

Case study

Hypercholesterolemia Familial: Early Cardiovascular Complications, Treatment Challenges, and the Fatal Consequences of Delayed Diagnosis- An In-Depth Case Study

Abstract:

Familial Hypercholesterolemia (FH) is among the most common genetic disorders, present from birth. The transmission is mainly autosomal dominant. It is characterized by a exclusive increase in low-density lipoproteins (LDL). It is associated with a high risk of premature cardiovascular complications. The diagnosis of FH is generally based on the clinical presentation or genetic tests. The commonly used criteria are those of the Dutch Lipid Clinic Network. FH is a hereditary condition still largely underdiagnosed and undertreated. The prognosis of the disease is related to atheromatous cardiovascular complications, which, in the absence of treatment, lead to the patient's death in the first three decades, often due to myocardial infarction or sudden death. The management of familial hypercholesterolemia systematically involves two categories of measures: so-called hygienic-dietary measures associated with the treatment of other risk factors when they exist, and drug treatments. Familial hypercholesterolemia is still poorly detected. It is necessary to develop systematic approaches to identify patients with FH, conduct cascade screening of their relatives, and increase awareness and control of FH.

Keywords: Familial hypercholesterolemia, LDL-cholesterol, atherosclerosis, Cardiovascular risk, aortic stenosis, cardiovascular diseases, recommendations, lipid-lowering drugs, LDL Apheresis.

Introduction:

Familial hypercholesterolemia (FH) is one of the most common genetic disorders, present from birth. Transmission is essentially autosomal dominant. It is characterized by an exclusive increase in low-density lipoproteins (LDL). It is associated with a high risk of premature cardiovascular complications. [1, 2, 3]

Early diagnosis and therapeutic management are essential. The diagnosis of FH is generally based on clinical presentation or genetic testing. The criteria most used are those of the Dutch Lipid Clinic Network (DLCN). Other criteria include the Simon Broome Registry and WHO criteria [3,4].

Despite the well-established knowledge of FH and its pathophysiology, as well as its avoidable complications, it remains an underdiagnosed and undertreated hereditary condition [5]. Diagnosis often occurs late, coinciding with the occurrence of the first cardiovascular event [6].

The prognosis of the disease is closely linked to atheromatous cardiovascular complications, which, in the absence of treatment, often lead to the patient's death within the first three decades, primarily through myocardial infarction or sudden death [7, 8]

We report the case of a patient with familial hypercholesterolemia who developed early atheromatous cardiovascular disease and aortic stenosis. Unfortunately, the subsequent evolution of his condition proved to be fatal.

Clinical case:

Patient F.K, 46 years old, has been monitored for dyslipidemia since childhood, with no other cardiovascular risk factors, notably no diabetes, hypertension, or smoking, and no family history of

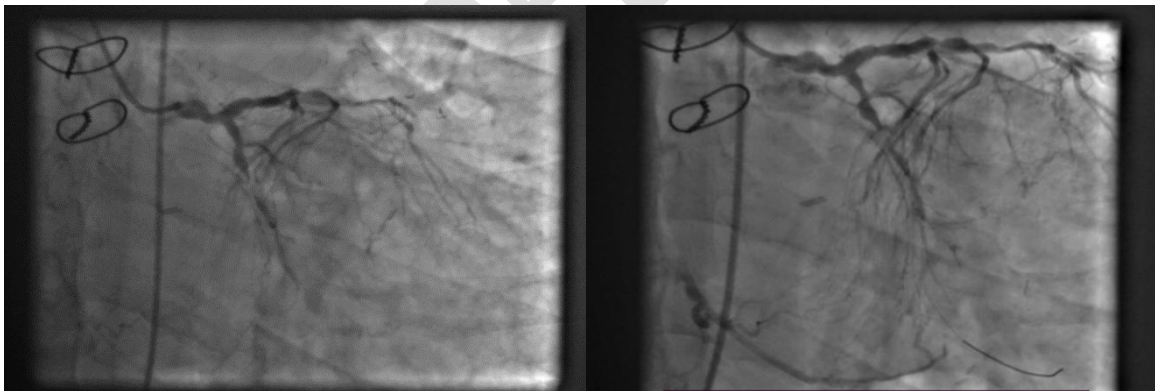
coronary issues. The patient reports that around the age of 8, painless and non-inflammatory subcutaneous formations resembling cutaneous xanthomas appeared on both knees, gradually increasing in size. He underwent surgery for these formations at the age of 14.

The patient underwent a lipid profile assessment, revealing elevated LDL cholesterol levels. He was prescribed lipid-lowering therapy with statins along with lifestyle and dietary measures. However, the patient did not undergo genetic testing to identify familial hypercholesterolemia. Due to poor adherence, the patient discontinued both follow-up appointments and treatment.

In 2014, at the age of 38, the patient experienced an acute coronary syndrome. Coronary angiography revealed significant coronary lesions, including chronic occlusion of the mid left anterior descending artery (LAD 2) and mid right coronary artery (CX2), as well as significant stenosis of the second diagonal and right marginal arteries. This necessitated quadruple coronary artery bypass grafting: left internal mammary artery to the left anterior descending artery and diagonal, and right internal mammary artery to the marginal and right coronary artery in a Y-anastomosis with the left internal mammary artery.

Subsequently, the patient was prescribed dual antiplatelet therapy, beta-blockers, and statin therapy with rosuvastatin 40 mg/day. Due to persistently high LDL cholesterol levels (> 3.3 g/L), early coronary syndrome, and the presence of cutaneous xanthomas, a diagnosis of familial hypercholesterolemia was confirmed with a Dutch Lipid Clinic Network Score (DLCN) of 16. Family history revealed no similar cases or early cardiovascular diseases, and no deaths from unexplained causes.

Despite high-dose statin therapy (rosuvastatin 40 mg/day), the patient's LDL levels remained elevated. Ezetimibe 10 mg/day was added to the treatment regimen, along with reinforced lifestyle and dietary measures. Unfortunately, LDL levels remained high despite these interventions. The use of PCSK9 inhibitors was proposed but was not feasible due to their unavailability in Morocco.



Figures 1 and 2. Coronary angiography illustrates the complexity of lesions in the coronary arteries in our patient.

In 2021, the patient underwent a follow-up coronary angiography (figure 1,2) due to chronic coronary syndrome (CCS Class III angina). The findings included a tight stenosis of the distal left main coronary artery, chronic occlusion of the mid left anterior descending artery (LAD 2), sub-occlusive stenosis of the mid circumflex artery (CX2), and chronic occlusion of the right coronary artery (RCA2). The left internal mammary artery to the diagonal was patent, while the right internal mammary artery to the marginal and right coronary artery showed occlusion in the distal portion. An attempt at

revascularization of the mid circumflex artery was made but failed (balloon passage was unsuccessful). The patient was then placed on optimal medical therapy, including dual antiplatelet therapy, lipid-lowering treatment with rosuvastatin 40 mg/day and ezetimibe 10 mg/day, Cardensiel 5 mg/day, and antianginal therapy with trimetazidine 35 mg twice daily.

A few months later, the patient presented to the emergency department due to worsening dyspnea (NYHA Class IV) and persistent effort angina (CCS Class III). He was admitted to the cardiology department for the management of global cardiac decompensation.

Clinical examination revealed stable hemodynamics and respiration, blood pressure of 109/66 mm Hg, and a heart rate of 70 beats/min. Cardiovascular examination identified a diastolic murmur at the mitral focus, a systolic murmur at the aortic focus radiating to the carotids, and a systolic murmur in the carotid region, predominantly on the right. Signs of left heart failure included basithoracic crackles, and signs of right heart failure included jugular venous distension and edema of the lower limbs. All pulses are easily felt. Skin examination revealed multiple xanthomas on the feet, hands, knees, elbows, buttocks, and ankles (figure 3,4,5 and 6).



Figure 3, 4, 5, and 6. multiple xanthomas on the feet, knees, elbows, and ankles.

Laboratory results showed a normal complete blood count. Other blood tests indicated urea of 1.35 g/l, creatinine of 12.7 mg/L, fasting glucose of 0.95 g/L, and normal TSH. Lipid profile revealed total cholesterol of 4.63 g/L, HDL cholesterol of 0.25 g/L, LDL cholesterol of 4.16 g/L, and triglycerides of 1.50 g/L. There was no evidence of inflammatory syndrome.

Chest X-ray showed cardiomegaly, especially involving the left chambers. Electrocardiogram revealed regular sinus rhythm at 71 beats/min, left atrial enlargement electrically, QRS at 100 ms, with left ventricular hypertrophy electrically (Sokolow index at 42 mm), incomplete left bundle branch block, and repolarization abnormalities with negative T waves in the inferolateral leads.

Transthoracic echocardiography identified a hypokinetic pattern suggestive of ischemic cardiomyopathy with moderate left ventricular ejection fraction (LVEF) at 42% (Simpson's biplane)

associated with severe ischemic mitral regurgitation (MR) with an eccentric jet (figure 11), restricted motion of the mitral valve leaflets, and a heavily calcified aortic valve with tight aortic stenosis (valve area 0.5 cm^2 , mean gradient 41 mm Hg) and moderate aortic insufficiency (figure 7,8,9 and 10). Left ventricle was hypertrophied, atria were dilated, and the right ventricle showed dilation without hypertrophy and manifested systolic dysfunction. Pulmonary hypertension at 51 mm Hg and dilated, poorly compliant inferior vena cava, with no pericardial effusion.

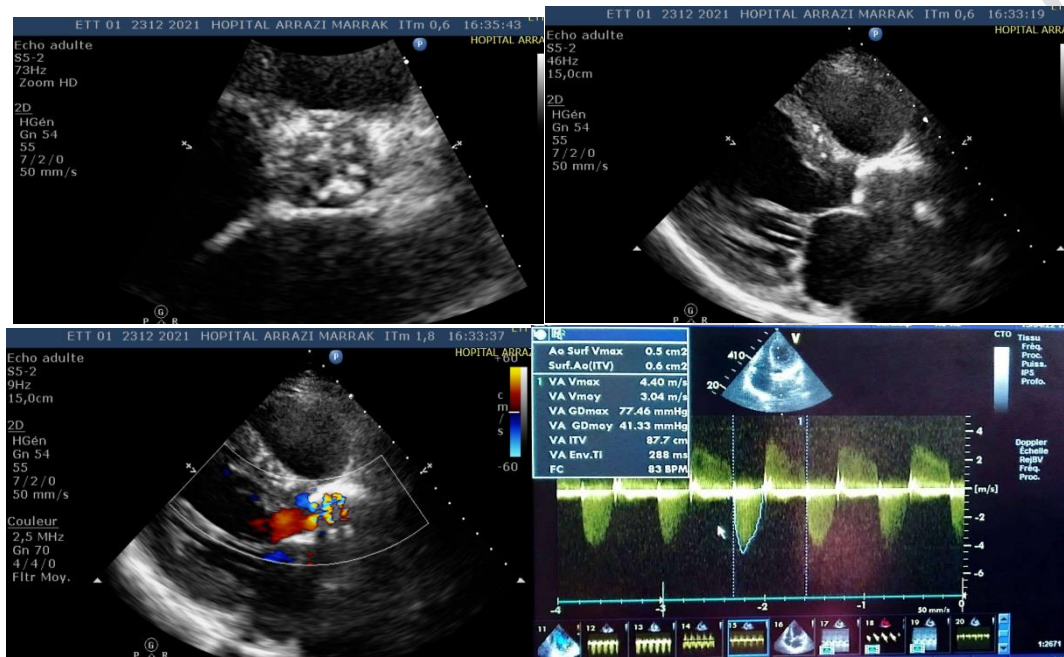


Figure 7,8,9 and 10. Echocardiography demonstrates a heavily calcified aortic valve with tight aortic stenosis (valve area 0.5 cm^2 , mean gradient 41 mm Hg) and moderate aortic insufficiency.



Figure 11. Echocardiography shows severe ischemic mitral regurgitation (MR) with an eccentric jet.

The patient was treated with intravenous diuretics followed by oral diuretics, showing good clinical improvement. In addition to Cardensiel 5 mg, heart failure treatment was initiated with perindopril 1.25 mg/day and spironolactone 50 mg/day according to blood pressure tolerance.

In the context of investigating other arterial involvement secondary to familial hypercholesterolemia, an arterial assessment was conducted:

- Doppler ultrasound of the supra-aortic trunks revealed common carotid arteries hosting extensive plaques along their entire length, with a very tight stenosis in the right common carotid and a tight stenosis in the left common carotid, accompanied by highly disturbed downstream flow (figure 12, 13,14 and 15). The left internal carotid artery had a tight stenosis at its origin. The remaining arteries were infiltrated without significant stenosis.

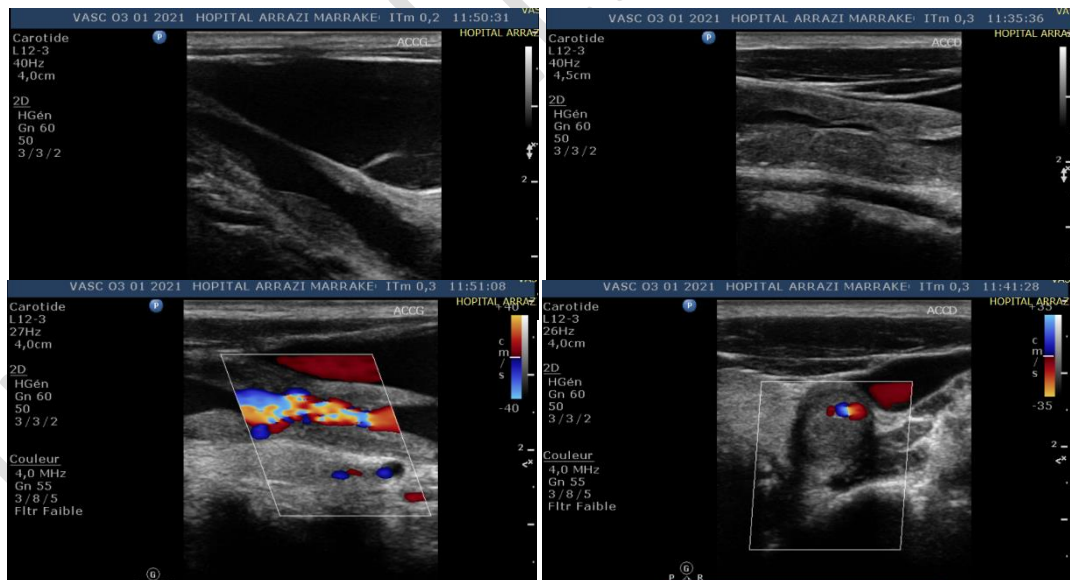


Figure 12, 13,14 and 15. Doppler ultrasound of the supra-aortic trunks revealed common carotid arteries hosting extensive plaques along their entire length, with a very tight stenosis in the right common carotid and a tight stenosis in the left common carotid.

- Doppler ultrasound of the lower limbs showed moderately infiltrated common femoral arteries without significant stenosis. The remaining blood flow was normal in both lower limbs.

- A thoraco-abdomino-pelvic CT angiography was performed after 1 month of arterial Doppler ultrasound, which showed significant calcified atheromatous infiltration of the thoracic aorta. Atheromatous infiltration of the supra-aortic trunks was noted. The right common carotid artery was occluded. Staggered stenoses of the left common carotid artery were present, with a significant pre-occlusive stenosis at 58 mm from its origin. Atheromatous infiltration of the abdominal aorta, its supra- and infrarenal portions, and its branching arteries was evident. Fusiform aneurysm of the subrenal abdominal aorta (figure 16) with a short upstream stenosis estimated at 50% (figure 17). Dissection of the subrenal abdominal aorta (figure 18,19) (2 images of intimal flap at the level of the right anterolateral wall of the aneurysm and at the level of the subrenal abdominal aorta just above the bifurcation). Non-significant stenoses of the primitive iliac arteries.

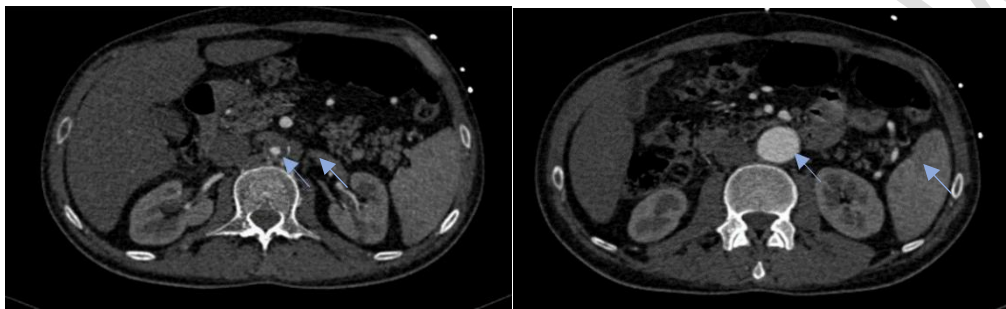


Figure 17. Stenosis of the subrenal abdominal aorta

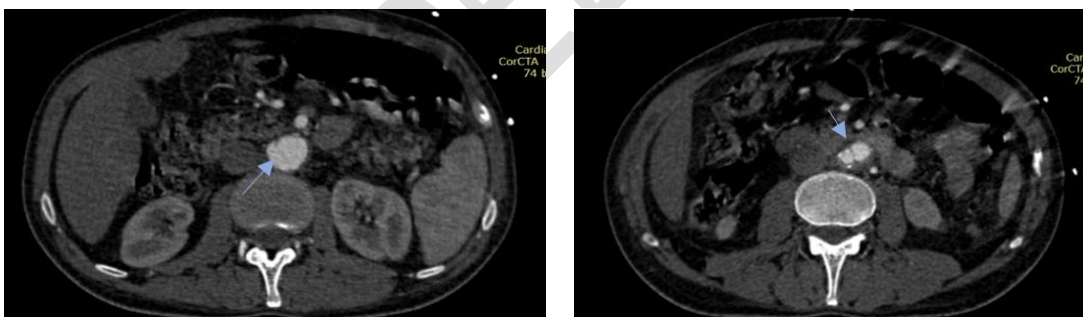


Figure 18 and 19. Dissection of the subrenal abdominal aorta

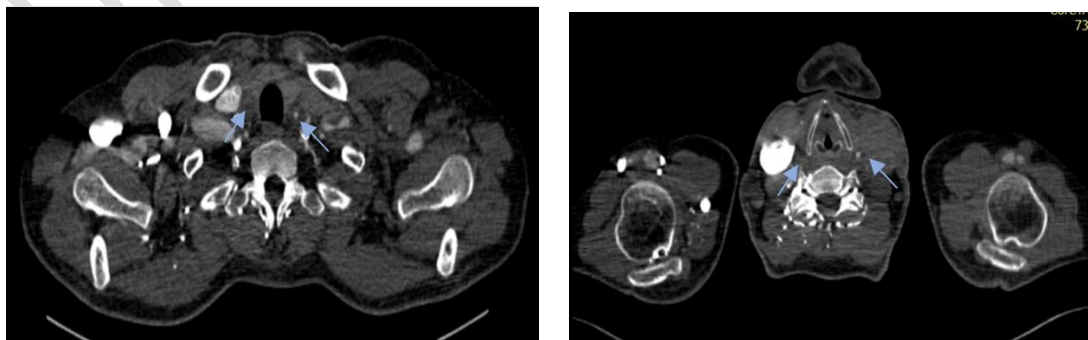


Figure 20 and 21. Occlusion of the right common carotid artery and significant pre-occlusive stenosis of the left common carotid artery.

Given the persistence of elevated LDL cholesterol levels and significant arterial involvement despite optimal lipid-lowering medical treatment, we decided to initiate LDL apheresis for our patient. The evolution was marked by a decrease in LDL levels from 4.16 g/L to 2.91 g/L after 4 sessions of LDL apheresis. However, the patient experienced another episode of global cardiac decompensation with hemodynamic instability, leading to the discontinuation of LDL apheresis sessions, which subsequently complicated with cardiogenic shock and resulted in the patient's demise.

Discussion:

1. Introduction and Epidemiology:

Familial hypercholesterolemia (FH) is an autosomal dominant genetic disorder characterized by significantly elevated levels of low-density lipoprotein cholesterol (LDL-C), often exceeding 2.20 g/L, from birth and complicated by early-onset cardiovascular diseases [1, 3, 4].

It manifests in two forms of varying severity. Heterozygous FH affects 1/200 to 1/500 individuals [2, 9, 10, 11]. The homozygous form, the most severe, occurs in one person per million [2]. Rare forms with autosomal recessive transmission are known but are found in populations with high rates of consanguinity [12, 13]

2. Pathophysiology:

The pathogenesis of familial hypercholesterolemia (FH) is based on an anomaly/mutation in one of the three genes involved in the catabolism of low-density lipoprotein (LDL) particles (figure 22). The implicated genes are [1,4]:

- The LDL receptor gene, which encodes the low-density lipoprotein receptor primarily found in the membranes of hepatocyte cells. This receptor is responsible for absorbing LDL particles and thereby eliminating cholesterol from the plasma. This gene is involved in approximately 70% of cases, with over 1500 pathogenic mutations identified to date.
- The Apo B gene, which codes for apolipoprotein B-100 responsible for the binding between LDL and its hepatic receptor. This gene is implicated in about 6 to 8% of cases.
- The PCSK9 gene, encoding the "Proprotein Convertase Subtilisin/Kexin type 9," which facilitates lysosomal degradation of LDL receptors, is involved in approximately 2% of cases.

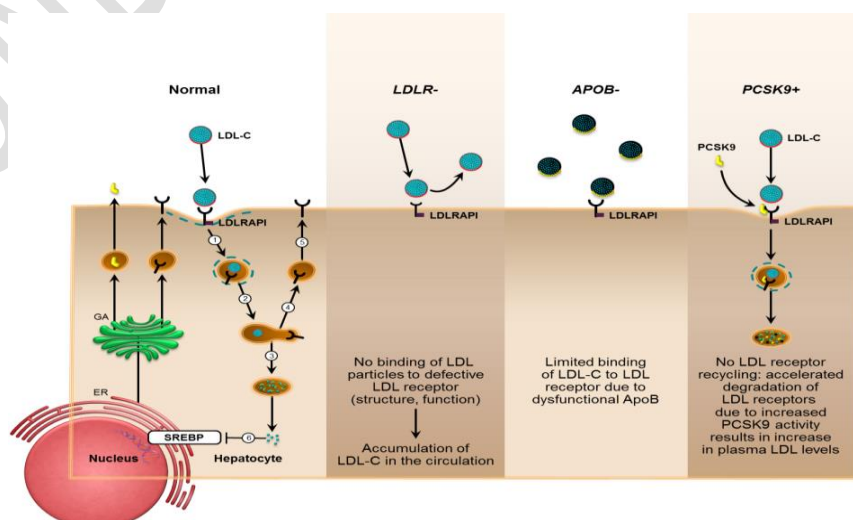


Figure 22. Basis of familial hypercholesterolemia: impaired clearance of LDL cholesterol due to pathogenic variants in LDLR, APOB and PCSK9 [90].

Finally, approximately 20% of FH cases still have an unknown cause, and new genes carrying mutations associated with the disease are yet to be identified [1, 14].

Regardless of the genetic anomaly, it results in elevated levels of plasma low-density lipoprotein cholesterol (LDL-C) and total cholesterol (TC) from an early age [1]. A single copy of the deficient gene (heterozygote) leads to a moderate accumulation of plasma LDL, while two copies of the same defective gene (homozygote) or two coexisting mutations (compound heterozygote) cause significant accumulation due to minimal or absent clearance of cholesterol from LDL [15]. This leads to cholesterol deposition in arterial walls, resulting in early cardiovascular complications.

3. Diagnosis of Familial Hypercholesterolemia:

A. Clinical and Biological Diagnostic Criteria:

Familial Hypercholesterolemia (FH) should be suspected in the presence of elevated LDL-C levels, extravascular cholesterol deposits, or personal/family history of early and severe cardiovascular disease [1, 4, 3, 16]. Essential clinical or biological diagnostic criteria for FH include:

• **Extravascular Cholesterol Deposits:**

- Tendinous or cutaneous xanthomas (figure 23) are almost pathognomonic. Tendinous xanthomas are most frequently observed in the Achilles tendons and extensor tendons of the fingers [17].
- Arcus cornea (figure 23) is pathognomonic when detected before the age of 45 [18].
- Xanthelasmas are less specific and can be observed without lipid disturbances. However, unlike arcus cornea, they are associated with a higher cardiovascular risk independently of cholesterol levels [18].

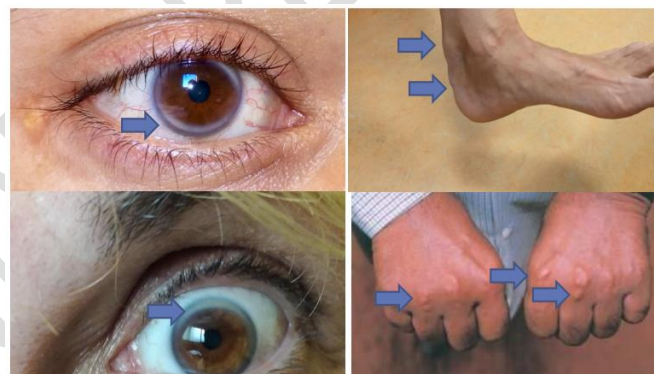


Figure 23. Tendinous xanthomas and arcus cornea [3].

The presence of these clinical signs should prompt a biological assessment and investigation into lipid disturbances and early vascular pathologies within the family. It's noteworthy that the absence of extravascular cholesterol deposits should not exclude the diagnosis of FH, as they occur with variable frequency, particularly being rare in young individuals.

• **Cardiovascular Complications:**

Cardiovascular complications, primarily coronary, can also serve as a possible entry point for the diagnosis of FH, especially if they occur early [1, 3, 4].

- **Biological Criteria:**

Biological evaluation is the most common diagnostic entry criterion. As part of a systematic examination or guided by family investigation. Firstly, it is necessary to confirm hyper-LDL-cholesterolemia and assess its significance in at least two fasting blood tests conducted a few weeks apart [19].

When LDL-C is above 1.90 g/L in adults or 1.60 g/L in children under 16 years old, the diagnosis is highly probable. It is essential to confirm its primary nature and exclude secondary causes, with the most common being obesity, hypothyroidism, overload diseases, liver diseases, kidney diseases (especially nephrotic syndrome), and certain medications (oral contraceptives, corticosteroids) [1, 3, 4].

In adults, there are clinical scores to identify those with FH, such as the Dutch Lipid Clinic Network Score (DLCN) (Table 1). Note that this score is not validated in children. The score considers the presence of personal and/or family history of premature cardiovascular diseases, the presence of clinical signs (tendon xanthomas and/or corneal arcs before the age of 45), and LDL levels to determine a probability score for having FH (Table 1) [16]. You simply add the score from each category. If the total score is above 8, the diagnosis is confirmed [4,3,6 ,16, 20]. In our case, the diagnosis of familial hypercholesterolemia is confirmed with a DLCN score of 16.

The score helps identify adults without clinical FH criteria (0–2 points) from those with possible FH (score between 3 and 5 points) or probable FH (score between 6 and 8). In these categories, 20 to 40% of patients with true monogenic familial hypercholesterolemia may be found, who do not exhibit the criteria with the highest points: corneal arcs before 45 years, tendon xanthomas, and LDL cholesterol levels above 3.30 g/L. Indeed, these criteria are rare, especially in young patients (between 18 and 35 years old) [3].

The negative predictive value of this score is very good (99.8%), making it a useful screening test to exclude FH when the patient has a score below 3 [6].

Table 1. Dutch Lipid Clinic Network diagnostic criteria for familial hypercholesterolemia [33].

Criteria	Points
1) Family history	
First-degree relative with known premature (men aged <55 years; women <60 years) coronary or vascular disease, or first-degree relative with known LDL-C above the 95th percentile	1
First-degree relative with tendinous xanthomata and/or arcus cornealis, or children aged <18 years with LDL-C above the 95th percentile	2
2) Clinical history	
Patient with premature (men aged <55 years; women <60 years) CAD	2
Patient with premature (men aged <55 years; women <60 years) cerebral or peripheral vascular disease	1
3) Physical examination^a	
Tendinous xanthomata	6
Arcus cornealis before age 45 years	4
4) LDL-C levels (without treatment)	
LDL-C ≥ 8.5 mmol/L (≥ 325 mg/dL)	8
LDL-C 6.5–8.4 mmol/L (251–325 mg/dL)	5
LDL-C 5.0–6.4 mmol/L (191–250 mg/dL)	3
LDL-C 4.0–4.9 mmol/L (155–190 mg/dL)	1
5) DNA analysis	
Functional mutation in the <i>LDLR</i> , <i>apoB</i> , or <i>PCSK9</i> genes	8
Choose only one score per group, the highest applicable; diagnosis is based on the total number of points obtained	
A 'definite' FH diagnosis requires >8 points	
A 'probable' FH diagnosis requires 6–8 points	
A 'possible' FH diagnosis requires 3–5 points	

CAD = coronary artery disease; FH = familial hypercholesterolaemia; LDL-C = low-density lipoprotein cholesterol; PCSK9 = proprotein convertase subtilisin/kexin type 9.
^aExclusive of each other (i.e. maximum 6 points if both are present).

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In children, the criteria for establishing a formal diagnosis are presented in Table 2. In a child with a parent having FH, a LDL-C level > 130 mg/dl indicates a high probability of FH (95%) (Table 2). In such cases, a genetic test is recommended to ensure the certainty of a diagnosis that will require lifelong medical treatment [3].

Table 2. How to diagnose familial hypercholesterolemia in children? [3].

- LDL-C level >190 mg/dl in a child
- LDL-C level >160 mg/dl in a child with a close relative who has experienced premature cardiovascular disease.
- LDL-C level >130 mg/dl in a child with a parent clearly diagnosed with FH.

In all cases, a genetic test is recommended to ensure the certainty of a diagnosis that will require lifelong medication.

B. Genetic Diagnosis:

Confirmation of the clinical diagnosis through genetic analysis is the gold standard, but it requires examinations that are not always easily available and can be costly. Ideally, when the diagnosis of FH is certain or probable, mutation identification should be systematically performed. It confirms or affirms the diagnosis when a mutation is found. However, a negative genetic test does not conclusively rule out the diagnosis of FH, as its sensitivity is approximately 80%, and in about 20 to 30% of families, the involved gene is still unknown to date [3, 21, 22].

Even when the diagnosis of FH is certain, searching for the mutation is valuable because, if present in the proband (the patient from whom the diagnosis is initiated), it helps confirm or reject the diagnosis

for other family members. This could be useful for organizing biological monitoring and treatment, especially for children.

When genetic analysis is not possible or non-contributory, the diagnosis can be established based on the family history of high LDL-C levels with autosomal dominant transmission and/or the presence of tendinous xanthomas and/or a very high probability score. In the case of our patient, considering the high cost of genetic analysis, we established the diagnosis based on the very high probability score of the DLCN.

Genetic analysis provides a definitive diagnosis and facilitates family screening. However, this analysis has limitations, with a low probability of identifying the mutation when the diagnosis is only possible. Given the complexity of the procedure and the cost involved, it seems logical to reserve genetic analysis for cases where patients have elevated LDL-C (> 1.90 g/L in adults and 1.60 g/L in children) and another criterion: family transmission and/or tendinous xanthomas and/or early coronary artery disease [23].

4. Different Genetic Forms:

Two forms of this pathology are distinguishable based on the number of alleles carrying the mutation responsible for the disease: the homozygous form and the heterozygous form.

- Heterozygous Form:

A single allele carries the mutation responsible for the disease. Often silent but diagnosed at any age [24,25]. It is characterized by elevated cholesterol levels from childhood. The onset of xanthomas is difficult to specify [26]. They typically begin during the second decade. Coronary artery disease is the major manifestation of atherosclerosis in heterozygotes [27]. It is early onset, indeed, in untreated heterozygous patients, 40% of men and 18% of women experience atherosclerosis complications before the age of 40 [28]. The heterozygous form is characterized by a significant shortening of life expectancy, and mortality is substantial in both sexes before the age of 60 [29].

- Homozygous Form:

Both alleles of the gene responsible for the disease carry the mutation. It is very rare, severe, and characterized by the presence, from childhood, of extra-vascular cholesterol deposits, very high LDL concentrations, and manifest arteriopathy before the age of 10 (aortic stenosis, coronary artery disease) [30, 31]. Despite early detection of these conditions and various palliative therapies, the prognosis remains very severe, and patients have a life expectancy of less than 30 years [32].

5. Familial Hypercholesterolemia and Cardiovascular Risk:

Patients with FH have a high long-term risk of cardiovascular diseases. European recommendations for the management of dyslipidemias clearly identify familial hypercholesterolemia in the high-risk group even when no other associated risk factors are present [33]. There is a direct correlation between the level of familial hypercholesterolemia and the onset of atherosclerotic complications over time [34].

The Copenhagen study, conducted in a large population, demonstrates that patients with the familial form have a 13-fold increased risk of coronary artery disease. Other studies confirm this very high risk [35,16]. In a more recent study in adults, it was shown that a patient with familial hypercholesterolemia is three times more likely to develop premature coronary artery disease than a patient with polygenic hypercholesterolemia [36].

Although clinically silent, arterial involvement begins in childhood and is more severe with higher LDL-C levels [37]. Vascular involvement is both structural and functional and develops over several decades. Several studies have shown a significant increase in carotid intima-media thickness as early as 8 years old [38] and impaired arterial function in children with familial hypercholesterolemia [39]. These arterial abnormalities explain the increased and early occurrence of cardiovascular events that often affect the coronary arteries, as in our patient who experienced his first acute coronary syndrome at the age of 38.

In untreated heterozygous patients, coronary artery disease is early onset, with the first coronary event occurring on average twenty years earlier than in the general population (average age 42 vs. 64 in the general population) [15, 40]. 40% of men and 18% of women suffer from atherosclerosis complications before the age of 40. These percentages rise to 68% for men and 45% for women before 50 and to 96% for men and 74% for women before 60 [28].

In the homozygous form, with the average age of the first angina attack around 11 years, life expectancy rarely exceeds 20 years without treatment, mostly due to myocardial infarction or sudden death [34]. Atherosclerosis is diffuse, but there is a preferential atheromatous involvement of the aortic root encompassing the coronary ostia, which can lead to supra-aortic stenosis [34,41, 42].

The earliness, severity, and frequency of cardiovascular involvement can be aggravated when other risk factors are present, such as hypertension, diabetes, smoking, and obesity. In the context of very high cholesterol levels, the effect of each risk factor is amplified, leading to a greater increase in cardiovascular risk [43,44]. The presence of elevated lipoprotein (a) [Lp (a)] is also a significant risk factor in a patient with FH [45,46], especially in the female population [46].

Identifying these monogenic forms is essential to prevent the occurrence of early cardiovascular events, which remain the main cause of morbidity and mortality in Western countries [1]. Therefore, all adult patients with FH, regardless of age, should benefit from lifestyle and dietary measures and drug therapy to reduce their excess cardiovascular risk associated with their genetic disease.

6. Familial Hypercholesterolemia and Aortic Stenosis:

LDL-C is a significant risk factor for aortic stenosis (AS), with lipid infiltration within the leaflets playing a crucial role in the development of fibro-calcific processes. The circulating level of LDL-C is associated with a higher risk of AS [47]. This explains the occurrence of aortic stenosis in our patient.

In homozygous FH patients, the prevalence of aortic valve calcification reaches 100%, and aortic valve replacement is often necessary [48, 49]. Compared to homozygous FH, heterozygous familial hypercholesterolemia is associated with less significant aortic valve dysfunction on echocardiography [50-51]. In a study comparing aortic valve calcification by Computed Tomography, individuals with FH had a higher prevalence of calcification (41%) and a higher calcification score (21%) than controls [52]. A recent study revealed that the incidence of AS is 7.7 times higher in all Norwegian FH patients followed between 2001 and 2009 compared to the general population [53].

However, randomized clinical trials of LDL-C-reducing therapies (statins) in patients with advanced AS have failed to demonstrate their effectiveness in reducing disease progression [54-55].

7. Role of Arterial Investigations in the Management of Heterozygous FH:

There is no specific equation to assess the cardiovascular risk of a patient with FH. There are also no straightforward means to adjust the results of a risk equation (such as the Framingham equation, for example) because the multiplicative factor varies considerably with age.

In the context of FH, non-invasive cardiovascular exploration is used empirically in this population, and the assessment of arterial risk essentially depends on three parameters: the patient's age, associated risk factors, and the duration and regularity of lipid-lowering treatment.

There is no study demonstrating a positive impact of systematic arterial exploration on a potential reduction in cardiovascular events. The interest of these examinations is, therefore, (1) for therapeutic education, (2) to optimize therapeutic strategy, and (3) to detect potentially dangerous arterial lesions. The discussion will be limited to three examinations: exercise ECG, arterial exploration by ultrasound-Doppler, and calcium scoring. The discussion here focuses on screening an asymptomatic patient. A baseline ECG is a necessary examination in adults with FH primarily to have a reference [4].

The screening of early atheromatous complications relies on non-invasive cardiovascular explorations, particularly cardiac and supra-aortic trunk ultrasound. Coronary angiography is guided by symptoms. The development of imaging techniques, especially multi-slice Computed Tomography, should improve the monitoring of aortic and coronary involvement [56].

8. Treatment of Familial Hypercholesterolemia:

The management of familial hypercholesterolemia (FH) systematically involves two categories of measures: hygienic-dietary measures combined with the treatment of other risk factors when they exist, and drug treatments.

The treatment goal for adults in primary prevention is an LDL cholesterol level below 0.7 g/l. In secondary prevention, the goal is an LDL cholesterol level below 0.55 g/l [9]. Patients with FH in secondary prevention are at a very high risk of a new cardiovascular event or death [33].

A. Hygienic-Dietary Measures:

In adults, recommended dietary measures primarily include reducing overall fat intake, especially a reduction in saturated fat intake, and simultaneously reducing cholesterol-rich foods. Additionally, patients with FH should be encouraged to maintain a satisfactory body weight through regular physical activity and appropriate total energy intake [1,4,16].

Hygienic-dietary measures should always be implemented, even if they are insufficient to achieve the desired LDL-C goals. The reduction in LDL-C achieved through dietary and lifestyle measures varies, depending on the patient's initial dietary habits, adherence to these dietary measures, and genetic factors. Generally, a decrease of around 10 to 15% can be achieved in most individuals [57,58].

B. Drug Treatment:

Treatment with a statin should be initiated in any individual with familial hypercholesterolemia (FH). The severity of hypercholesterolemia in these patients often requires the use of the most potent statins (atorvastatin, rosuvastatin) [59,60,61,62]. With the most potent statins at maximum doses, reductions in LDL-C of up to 50 to 60% have been achieved in patients with hypercholesterolemia (not necessarily with FH) [63, 64]. Statins are generally well-tolerated, with an excellent safety profile [65,66].

To prevent the occurrence of cardiovascular complications, the latest recommendations from the European Atherosclerosis and Cardiology Societies (2,3) suggest initiating treatment, if possible, from the age of 8 to 10 years. Statin treatment should start with low doses (e.g., rosuvastatin 5 to 10 mg or

atorvastatin 10 mg), and the dose should be increased to achieve goals. The target in children over 10 years old is an LDL-C level <3.5 mmol/L (<135 mg/dL), and in younger children, a >50% reduction in LDL-C [33]. (Table 3)

For patients treated later, according to recent European recommendations [3], FH patients with a very high cardiovascular risk due to a history of atherosclerotic cardiovascular disease or another major cardiovascular risk factor, the LDL-C goals are a reduction of >50% from baseline and an LDL-C <1.4 mmol/L (<55 mg/dL) [33]. (Table 3)

In the absence of atherosclerotic cardiovascular disease or another major risk factor, FH patients are categorized as high risk, and the LDL-C goals are a reduction of >50% from baseline and an LDL-C <1.8 mmol/L (<70 mg/dL) [33]. (Table 3)

Given the very high levels of LDL-C typically observed in a patient with heterozygous FH without treatment, it is challenging to achieve the therapeutic goals traditionally proposed for patients at high cardiovascular risk with statins alone, even using maximum tolerated doses, justifying the use of combination therapies [64, 67, 68, 69, 70].

For an adult with heterozygous FH not achieving the LDL-C target on statin therapy alone, combination with ezetimibe is recommended, which induces an additional reduction in LDL-C of 20 to 30%, according to studies [71]. Ezetimibe is the preferred treatment in combination with a statin due to its good tolerance and ease of use. However, in severe forms of heterozygous FH, this dual therapy may still be insufficient to achieve the LDL-C target <1.00 g/L. Therefore, triple therapies are sometimes necessary to treat a patient with heterozygous FH [69].

According to the latest European recommendations, in individuals with familial hypercholesterolemia and very high cardiovascular risk (i.e., with established atherosclerotic cardiovascular disease or another major cardiovascular risk factor) in whom the LDL-C target is not reached with a statin at the maximum tolerated dose, combined with ezetimibe, the addition of a PCSK9 inhibitor is recommended [33]. The combination of these treatments currently allows achieving a reduction in LDL cholesterol of nearly 85% [3].

The challenges in reaching desirable LDL-C levels in patients with FH, especially in secondary prevention, justify the development of new therapeutic strategies for these patient categories, and in some cases, the use of LDL apheresis.

In our patient, the LDL-C target is <55 mg/dl (given the history of acute coronary syndrome), but unfortunately, this goal is not achieved despite maximum-dose lipid-lowering treatment with rosuvastatin 40 mg and ezetimibe 10 mg. Due to the unavailability of PCSK9 monoclonal antibodies, our decision was to complement the treatment with sessions of LDL apheresis.

Table 3. Familial Hypercholesterolemia Treatment

- **In children < 8 years:**
Initiate a hypocholesterolemic diet from the age of 4.
- **In children > 8 years:**
Start a potent statin at a low dose (target LDL-C <135 mg/dL).
- **In adults:**
Target LDL-C < 70 mg/dL in general (statin ± ezetimibe).
Target LDL-C < 55 mg/dL with a history of cardiovascular events or risk factors (statin ± ezetimibe ± * ...).

*Other additional therapies such as anti-PCSK9 monoclonal antibodies.

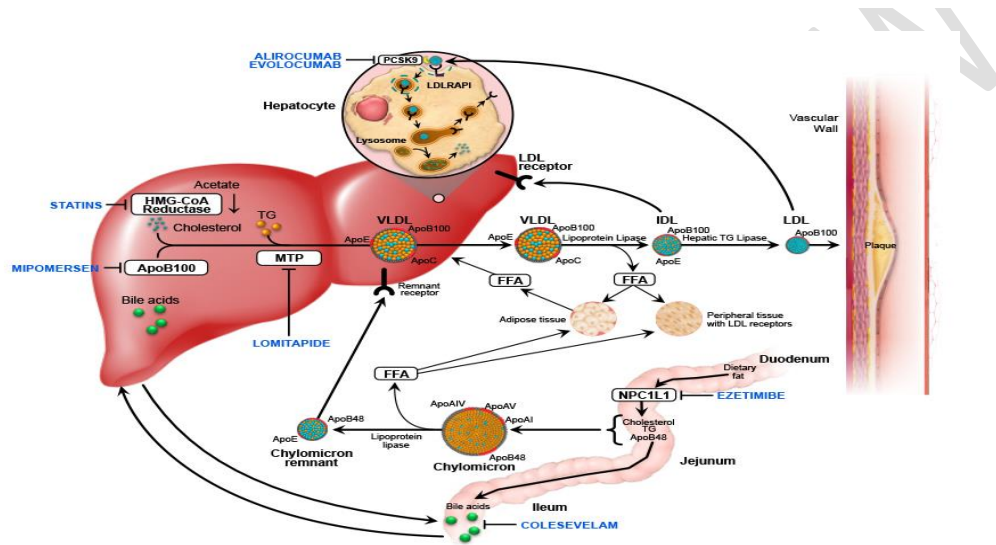


Figure 24. LDL receptor-mediated regulation of low-density lipoprotein cholesterol levels and recommended drugs that affect various steps of these pathways [91].

C. Role of LDL Apheresis in the Treatment of FH:

In some FH patients, LDL-C levels may remain high despite maximum dietary and drug treatment due to a very high baseline LDL-C level, limitations in the use of treatment, or high doses due to intolerance or true therapeutic resistance. After reasonably ruling out the possibility of therapeutic non-adherence or an aggravating secondary cause, LDL apheresis treatment may be proposed.

Lipoprotein apheresis involves the physical removal of lipoproteins from the blood and is only used in patients whose lifestyle and pharmacological treatment cannot reduce lipoproteins to acceptable levels [72]. The effectiveness of LDL apheresis on lipid parameters is well demonstrated [72, 73, 74, 75]: One apheresis session can reduce LDL cholesterol, apo B, and lipoprotein (a) by approximately 65%, resulting in an average reduction over time of 30 to 50%. Concurrent statin therapy enhances the effectiveness of LDL apheresis [76, 77]. Although lengthy and costly, regular apheresis is very well tolerated and has proven safe for decades.

Apheresis reduces cholesterol levels independently of residual LDL receptor function and not only helps reduce or eliminate xanthomas but also inhibits or mitigates the progression of valvular stenosis and supravalvular aortic stenosis, as well as coronary arteries and other atherosclerotic lesions [72, 73, 78].

Several clinical studies have confirmed the benefit of LDL apheresis in preventing or slowing the progression of atherosclerotic lesions [79, 80]. Other favorable effects of LDL apheresis have been described, such as improved endothelial dysfunction [81], coronary vasodilation, or myocardial perfusion [82, 83]. In a recent review, Thompson reported a reduction in cardiovascular events in patients undergoing LDL apheresis [79], but this result is challenging to interpret because most studies are not randomized.

The indications for apheresis for high LDL cholesterol levels vary considerably from country to country [72, 73, 84]. There are several different guidelines for the use of lipoprotein apheresis. In the United States (Table 4), homozygous familial hypercholesterolemia is the main indication for lipoprotein apheresis. It is also approved for patients with other severe forms of high LDL cholesterol that persist despite maximal drug treatment (LDL cholesterol > 300 mg/dl without concomitant cardiovascular disease or > 200 mg/dl with concomitant cardiovascular disease) [72, 73, 85]. In Germany (Table 5), apheresis for high LDL cholesterol can be performed in cases of severe hypercholesterolemia if, despite a diet and maximal drug treatment, LDL cholesterol cannot be sufficiently reduced (documented for 12 months) [72, 73]. No specific threshold is given because the patient's overall risk profile must be considered in assessing the indication for apheresis. However, PCSK9 inhibitors must be administered before the patient is evaluated for apheresis [86].

Other countries have fewer specific recommendations regarding apheresis for high LDL cholesterol [72, 87].

Table 4. Patients approved for lipoprotein apheresis in the United States [72].

1. Homozygous familial hypercholesterolemia with LDL-C > 500mg/dl
2. Heterozygous familial hypercholesterolemia with LDL-C > 300mg/dl
3. Heterozygous familial hypercholesterolemia with LDL-C > 160 mg/dl with coronary artery disease
Patients must follow a diet and maximum tolerated drug treatment for at least 6 months.

Table 5. Indications for lipoprotein apheresis in Germany [72].

1. Primary prevention: Patients with familial hypercholesterolemia and LDL cholesterol > 160 mg/dl and cardiovascular events in close relatives.
2. Secondary prevention: Patients with progressive cardiovascular events and LDL cholesterol concentrations > 120 to 130 mg/dl.
3. Lp(a): Independent of LDL cholesterol concentrations in patients with progressive cardiovascular disease and Lp(a) concentrations > 60 mg/dl.
Initiation of lipid apheresis treatment should be considered when diet and lipid-lowering medications are ineffective.

In general, homozygous familial hypercholesterolemia (FH) is widely recognized as an indication, while other forms of LDL hypercholesterolemia are not.

For over 40 years, apheresis has been a last-resort therapy for treating dyslipoproteinemias that cannot be otherwise treated [73]. However, the development of new drugs, such as PCSK9 inhibitors, has altered the indications. The availability of PCSK9 inhibitors has significantly reduced the number of patients requiring apheresis for high LDL cholesterol, as patients with familial hypercholesterolemia

generally respond well to PCSK9 inhibitor treatment, and most patients with statin intolerance tolerate PCSK9 inhibitors well [88].

Therefore, in patients undergoing regular apheresis, the use of PCSK9 inhibitors allows for discontinuation of apheresis treatment in 63.4% of cases and lengthening of intervals between treatments in 92.7% [89]. Overall, PCSK9 inhibitors decrease LDL cholesterol to a similar extent as apheresis [73].

Conclusion:

Familial hypercholesterolemia is a common genetic disorder associated with a significant risk of premature atherosclerotic cardiovascular diseases, leading to a considerably reduced life expectancy, with sudden death and myocardial infarction (MI) being the primary causes of mortality. Despite being frequent and severe, FH remains underdiagnosed and undertreated, unfortunately resulting in late management that fails to prevent cardiovascular complications.

Early diagnosis and appropriate treatment can reduce this risk and achieve a life expectancy like the general population in adulthood. Ideally, the diagnosis should be made as early as possible, preferably starting at the age of 8 to 12, enabling the early initiation of treatment.

Familial hypercholesterolemia remains poorly detected. It is necessary to develop systematic approaches to identify patients with FH, conduct cascade screening of their relatives, and increase awareness and control of FH. Children should be screened from the age of 3 and treated from the age of 8-10.

Despite the availability of lipid-lowering medications, most FH patients do not achieve an LDL-C level below 100 mg/dL. Therapeutic advancements and the emergence of new drugs for FH provide hope that the most severe forms can be treated, and an increasing number of patients can reach LDL-cholesterol goals.

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