparently negative family history cannot be confirmed until appropriate evaluations have been performed. [16, Rank 5]

Although most individuals diagnosed with familial hypercholesterolemia have an affected parent, the family history may appear to be negative because of failure to recognize the disorder in family members, early death of the parent before the onset of symptoms, or late onset of the disease in the affected parent. [22, Rank 1]

Siblings of a Proband

The risk to the sibs of the proband depends on the genetic status of the proband's parents. If a parent of the proband is affected or has a pathogenic variant; the risk to the sibs is 50%.

If both parents of the proband are affected with familial hypercholesterolemia or have a pathogenic variant, the risk to sibs of having familial hypercholesterolemia is 50%, the risk to sibs having homozygous familial hypercholesterolemia is 25%.

When the parents are clinically unaffected, the risk to the sibs of a proband appears to be very low. The sibs of a proband with clinically unaffected parents are still at increased risk for familialhypercholesterolemia because of the possibility of reduced penetrance in a parent. However, this is a very unlikely scenario.

If the pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the risk to sibs is low but greater than that of the general population because of the theoretic possibility of parental germline mosaicism. [33, Rank 3]

Offspring of a Proband

Each child of an individual with familial hypercholesterolemia has a 50% chance of inheriting the pathogenic variant. If both parents of a child are affected with familial hypercholesterolemia, the child has a 50% chance of having familial hypercholesterolemia and a 25% chance of having homozygous familial hypercholesterolemia. [35, Rank 5]

Other family members

The risk to other family members depends on the status of the proband's parents. If a parent is affected or has a pathogenic variant, his or her family members may be at risk. [40, Rank 5]

Considerations in families with an apparent *de novo* pathogenic variant

When neither parent of a proband with an autosomal dominant condition has the pathogenic variant identified in the proband, the pathogenic variant is likely de novo. However, possible non-medical explanations including alternate paternity or maternity (e.g., with assisted reproduction) or undisclosed adoption could also be explored. [44, Rank 4]

Treatment for Heterozygous Familial hypercholestrolemia

In patients with heterozygous familial hypercholesterolemia, lifestyle modification should always be instituted but is unlikely to result in acceptable low-density lipoprotein cholesterol levels; therefore, cholesterol-lowering medication (usually more than one) is necessary. [9, Rank 5]

Lifestyle modifications include a diet that severely limits saturated fats, trans fats, and cholesterol. Desirable weight should be attained. Significant weight loss should improve all lipid parameters (low-density lipoprotein cholesterol, high density lipoprotein cholesterol, triglycerides). [18, Rank 4].

Aerobic and toning exercises improve blood lipid levels if performed for longer than 30 minutes, 4 or more days per week. [15, Rank 3].

HMG-CoA reductase inhibitors To approach the recommended low-density lipoprotein cholesterol goals, a high dose of one of the 3 strongest HMG-CoA reductase inhibitors (statins), simvastatin, atorvastatin, or rosuvastatin, and one or more other low-density lipoprotein lowering medications, bile acid sequestrants, ezetimibe, or niacin, is recommended. [11] To decrease the risk of myopathy, one step below the maximum dose of the statin should be considered. [34, Rank 3]

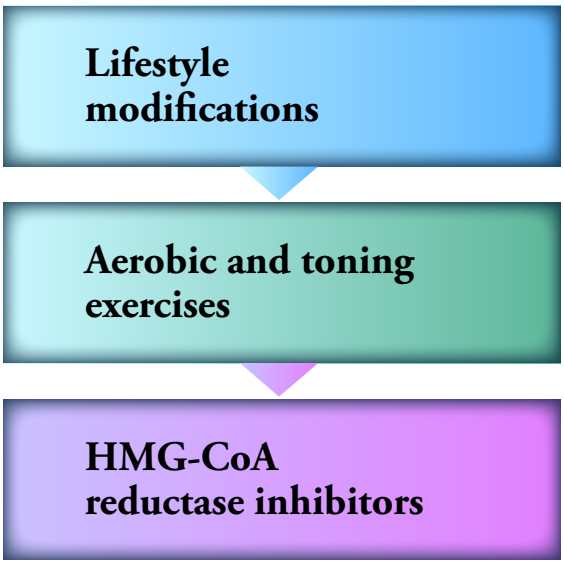

Figure 31: Treatment of HoFH

Evolocumab (Repatha) is the second PCSK9 inhibitor approved in the United States in 2015. It is approved for adults as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with hete-

rozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic CVD who require additional lowering of low-density lipoprotein cholesterol. It is also approved for adults and adolescents with homozygous familial hypercholesterolemia (HoFH). [7, Rank 1]

> **"Statin therapy in children ›10 years is safe and well tolerated.**
>
> **Initiation of statins depends on additional variables, such as high burden of cardiovascular disease risk factors, family history and absolute LDL-C level"**

In pediatric heterozygous familial hypercholesterolemia, a study suggests rosuvastatin slows atherosclerotic progression. In a randomized study (CHARON trial) of 196 children and adolescents (age range, 6-17 y) with heterozygous familial hypercholesterolemia and 65 unaffected sibling controls, treatment with rosuvastatin in affected patients for two years slowed the progression of subclinical atherosclerosis. At baseline, the mean carotid intima-media thickness (IMT) was significantly higher among those with heterozygous familial hypercholesterolemia (0.398 mm) compared with their healthy siblings (0.376 mm); following 2 years of treatment with rosuvastatin, there was no difference in the mean carotid IMT between the groups, and 38% of those receiving rosuvastatin met the target low-density lipoprotein cholesterol of less than 110 mg/dL. Over 85% of patients in the treatment group reported adverse events that the investigators considered as mild (eg, headaches, nasopharyngitis and influenza like symptoms). All patients remained within the normal height and weight range for their age. [2, Rank 1]

Surgical Management

Liver transplantation for homozygous familial hypercholesterolemia

Liver transplantation is rarely performed because of the considerable risks associated with the surgery itself and long-term immunosuppression. But a new liver provides functional low-density lipoprotein receptors and causes dramatic decreases in low-density lipoprotein cholesterol levels. If not normalized, low-density lipoprotein cholesterol levels then can be treated with the usual low-density lipoprotein lowering medications. [22, Rank 2]

Whom to Consult

Homozygous familial hypercholesterolemia

Because the risk of sudden death or nonfatal myocardial infarction is so high, early or highly specialized treatment is necessary. As soon as a child is diagnosed with homozygous familial hypercholesterolemia, a

referral should be made to a medical centre specializing in severe lipid disorders. Referral to centre providing low-density lipoprotein aphaeresis [27, Rank 2]

Heterozygous familial hypercholesterolemia

Refer to qualified nutritionist to provide guidance in reducing intake of saturated and trans fats and cholesterol and assist in weight reduction if indicated. If patients do not reach recommended treatment goals under the care of their primary care physicians, they should be referred to an endocrinologist or lipid specialist and to a qualified nutritionist. If patients are considered candidates for low-density lipoprotein aphaeresis and are willing to undertake this arduous procedure, referral should be made to a medical facility offering this procedure. [35, Rank 3]

Dietary Management

Predicting the degree of improvement in an individual's lipids levels with dietary change is difficult because many variables affect the response, including the makeup of the baseline diet, the degree of patient compliance, and the individual's low-density lipoprotein responsiveness to the diet, which is genetically determined. A decrease of at least 15% can be expected in heterozygous patients who are willing to make significant dietary changes. [33, Rank 2]

The 2001 NCEP ATPIII guidelines emphasize a multifaceted approach to the prevention of CHD. Designated therapeutic lifestyle changes (TLC), its features include increased physical activity, weight reduction, and diet modification. The same diet is recommended for all patients with lipid abnormalities. The NCEP recommendations for the dietary management of hypercholesterolemia are not highly restrictive, but a more stringent regimen may have a greater impact on lipid levels. [35, Rank 1]

Restricting total fat is less important than reducing the intake of saturated fat, trans fat, and cholesterol. Moreover, diets very low in total fat are high in carbohydrates, which may increase triglyceride levels and lower low-density lipoprotein cholesterol levels. Substituting monounsaturated fats (eg, olive and canola oils, avocados, nuts) for carbohydrates does not increase low-density lipoprotein cholesterol levels and, in the absence of weight gain, may increase high density lipoprotein cholesterol levels and lower triglyceride levels in patients who have maintained a diet very low in fat. [54, Rank 3]

Diets should be rich in whole grains, whole fruit, and legumes and other vegetables. These foods are high in soluble fibre, which has a small (approximately 5%) cholesterol-lowering effect; they are also high in antioxidants and flavonoids, which may be cardioprotective. [50, Rank 5]

Features of the NCEP Dietary Recommendations

(as shown in figure 32)

➤ Fiber (soluble fiber): Intake should be 20-30 g/d.

➤ Carbohydrates: Intake should be 50-60% of total energy (caloric) intake. Carbohydrates should be derived predominantly from foods rich in complex carbohydrates, including grains, especially whole grains, fruits, and vegetables.

➤ Plant sterols and stanols: Intake should be 2 g/d. These are present in commercial margarines (eg, Benacol, Take Control).

➤ Total energy (caloric) intake: Balance energy intake and expenditure to maintain desirable body weight and prevent weight gain. Daily energy expenditure should include at least moderate physical activity, contributing approximately 200 Kcal/d (eg, a brisk walk of 2 miles or more).

➤ Trans- fatty acids (trans fats): Intake should be avoided. Products made with hydrogenated fats contain variable amounts of trans fats. Similar to saturated fats, trans fats increase low-density lipoprotein cholesterol levels. However, unlike saturated fats, trans fats decrease high density lipoprotein cholesterol levels. Hydrogenated fats and trans fats are found in many margarines, cakes, cookies, crackers, and frosting. [53, Rank 3]

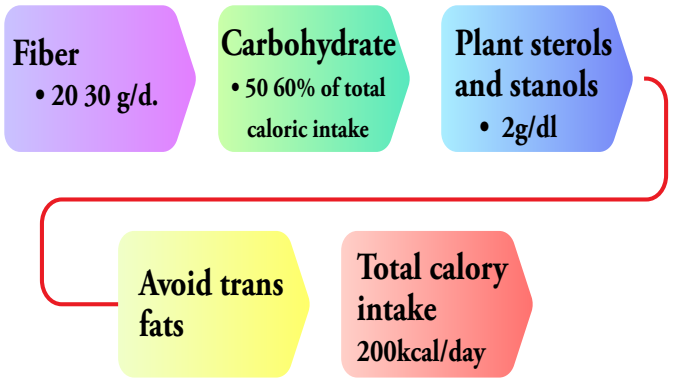

Figure 32: Dietary recommendations

Exercise

Exercise has many cardiovascular benefits and can improve blood lipid levels. Although a greater proportion of time should be spent doing aerobic exercise because of its greater impact on lowering blood pressure and decreasing insulin resistance, resistance training also has benefits.

Patients with coronary artery disease or symptoms suggestive of ischemic heart disease should undergo a symptom-limited exercise stress test before undertaking a new program of vigorous exercise. [56, Rank 5]

Gene Mutations

Familial hypercholesterolemia is caused by mutation in the gene for the low-density lipoprotein receptor, which is involved in low-density lipoprotein recycling. Mutations in other genes can also cause inherited high cholesterol. Those genes include the PCSK9 gene and the gene for

Apolipoprotein B. All these genes are connected with one another. If an individual inherit a specific type of mutation in any of these three genes, he/she can develop familial hypercholesterolemia or inherited high cholesterol. [23, Rank 1]

Genotype Correlations

Both receptor-absent and receptor-defective mutants occur and some of the 'homozygotes' are in fact genetic compounds. An internalization mutant of the low-density lipoprotein receptor binds low-density lipoprotein but is unable to facilitate passage of low-density lipoprotein to the inside of the cell. A patient was found to be a genetic compound, having inherited the internalization mutant from the father and the binding mutant from the mother. From the fact that an individual was shown by family studies to be a genetic compound and that complementation did not occur, it can be concluded that the gene for binding of low-density lipoprotein and the gene for internalization of low-density lipoprotein are allelic mutations at the structural locus for the low-density lipoprotein receptor. [59, Rank 1]

Inheritance of the Disease

In familial hypercholesterolemia there is a dose effect so that homozygous familial hypercholesterolemia is more severe than heterozygous familial hypercholesterolemia. Heterozygous familial hypercholesterolemia occurs when a child inherits a non-functional copy of one of their familial hypercholesterolemia genes from an affected parent and a functional copy from their unaffected parent. Each egg or sperm they produce has a 50% chance of getting the non-functional copy (passing down familial hypercholesterolemia) and a 50% chance of getting the functional copy, Therefore, the risk of passing the familial hypercholesterolemia from the affected parent to a child is 50% in each pregnancy (as shown in figure 33). New, spontaneous variants appear to be very rare. [60, Rank 3]

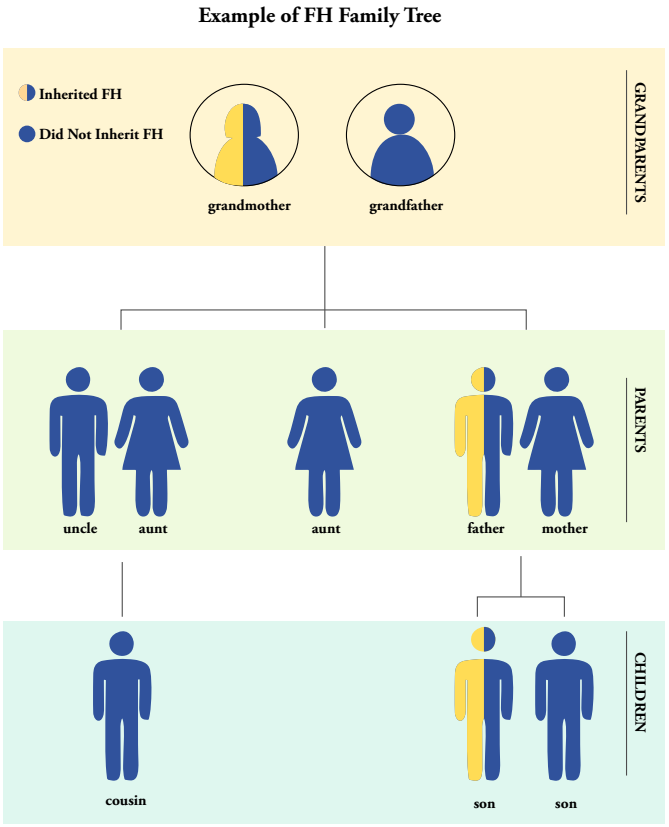

Figure 33: Inheritance of FH

Most individuals with homozygous familial hypercholesterolemia have inherited one mutated gene from each parent, such that each parent has heterozygous familial hypercholesterolemia. These parents have a 25% risk in each pregnancy to have a child with homozygous familial hypercholesterolemia, a 50% chance of having a child with heterozygous familial hypercholesterolemia, and a 25% chance that the child will inherit a normal gene from each parent. The risk is the same for males and females.

When one parent has heterozygous familial hypercholesterolemia and the other has homozygous familial hypercholesterolemia, there is a 50% chance with each pregnancy to have a child with heterozygous familial hypercholesterolemia and a 50% chance to have a child with homozygous familial hypercholesterolemia.

When one parent has homozygous familial hypercholesterolemia and the other has two normal genes, all children will have heterozygous familial hypercholesterolemia. [44, Rank 5]

When both parents have homozygous familial hypercholesterolemia, all children will have homozygous familial hypercholesterolemia. [33, Rank 4]

Abnormal Gene Product

The PCSK9 protein product binds to low-density lipoprotein lipid receptors and promotes their degradation in intracellular acidic compartments. Pathogenic variants in this gene have been associated both with hypercholesterolemia and hypocholesterolemia. [27, Rank 4]

Gain-of-function pathogenic variants cause hypercholesterolemia by excessive degradation of low density lipoprotein receptors, reducing the amount of low-density lipoprotein cholesterol removed from the blood. Loss-of-function pathogenic variants cause hypocholesterolemia (reduced blood cholesterol levels) by increasing the number of low density lipoprotein receptors on the surface of liver cells, resulting in a quicker than usual removal of low-density lipoprotein cholesterol from the blood and reduced incidence of coronary artery disease [22, Rank 4]

Specific Gene Variants

Among patients with identifiable pathogenic gene variants, a low density lipoprotein receptor gene variant is the most common cause of heterozygous familial hypercholesterolemia, accounting for ~90% of pathogenic variants. Since the original pathogenic variant discovered by Goldstein and Brown, over 1600 other variants in the same gene have been identified. An adequate number of functioning low-density lipoprotein receptors are needed to remove cholesterol from the bloodstream.

A pathogenic variant in the APOB gene is responsible for ~10% of familial hypercholesterolemia cases; this variation is seen most commonly in those of European Caucasian ancestry. Apolipoprotein B-100 is a protein that binds to low density lipoprotein receptors, which enables uptake of lipoproteins by the liver and reduces the cholesterol level in the blood. Pathogenic variants in the APOB gene lead to faulty uptake and increased cholesterol level.

PCSK9 gene variants are responsible for only a small percentage of familial hypercholesterolemia cases. The normal PCSK9 gene codes for an enzyme that breaks down the cholesterol receptors after they have done their job. A pathogenic variant in this gene is unlike most variants, which cause dysfunction of the affected gene. The PCSK9 variant increases the gene's function, leading to too few remaining low density lipoprotein receptors and thus an increase in the low-density lipoprotein cholesterol level.

Recent research suggests that the gene and the type of DNA variant an individual has may confer individual risks. However, there is wide enough variation even among those data sets. [30, Rank 5]

Screening Methodology

Familial hypercholesterolemia should be considered in an untreated child with low-density lipoprotein cholesterol above 160 mg/dL and in an untreated adult with low-density lipoprotein cholesterol above 190 mg/dL, or in those with a personal and/or family history of early coronary artery disease, physical signs such as those described under symptoms or a relative known to have familial hypercholesterolemia.

Familial hypercholesterolemia can be diagnosed using DNA testing (as shown in figure 34) or by utilizing one of three well-accepted sets of criteria — Simon Broome (UK), Dutch Lipid Clinic Network (Netherlands), or MEDPED (US). DNA testing confirms the diagnosis and is considered the "gold standard", but is not always necessary or feasible. DNA testing should definitely be considered when it's not clear whether an individual is affected or not, and is very helpful for testing family members. Recent studies also suggest that individual risks for CAD vary among the affected gene and type of DNA variation (substitution vs. partial deletion of a gene, etc.). [30, Rank 5]

Once an individual is diagnosed with familial hypercholesterolemia (either with or without the use of DNA testing) a process called "cascade screening", "cascade testing" or "family screening" (testing of close relatives, in a step-wise fashion) is recommended to identify those with familial hypercholesterolemia before symptoms appear, so that early and intensive treatment can be initiated and disease and death prevented. If a pathogenic

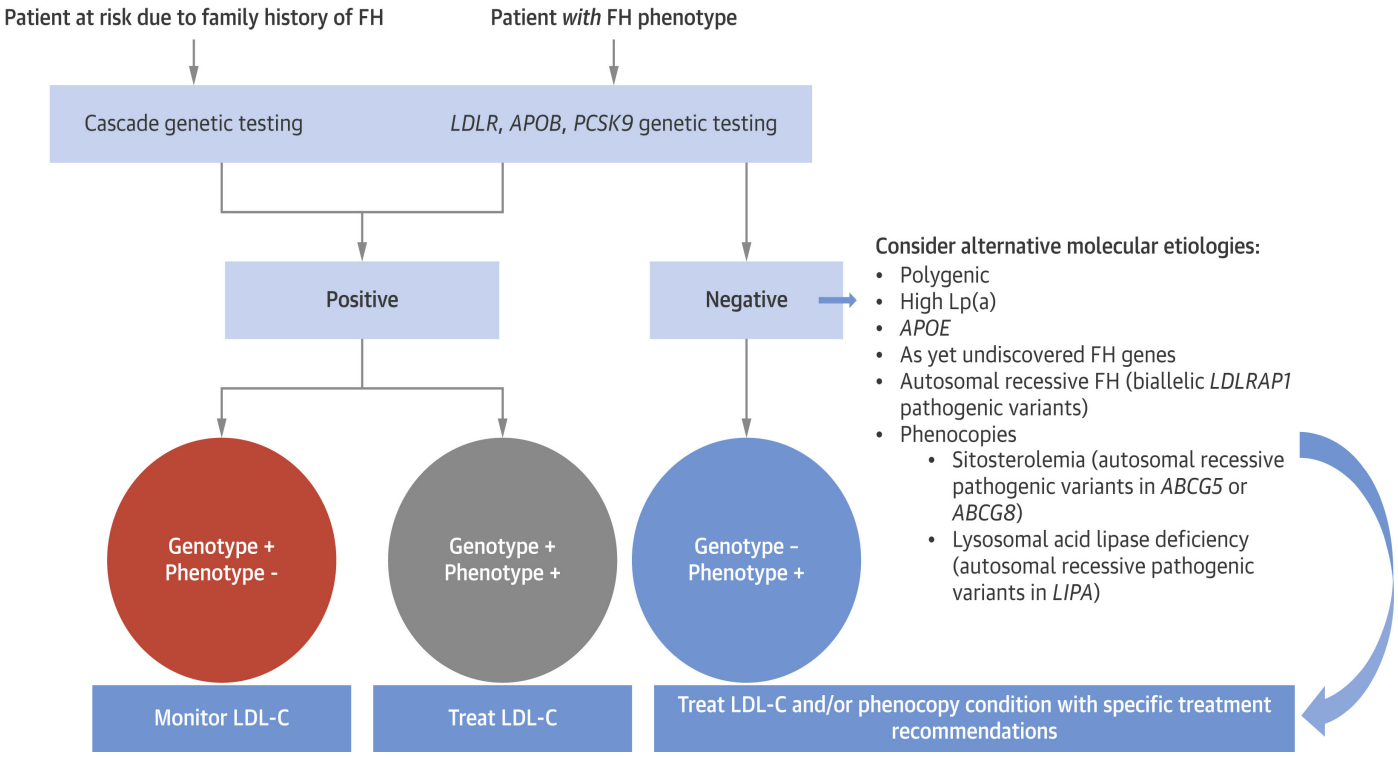

Figure 34: Clinical genetic testing for FH

variant is identified, risk in the patient's first degree relatives (parent, sibling and child) and when appropriate, more distant relatives, can be accessed via DNA testing by tracing the altered gene through the family. If DNA testing is not performed, another version of cascade screening can be implemented using cholesterol testing. Cascade screening by either means has been shown to be effective in finding patients with familial hypercholesterolemia who were not being appropriately treated. A genetic counsellor can help a family through this process. [10, Rank 1]

Children with Heterozygous familial hypercholesterolemia

Parents should discuss with the paediatrician when to initiate treatment in a child with familial hypercholesterolemia. Treatment should be considered when low-density lipoprotein cholesterol level is greater than 190 mg/dl, or greater than 160 md/dl with at least two other risk factors present. The National Lipid Association guidelines recommend referral to a lipid specialist, management of diet and physical activity from an early age, and consideration of statin treatment. Atorvastatin and rosuvastatin, two of the stronger statins, are approved for use in children by the Federal Drug Administration, as are all of the weaker statins. The goal is at least a 50% reduction in low-density lipoprotein cholesterol or low-density lipoprotein cholesterol below 130 mg/dL. [15, Rank 3]

Adults and Children with Homozygous Familial hypercholesterolemia

Early initiation of therapy and monitoring using computerized tomography coronary angiography and other imaging are recommended; these patients often require additional treatment strategies, as pharmacological treatment and lifestyle changes may not be sufficient. Statins are usually started as soon as the diagnosis is made (though may not be effective as explained above). Two new drugs (lomitapide and mipomersen) have now been FDA-approved for the treatment of adults with homozygous familial hypercholesterolemia, and should be considered for these patients, especially if low-density lipoprotein cholesterol level cannot be controlled using other drugs. A PCSK9 inhibitor (evolocumab) was also approved for homozygous familial hypercholesterolemia. Additional options include low-density lipoprotein apheresis or liver transplantation. [17, Rank 2]

Removal of low-density lipoprotein

Using a process similar to kidney dialysis, blood is withdrawn from a vein via a catheter and processed to remove low-density lipoprotein particles. Normal blood products are returned via another catheter. Low-density lipoprotein cholesterol levels will decrease approximately 50% but will rise between apheresis sessions, so they are necessary approximately weekly or every other week. The procedure is effective and well tolerated though time-consuming and only available in 50-60 sites in the US. [19, Rank 3]

Liver Transplantation – A Rare Procedure

Liver transplant is extraordinarily rare and may become even less common with the new medications available. As the donor liver will have normal low density lipoprotein receptors, the low density lipoprotein cholesterol quickly normalizes after the procedure, but the risks of any organ transplant are significant and include complications from major surgery and the effects of lifelong suppression of the immune system. Donor organs are often not available. Patients with familial pathogenic APOB or PCSK9 gene variants have normal low density lipoprotein receptors, so low-density lipoprotein transplantation is not an option for them.

Various imaging modalities such as echocardiograms, computerized tomography angiograms and cardiac catheterization may be recommended to monitor individuals with homozygous familial hypercholesterolemia. [26, Rank 1]

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