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I BRAZILIAN GUIDELINE FOR FAMILIAL HYPERCHOLESTEROLEMIA (FH)

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Conflict of interest statement

Names of the Guideline Participants	Took part in clinical and/or experimental trials subsidized by pharmaceutical or medical equipment industry related to this guideline	Was speaker in events or activities sponsored by the industry related to this guideline	Was (is) a member of the pharmaceutical or medical equipment industry's advisory or directive board	Took part in normative committees of scientific trials sponsored by the industry	Received personal or institutional support of the industry	Prepared scientific texts in journals sponsored by the industry	Has pharmaceutical industry shares
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Definition of classes of levels of evidence

Recommendations

Class I: Conditions for which there is conclusive evidence and, if missing, general consensus that the procedure is safe, useful/effective.

Class II: Conditions for which there is conflicting evidence and/or divergence of opinion about the safety and usefulness/efficacy of the procedure.

Class IIa: Weight or evidence/opinion is in favor of the procedure. Most experts approve.

Class IIb: Less well established safety and usefulness/efficacy, not existing predominance of opinions in favor.

Class III: Conditions for which there is evidence and/or consensus that the procedure is not useful/effective and, in some cases, may be harmful.

Evidences

Level A: Data derived from multiple good-size, randomized trials, in agreement with and/or with robust metanalysis of randomized clinical trials.

Level B: Data derived from a less robust metanalysis, from a single randomized trial or from non-randomized studies (observational).

Level C: Data derived from consensus opinion of experts.

Abbreviations used in texts and tables

Abbreviations	Meaning
FH	Familial hypercholesterolemia
LDL-c	Low-density lipoprotein
LDLR	LDL receptor
ApoB	Apolipoprotein B
ApoB-100	Apolipoprotein B-100
PCSK9	Proprotein convertase subutilisin/kexin type 9
CAD	Coronary artery disease
LDLRAP1	LDLR adaptor protein type 1
CYP7A1	Cholesterol 7-alpha hydroxylase
Mg/dL	Milligrams/ deciliter
WHO	World Health Organization
VLDL	Triglyceride-rich Lipoprotein [very low density lipoprotein]
IDL	Intermediate density lipoprotein
Apo	Apolipoprotein
apoE	Apolipoprotein E
FDB	Familial Defective apo B
ARH	Autosomal recessive hypercholesterolemia
ABCG5	ABC (ATP-binding cassette) transporter protein
EDTA	Ethylene diamine tetraacetic acid
PCR	Polymerase chain reaction
CI	Confidence interval
Lp(a)	Lipoprotein (a)
CRP	C-reactive Protein
CV	Cardiovascular
IDF	International Diabetes Federation
AP	Arterial pressure
mmHg	Millimeters of mercury
SAH	Systemic arterial hypertension
CIMT	Carotid intima-media thickness
CAC	Coronary artery calcification
CCTA	Coronary Computed Tomography Angiogram
TC	Total cholesterol
HDL	High-density lipoprotein

Abbreviations	Meaning
FA	Fatty acids
MUFA	Monounsaturated fatty acid
SFA	Saturated fatty acid
PUFA	Polyunsaturated fatty acid
TFA	Trans fatty acid
FDA	Food and Drug Administration
CVD	Cardiovascular disease
TCV	Total caloric value
CTT	Cholesterol treatment trialists
AAS	Acetyl-salicylic acid
g	grams
TG	Triglycerides
n-HDL	No-HDL particles
%	Percentage
MTP	Microsomal triglyceride transfer protein
HMG Coa	3-hydroxy-3-methylglutaryl-coenzyme A
ASO	Antisense oligonucleotides
DNA	Deoxyribonucleic acid
RNA	Ribonucleic acid
NAFLD	Non-alcoholic fatty liver disease
NASH	Nonalcoholic steatohepatitis
TNF-alpha	Tumor necrosis factor alpha
IL-6	Interleukin 6
SAT	Saturated fatty acid
TRANS	Trans fatty acid
MCP-1	Monocyte chemoctatic protein
TCV	Total caloric value
Anvisa	*Agência nacional de vigilância sanitária* [National health surveillance agency]
CYP7A1	Cholesterol-7-hydroxylase
UFA	Unsaturated fatty acid
LCAT	Lecithin-cholesterol-acyl-transferase
°C	Degrees Celsius
INMETRO	*Instituto Nacional de Metrologia, Normalização e Qualidade Industrial* [National Institute of Metrology, Standardization and Industrial Quality]
Kcal	Kilocalories

Letter of Presentation

Familial hypercholesterolemia (FH) is a severe disease accounting for 5-10% of the cases of cardiovascular events in patients aging younger than 50 years old. The risk of a subject with untreated heterozygous FH developing coronary disease or dying reaches 50% in males and 12% in females aging 50 years. It is estimated that, worldwide, there are more than 10,000,000 subjects with FH; however, at least 10% have a known diagnostic of FH, and less than 25% receive hypolipemiant treatment. In Brazil, this is certainly not different, in view of the estimate saying that there are 250,000-300,000 people with this disease. Fortunately, early diagnosis, family cascade screening (since, in these, one in each 2 families may be affected) may change the natural history of this severe illness. We, from the SBC Department of Atherosclerosis, have as a duty of aware the population, medical class and authorities about how important the FH is for the Brazilian's health and not measure efforts to control it in an adequate manner. We should remember that, with patents of highly effective statins ending in our country, the cost of early treatment of these subjects certainly had a dramatic fall and will be possible to conduct prevention in a cost-effective manner. However, for this, early diagnosis and constant follow-up are required. This guideline gathered the most important Brazilian experts in FH; we hope that we are able to succinctly convey the best information available to improve the medical practice in Brazil, for early cardiovascular disease prevention and finally relief for the families affected by the FH.

Best regards,

Raul D. Santos, MD, PhD - Editor

1. Natural history of the familial hypercholesterolemia

1.1. Definition of familial hypercholesterolemia

The Familial Hypercholesterolemia (FH) is a genetic disorder of the lipoprotein metabolism, with autosomal codominant inheritance and characterized by very high levels of low density lipoprotein cholesterol (LDL-c), and by the presence of characteristic clinical signs, such as tendinous xanthomas and increased risk of early coronary artery disease[1].

The clinical phenotype of FH is generally due to defects on the *LDLR* gene, which encodes the LDL receptor (LDL-R) (OMIM# 143890)[2], location of more than 1,600 mutations described so far; it can also be secondary to *APOB* gene defects, which encodes the apolipoprotein B-100 (Apo B-100) (OMIM# 144010)[3], where the defective Apo B-100 has less affinity to the LDL-R; or even, when there is accelerated catabolism of the LDL-R, due to mutations with gain of function in the gene proprotein convertase subutilisin/kexin type 9 (PCSK-9), which encodes the NARC-1 protein (OMIM# 603776)[4], which takes part in the LDL-R catabolism.

All these conditions are associated to high levels of LDL-c. The clinical phenotype is very similar in the three more common forms of FH, but the *APOB* gene defects are more common among some European populations (1:300 to 1:700 in Central Europe)[5], while *PCSK-9* gene mutations do not have an established frequency and are not frequent in our environment. The FH has penetrance of almost 100%, meaning that half of the first-degree offspring of an affected subject will have genetic defect and will present elevated LDL-c levels from birth and throughout their lives, with males and females equally affected. The heterozygotes have half of the functioning LDL receptors.

1.2. History of the FH

The first observations of the disease came from the pathologist Harbitz[6], who, in the mid-18th century, reported sudden death in subjects with xanthomas for the first time. In 1938, Müller[7] described FH as a clinical entity and observed that the coincidence of hypercholesterolemia, xanthomas and CAD manifestations was common findings in some families and was inherited as a dominant trait. Around 50 years later, Brown and Goldstein[8-10], studying patients and cell cultures, unraveled the complex endogenous cholesterol synthetic pathway and identified the defect in the internalization of the receptor-bound LDL. In 1983, this gene was cloned and mapped to the short arm of chromosome 19[11], being then referred to as low-density lipoprotein receptor gene, or *LDLR* gene, in 1989[12].

Mutations in the *LDLR* gene reduce the number or impair function of LDL-R at the hepatocyte surface, leading to marked elevations of LDL-c levels and causing cholesterol deposition in tissues. In the majority of cases, the mode of inheritance is autosomal dominant, but there may be recessive autosomal inheritance. The recessive (very rare) forms may be due to mutations in the gene encoding the LDL-R adaptor protein (LDLRAP1)[13,14], to the deficiency of cholesterol 7-alpha hydroxylase (CYP7A1)[15], or by defects in the ABCG5/G8 transporters, as happens in sitosterolemia[16].

In dominant forms, Khachadurian[1] observed a dose-effect relationship with the number of mutated alleles and differentiated the heterozygous forms from the homozygous ones in Lebanese-origin subjects affected by FH, by the grade of clinical manifestations.

The starting point to be considered the diagnostic possibility of LDL-c $\geq$190 mg/dL in adults[17,18]. Clinical signs, such as the presence of some degree of corneal arch, take place in 50% of the subjects with FH aging 31-35 years. On other hand, the complete corneal arch is present in 50% of the subjects with FH aging 50 years old[19]. However, there is no correlation between the degree of corneal arch and CAD manifestations. Thickened tendons happen in 63% of the subjects with FH; changes in the tendon echogenicity are present in 90% of the subjects with FH; xanthomas are detected in 68% of the subjects with FH with LDLR gene mutations[20].

1.3. FH as a world health problem

FH is one of the most common inherited monogenic diseases in general population. The frequency of FH in its heterozygous form is approximately 1:500 subjects, being very rare in homozygous form, where it is estimated a frequency of 1:1,000,000 of affected subjects[21]. However, the FH is more prevalent in some populations, due to a "founder" effect". These are the South-Africans (1:100), Lebanese (1:170), French Canadians (1:270) and Finnish[22-25].

FH is a world health problem recognized by the World Health Organization (WHO)[25]. It is estimated that, all around the world, there are more than 10,000,000 subjects with FH; however, less than 10% have known diagnostic of FH, and less than 25% receive hypolipemiant[25]. A worrying data is the high incidence of early atherosclerotic disease (in males younger than 55 years old and in females younger than 65 years), especially due to the early Coronary Artery Disease (CAD), reducing the life expectancy in many families of subjects with FH[26].

The FH is responsible for approximately 5%-10% of the CAD cases in subjects younger than 55 years old[27]. Without treatment, 50% of the heterozygous males will develop CAD before 50 years old and 100%, at 70 years old; among heterozygous females, 12% will have some manifestation of CAD at 50 years and 74%, at 70 years[28]. Approximately 85% of males and 50% of females with heterozygous FH will have a cardiovascular event before 65 years old. However, the clinical expression of CAD in subjects with FH is heterogeneous as for age of appearance and its severity. The CAD manifestations tend to present a higher frequency in some families, but there may be marked differences among subjects[29], even among those coming from families that have the same *LDLR* gene mutation, suggesting that environmental factors and other genetic factors play a role modulating the development of atherosclerosis in FH[30].

Long-term follow-up studies in patients with FH show that the main cause of death among the subjects with FH is the CAD[26]. In

addition, approximately 200,000 deaths by CAD that take place every year in the entire world could be avoided with proper treatment[31]. It is believed that the use of hypolipemiants might increase the life expectancy of these subjects in 10-30 years[25].

Even though there are no clinical studies of intervention with hypolipemiants with long-term follow-up for analyses of cardiovascular outcomes in subjects with FH, some groups used substitute outcomes to evaluate the effectiveness of the reduction of LDL-c in the evolution of the coronary atherosclerosis, of the aortic lesions, of the carotid intima-media thickness, of the endothelial function, myocardial perfusion scintilography modifications, or of inflammatory biomarkers, generally showing, improves in these parameters with expressive reductions of the LDL-c reviewed by Civeira[17], in 2004. Consistent with these findings, the increasing use of hypolipemiant drugs, specially of statins, showed in a cut followed by 8.5 years that the early start of the hypolipemiant treatment reduces in 80% the risk of CAD in FH and that, subjects older than 55 years with FH, which received hypolipemiant treatment along with their lives had the same myocardial infarction rate than their pairs of the general population without FH, not being observed increase of mortality due to non-cardiovascular related to the hypolipemiant treatment[32]. Other study in a cohort of South-African subjects with homozygous FH showed delay in the occurrence of death and longer survival with the hypolipemiant therapy[33].

In children with FH, there is endothelial disorder and increase of the intima-media thickness of the carotid arteries, predictor of early atherosclerosis in adult life. Hypolipemiant treatment for two years in the children with FH induced significant regression in the carotid atherosclerosis, not affecting the growth, sexual maturation, hormonal levels, hepatic or muscle enzymes[34].

By the exposed reasons, the identification of subjects with FH and their family, and the early institution of hypolipemiant therapy and its maintenance along the life are important appearance in prevention of the early cardiovascular disease and of the death risk in this population.

2. Lipid metabolism in the familial hypercholesterolemia

The whole-body cholesterol homeostasis depends on the balance between the hepatic synthesis and intestinal absorption of this component, on one hand, and its excretion, specially by the biliary pathways, of the other. When there is an unbalance of this equation, as seen in the familial hypercholesterolemia, the accumulated cholesterol forms deposits such as the xanthomas and atheroma plaques. The entrance and exit of the body cholesterol are regulated by a feedback system in which the dietary cholesterol absorption determines the decrease of the synthesis by liver. On contrary of the food fats, which are absorbed by the intestine almost completely, the absorption of the cholesterol is partial, and when the quantity of the component in the diet increases, the absorption decreases proportionally.

In males, most cholesterol present in plasma is composed by the low density lipoprotein (LDL) portion. In normolipidemic subjects, around 70% of the cholesterol are contained in the LDL. The LDLs are the degradation product of the VLDL, lipoproteins rich in triglycerides that, in the surface of the capillaries, suffer continued lipolysis, by the action of the lipoprotein lipase. In this degradation cascade, in parallel with the loss of the triglycerides, the cholesterol content is proportionally increasing in the lipoprotein particles until reaching the final product, the LDL. In this, the content of triglycerides is only residual and the cholesterol, especially in the esterified form, constitutes the most part of lipids constituting lipoprotein.

Substantial part of the degradation products of the VLDL, the rest of VLDL and the IDL, intermediate density lipoproteins, is removed by the soft tissues before suffering complete catabolism, that is, before reaching the final product, the LDL. A lower proportion of the LDL is not degradation product of the VLDL, but it is synthesized by the liver already in the LDL form.

The LDLs are removed from circulation to the interior of the cells by cell membrane receptors that recognize the apolyprotein (apo) B100, the single protein existing in the LDL. Rests and IDL are removed also for these receptors, but in a very rapid form than the LDL. This is giving because these particles, in addition to the apo B100, have apo E in the surface, and the apo E has affinity very bigger by the receptors than the apo B100.

In the familial hypercholesterolemia, there are genetic defects affecting the LDL receptor and that result in decreased lipoprotein endocytosis[17]. The existence of the LDL endocytosis measured by receptor and the defects that result in deficiency of the function of the receptors and in hypercholesterolemia were described by Brown and Goldstein[9] in the 1970s. The several hundreds of polymorphisms in the receptor gene can affect birth the receptor structure that links the LDL apo B100 and other protein domains and until the same the recirculation of the receptors and until even the recirculation of the receptors that normally are recycled after endocytosis, returning to the cell membrane. Defects in the apo B100, very rarer than the LDL receptor (LDL-R), are also the cause of familial hypercholesterolemia, but the designation familial hypercholesterolemia refers to the receptor defects[3]. There are also cases of familial hypercholesterolemia in reason of mutations with function gain in the gene proprotein convertase subutilisin/kexin type 9 (PCSK-9)[4], which encodes the NARC-14 protein, which participates of the catabolism of the LDL-R. As described, the familial hypercholesterolemia is a defect of removal of the LDL from circulation. As the LDL particles circulate longer in the patients with familial hypercholesterolemia, are more subject to oxidation and other chemical and other chemical transformations. This results in increased capture of the modified LDL by the macrophages, triggering proatherogenic mechanisms.

The studies by Müller[7], in Norway, and Khachadurian[1], of Lebanon, in the 1960s, were pioneers to establish the familial hypercholesterolemia as a disease of monozygotic and dominant autosomal character.

In the heterozygous form, half of the receptors are compromised and the other half are normal, while in the homozygous form, all the receptors are affected.

3. Clinical diagnostic of the familial hypercholesterolemia

The clinical and laboratory criteria for the diagnostic of the Familial Hypercholesterolemia (FH) are mandatory and based on the following data:

- clinical signs of extravascular deposits of cholesterol;
- high plasma rates of LDL-c or total cholesterol;
- family history of hypercholesterolemia and/or early atherosclerotic disease;
- identification of mutations and genetic polymorphisms favoring the development of FH

Some diagnostic criteria have been proposed in an attempt of standardize and shape the FH diagnostic, such as for example, those of the Dutch Lipid Clinic Network (Dutch MEDPED, see tab. 1)[35], those of the US Make Early Diagnosis Prevent Early Death Program (USA MEDPED)[36] and those of the Simon Broome Register Group[37].

Table 1 - Diagnostic criteria of the HF (based on the criteria of the *Dutch Lipid Clinic Network [Dutch MEDPED[35]]*)

Parameter	Points
Familial history	
First-degree relative with early vascular/coronary disease (male < 55 years, female < 60 years) OR	1
Adult first- or second-degree relative with total cholesterol > 290 mg/dL*	
First-degree relative with tendinous xanthoma and/or corneal arch OR	2
First-degree relative <16 years with total cholesterol > 260 mg/dL*	
Clinical history	
Patient with early coronary artery disease (male < 55 years, female < 60 years)	2
Patient with early cerebral or peripheral arterial disease (male < 55 years, female < 60 years)	1
Physical exam	
Tendinous xanthoma	6
Corneal arch < 45 years	4
Level of LDL-c (mg/dL)	
≥ 330 mg/dL	8
250 - 329 mg/dL	5
190 - 249 mg/dL	3
155 - 189 mg/dL	1
DNA Analysis	
Presence of functional mutation of the LDL receptor gene, of apoB100 or of *PCSK9**	8
Diagnostic of FH:	
certainty of	> 8 points
probable if	6 - 8 points
possible if	3 - 5 points

** Modified from Dutch MEDPED1 adopting a criterion present in the proposal of the Simon Broome Register Group3*

This guideline recommends the use of simple criteria to diagnose suspected FH and for the decision of starting the treatment (see below). An algorithm based on the Dutch MEDPED[35] can be used for better diagnostic precision, even though it is not available until now a validation for the Brazilian population.

3.1. Case history

Given the high FH prevalence in the general population and its great impact on the cardiovascular disease and mortality rates, all physical examination should include the research of familial history of hypercholesterolemia, use of hypolipemiant drugs and early atherosclerotic disease, including the age of onset.

The possibility of FH is Always reinforced in the presence of family history of hypercholesterolemia and/or early atherosclerotic disease.

3.2. The physical exam

The research by the clinical signs of the FH (xanthomas, xhantelasmas and corneal arch) should make part of the routine physical exam and can be complemented by subsidiary exams, such as the tendon ultrasound, in selected cases.

Generally, these clinical signs are not very sensible, but can be very specific. That is, even though there is no necessity of his/her presence for the diagnostic of the FH, these signs, when identified, suggest this etiology.

The tendinous xanthomas (Figure 1 and Figure 2) are more commonly observed in the Achilles' tendon and in the finger extensor tendons, but can also be found in the patellar tendon and the triceps tendon. They should be researched not only by visual inspection, but also by palpation. They are practically pathognomonic of FH, but happen in less than 50% of the cases[38]. Intertriginous planar xanthomas, especially in the FH homozygous form can also be found (Figure 2).

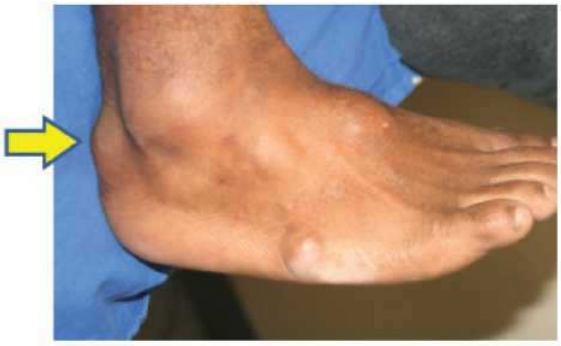


Fig. 1 - Xanthoma in the Achilles' tendon in subject with homozygous FH.

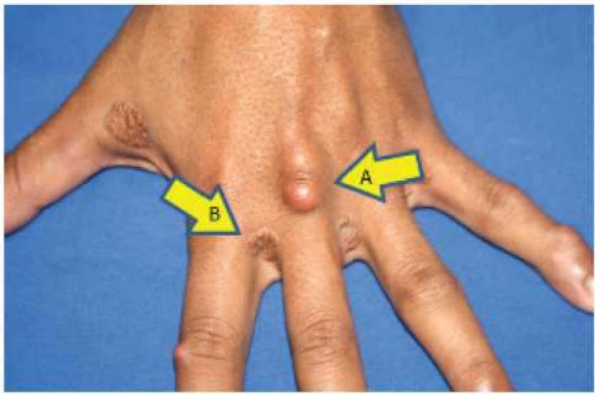


Fig. 2 - Tendinous xanthoma (A) in region of the dorsum of the hand and intertriginous planar xanthomas (B) in subject with homozygous FH.

The orange-yellowish tuberous xanthomas and the eyelid xhantelasmas are not specific of FH and should be valorized when found in patients aging around 20-25 years old.

The presence of corneal arch, partial or total, suggests FH when observed before 45 years old (Fig. 3).

Subjects with the homozygous FH form also present ejection systolic murmur due to the aortic valve stenosis and of the supra-aortic region.

Fig. 3 - Corneal arch in subject with homozigous FH.

3.3 Screening and the lipid levels

Blood collection for determination of total cholesterol and LDL-c levels aiming to track the FH is of key importance for the diagnostic of the as high as possible number of cases and, thus, to reduce the impact of the FH on the cardiovascular morbid-mortality in the general population. This screening can be performed through two methods: the so-called universal screening and the cascade screening.

3.3.1. Universal screening

All people older than 10 years old should undergo the analysis of the lipid profile. The obtainment of the plasma lipids should also be considered from 2 years old in the following situations:

- when there is Family history of early atherosclerotic disease (males < 55 years or females < 65 years) and/or of dyslipidemia;
- if the child presents xanthomas or corneal arch, risk factors (arterial hypertension, diabetes mellitus, smoking, obesity) or atherosclerotic disease.

The recommended periodicity for the determination of the plasma lipids is reason for debate. Generally speaking, if the lipid profile is normal, but there are other criteria of possible FH, such as family history of early atherosclerotic disease or significant hypercholesterolemia, the same can be repeated after one year. In the absence of these factors, the exam can be repeated in up to five years. Other data, such as age, presence of other risk factors for atherosclerosis, control degree of the risk factors, life habits and occasional use of drugs that may interfere with the lipid metabolism can be considered to custom-make the periodicity of the lipid dosages.

The diagnostic of FH should always be suspected in adults ($\geq$20 years) with LDL-c values $\geq$ 190 mg/dL.

In the general population, the probability of FH is of approximately 80% in the presence of LDL-c $\geq$ 250 mg/dL in subjects $\geq$ 30 years, or LDL-cholesterol $\geq$ 220 mg/dL in subjects between 20-29 years, or LDL-c $\geq$ 190 mg/dL in subjects < 20 years[36].

The diagnostic of FH is also more likely in subjects with LDL-c $\geq$ 190 mg/dL in families characterized by a bimodal distribution of the LDL-c, in which some members present typically low levels (LDL-c < 130 mg/dL), while others (the affected by HF) present rates of typically $\geq$ 190 mg/Dl[38].

Before making the diagnostic of FH, however, should be withdrawn secondary causes of hypercholesterolemia, including hypothyroidism and nephrotic syndrome.

It also should be highlighted that the presence of hypertriglyceridemia does not exclude the diagnostic of FH.

Finally, it should be considered that the determination of the lipid profile is subjected to a series of variations related both to the method and procedures used as to intrinsic factors of the subject such as life style, use of medications and associated diseases. Thus, the confirmation of a laboratorial chance with new sample, ideally collected with minimal interval of one week after the first collection, increases the diagnostic precision.

3.3.2. Cascade screening

The cascade screening involves the determination of the lipid profile in all the first-degree relatives (father, mother and siblings) of the patients diagnosed with FH. The identification chances of other subjects with FH from a case-index are: 50% in the first-degree relatives, 25% in the second grade and 12.5% in the third degree[38].

As the new cases are being identified, new relatives are going to be recommended for the screening.

This is considered the more cost-effective form to identify the bearers of HF

3.4. Recommendations*

- Clinical signs of FH and family history of early atherosclerotic disease and/or dyslipidemia should be researched in all subjects (Class I, Level of evidence C).
- The lipid profile should be obtained in all subjects older than 10 years old (Class I, Level of evidence C).
- The determination of the lipid profile should be considered from 2 years old in the presence of risk factors, clinical signs of FH or atherosclerotic disease, as well as in the presence of family history of early atherosclerotic disease and/or of dyslipidemia (Class I, Level of evidence C).
- The lipid profile should be obtained in all first-degree relatives of the subjects diagnosed as subjects with FH (Class I, Level of evidence C).

4. Genetic diagnosis of the familial hypercholesterolemia

Classically, the familial hypercholesterolemia (FH) was described as a autosomal dominant inheritance disease[1], characterized by elevation of the total cholesterol and of the LDL-c, caused by mutations in the gene that encodes the LDL receptor or in the apo B codifying genes and of the proprotein convertase subutilisin/kexin 9 (PCSK9)[4].

The primary defect in the familial hypercholesterolemia is a mutation in the specific receptor gene for plasma LDL[4]. Located at the surface of hepatic cells and other organs, the receptor is linked to the LDL and facilitates its capture, performed by endocytosis mediated by the own receptor. The LDL is degraded in the lysosomes and the cholesterol is released in the cell for metabolic use. When LDL receptors are defective, the plasma level of removal of LDL decreases, and the plasma level of LDL increases in inverse proportion to the number of present functional receptors[17].

In heterozygous patients, a defective gene for the LDL receptor is inherited from one of the parents and a normal gene, from the other. Since two functional genes are necessary to maintain the normal plasma level of LDL-c, the absence of a functional gene causes an increase in the LDL level for approximately two-fold the normal already in the childhood[21].

The homozygous patients inherit two defective genes, thus the LDL receptors do not have functionality and the patients have a severe hypercholesterolemia (650 to 1,000 mg/dL)[21].

The gene that encodes the human receptor for LDL comprises approximately 45,000 pairs of DNA pairs and is located in the chromosome 19. The gene is divided in 18 exons and 17 introns. There is a strong correlation between the structural domains in the protein (LDL receptor) and the sequence of the exons in the gene. The LDL receptor is a protein composed by 839 amino acids, containing several functional domains.

The production is finally regulated by a sophisticated feedback mechanism that controls the transcription of the LDLR gene in response to variations in the intracellular content of sterois and of cellular demand of cholesterol[21].

There are more than 1,600 LDLR gene mutations documented as cause of FH up to the moment. These account for approximately 85%-90% of the cases of FH. A large number of mutations in the LDLR were catalogued all around the world and the listing resources can be researched[39-41].

The FH is more commonly attributable to mutations (including deletions, missense, nonsense and insertions) in LDLR gene, resulting in LDL receptors with functional reductions (partial to complete) in its capacity of removing LDL-c from circulation. The patients can be receptor-negative, expressing few or no activity of the LDL receptor, or defective receptor, taking to the expression of isotypes of LDLR with reduced affinity to LDL in the surface of hepatocytes[42-47].

There are five main defect classes in the LDLR gene[45-46].

- Class I: LDL receptor is not synthetized.
- Class II: LDL receptor is not duly transported from the endoplasmic reticulum to the Golgi complex and there is small expression. In the cellular surface.
- Class III: the LDL receptor does not correctly link to the LDL in the cell surface due to a defect in any apolyprotein (apo) B-100 (R3500Q) or in the LDL-receptor.
- Class IV: transport proteins normally link to the LDL, but are not located in the coated depressions and, therefore, the LDL is not internalized.
- Class V: the LDL-receptor is not recycled back to the cellular surface.

The hypercholesterolemia due to mutation in the APOB gene is referred as Familial Defective apo B or familial defect of the apo B (FDB)[48,49]. The FDB is clearly less severe than the typical FH caused by mutations in the LDLR[50,51]. The most common mutation in the APOB gene is replacement Arg35000Gln, corresponding to 5%-10% of the cases of FH in the populations of the Northern Europe, being, however, rare in other populations[52].

Other etiology for the phenotype FH is autosomal dominant hypercholesterolemia attributable to the increase of the PCSK9 activity, also called HF3, where mutations with gain of function take to more degradation of the LDL-receptor[52,53]. This is the most common cause of FH, representing less than 5% of the cases[52].

The causal gene, if LDLR, APOB, or PCSK9[54], cannot be clinically determined, being necessary genetic test for its verification.

Recessive autosomal hypercholesterolemia (RAH) has been attributable to reduced expression of the adaptor protein of the LDL-receptor type 1 (LDLRAP1), which facilitates the association of LDL receptors with clathrin in the coated gaps of the cellular surface[13,55,56].

*Suggested site: Make early diagnosis to prevent early deaths (MEDPED). http://www.medped.org/

Other rare forms of ARH include sitosterolemia or phytosterolemia, due to mutations in two adjacent genes and with opposed directions (ABCG5 and ABCG8) that codify transport proteins of the ABC (ATP-binding cassete) family called steroline-1 and steroline-2[57]; deficiency of cholesterol 7-alpha hydroxylase

(CYP7A1), which is the enzyme of the first step in the synthesis of biliary acids, resulting in increased intra-hepatic cholesterol and reduced expression of LDL receptors in the surface of the hepatocyte. The deficiency of CYP7A1 is the less common of the recessive autosomal conditions that may cause severe hypercholesterolemias[56].

The elevated hereditary cholesterol can include other forms of hypercholesterolemia, such as dysbetalypoproteinemia (Friedrickson's type III), combined familial hyperlipidemia, hypercholesterolemia by polymorphisms in the APOE gene, as well as polygenic hypercholesterolemia, in addition to other variants in not yet identified genes, which can mimic the FH[58,59], but that are not the focus of this Guideline.

4.1. Methodologies for genetic diagnostic

By the large number of possible mutations, the method of genetic diagnostic shall include the sequencing of the codifying region of the LDLR gene, polymorphisms of the *APOB* gene e *PCSK9*[60,61].

In summary, for the genetic study is performed the peripheral blood collection in tube containing EDTA, obtaining the genomic DNA of leucocytes. The interest regions of the studied gene(s) are amplified through polymerase chain reaction (PCR). The amplification products obtained by PCR are analyzed through electrophoresis and submitted to digestion by restriction enzymes, in case of the *APOB* and *PCSK9*, and compared with standard sequences, or sequenced, in case of the LDLR gene.

4.2. Cascade screening

Cascade screening for FH generally is not necessary for clinical diagnostic or treatment, but can be useful when the diagnostic is uncertain and for diagnostic of the affected subject's relatives.

Identification of a causal mutation can provide an additional motivation for some patients to start the adequate treatment, and the genetic test is standard of reference for the diagnostic of certainty of FH. It may be particularly useful in cases of relatives with wrong clinical diagnostic or only with level of LDL-c suggestive of FH. Genetic tests can also be important to identify a causal mutation in newly-identified families or with strong suspicion of FH.

In addition, when the mutation is found, the test provides a simple and definitive answer to the diagnostic of FH, being this way a definitive tool for the presence of hypercholesterolemia as a family trait[59].

The genetic tests, however, have limitations. Among the hypercholesterolemic patients with diagnostic of possible FH, the identification rate of a causal mutation through genetic test is 50% or less, while in patients with definitive FH, the identification rate of mutation can be as high as 86%[59,60].

It is important to emphasize that a negative genetic test does not exclude the FH. In addition, subjects with elevated LDL-c remain in high risk and should be treated according to the accepted guidelines, regardless the results of the genetic tests.

The most cost-effective strategy for diagnostic of FH is the screening of mutations in first-degree relatives of subjects where a causal mutation for FH has been identified[28,61]. The subjects diagnosed with FH through genetic test become cases-index, being from these screened the first-degree relatives, and subsequently the other relatives (second and third grades) in a combined genetic approach to the analysis of the lipid profile of the suspected relatives and from a directed medical exam and physical exam, researching the typical clinical findings of the FH (early corneal arch, tendinous xanthomas, xhantelasmas). This is referred as genetic cascade screening[62]. It can be, however, as first approach, to conduct the genetic test, where it is searched the same change of the case-index. There are 50% of probability of detection in first-degree relatives; 25% of probability in second-degree relatives; and 12.5% of probability in third-degree relatives[4].

Studies show that too few subjects with FH are diagnosed. In any population, it is estimated that approximately 20% of the patients with FH are diagnosed and less than 10% of the patients with FH receive adequate treatment[4]. The cascade screening increases the number of diagnostics and decreases the age with which the subject is diagnosed, and there is a higher chance of early treatment and decrease of the overall cardiovascular risk.

Marks et al.[28] analyzed the cost-effectiveness of the cascade screening of subjects with familial hypercholesterolemia. The incremented cost per life-year acquired of £ 3,300 per life/year was determined. In another study[60], the result showed that the cascade screening program was the most cost-effective in Denmark and the cost per life/year was $ 8,700. Both studies show a lower estimate of costs that the expense with secondary prevention in subjects not having FH[61]. Therefore, the cascade screening for subjects with FH can be considered as highly cost-effective[28].

4.3. Recommendations

1. The genetic diagnostic (analysis of *LDLR, APOB* and *PCSK9* genes) is standard of reference for diagnostic of Familial Hypercholesterolemia (FH), and, when available, should be offered for patients with probable or definitive (certainty) diagnostic for FH with the purpose of make possible cascade familial screening in a more cost-effective manner. The offer of the genetic test for cases in which the diagnostic of FH is possible should be analyzed case by case[62].
2. The best method for genetic diagnostic of FH is the sequencing of the encoding region of the *LDLR* gene, and of hot-spots in the *APOB* and *PCSK9* genes, associated to the research of microdeletions in the *LDLR* gene in cases where a mutation is not identified. The conduction of the genetic test should be performed by specialized team and offered within the context of genetic counseling, comprising pre- and post-test information and specific treatment referral.
3. The cascade screening is cost-effective and should be conducted in all patients and first-degree relatives of patients diagnosed with FH. The most cost-effective

cascade screening is the one using genetic information of affected subjects, in which a disease causing mutation has been identified. However, the clinical/biochemical screening should be performed even when it is not possible to conduct genetic test[63,64].

5. Cardiovascular risk stratification

5.1. Cardiovascular risk epidemiology in FH

The association between heterozygous familial hypercholesterolemia (FH) and coronary artery disease (CAD) is well established[65,66]. There is a cumulative risk in the lack of hypolipemiant therapy for fatal and non fatal coronary disease in a ratio of 50% in 50-year-old males and 30% in 60-year-old females[67,68]. In the study by Simon Broome Register Group[69], conducted in the period from 1980 to 1995, there was an increase in the relative risk of death by coronary disease of 50 times for males (95% confidence interval - 95% CI: 17-105) and 125 for females (95% CI: 15-140) in the age range of 20-39 years old[69].

It is significant to emphasize that even with the advent of statins for reducing LDL-c, the rates of cardiovascular events in males and females presenting FH without previous manifestation of coronary disease in the age ranges from 15 to 66 years old are 3% and 1.6%, respectively, up to 70 years old. In the same study, subjects presenting established CAD had average annual rates of cardiovascular events of 15% for males and 14% for females[70].

Annual mortality rates for subjects presenting CAD were 1.6% for males and 0.5% for females, respectively[70]. In spite of that, the treatment with statins in FH presents clear benefits, as the FH cohort studied by Versmissen *et al*[32] shows, where the statin-treated group presented a 76% reduction in risk of coronary disease, compared to the statinless group (hazard ratio 0.24, $p < 0.001$). Nonetheless, it is significant to stress that, in spite of the high cholesterol levels and the high relative risk of CAD, the clinical behavior of atherosclerosis in patients with FG may be variable in short-medium term, and some subjects develop clinical events late in their life[71].

This fact was well demonstrated at the cohort of 526 subjects presenting FH in Simon Broome Register Group[71], with 2,234 persons-follow-up year, where a higher mortality rate adjusted for CAD was seen in the age range of 20-29 years old, compared to older age ranges, that is, some FH patients present coronary event very early and other develop it very late or even will not die from a cardiovascular disease. Thus, risk stratification in this population is very significant, as it interferes with cost-benefit in managing and treating those patients[17].

5.2. Recommendations

The cardiovascular risk in familial hypercholesterolemia is increased, and the stratification of cardiovascular risk must be stimulated to be conducted (Class I, Evidence level A).

5.3. Role of classic risk factors in FH: diabetes, smoking, arterial hypertension, MS, FA of early CAD, low HDL, very high LDL-c values, gender, age, non HDL cholesterol

The classic risk factors for CAD in FH are also significant in the risk stratification of that population. The study by Simon Broome Register Group had already demonstrated higher cardiovascular risk in males compared to females. That fact was confirmed in the Dutch cohort study by Jansen *et al.*[72], where an almost three times higher risk for males presenting cardiovascular event compared to females[72]. The association between smoking and FH also presents strong relationship with CAD development, and a previous study a 1.8 time higher chance for smokers[73].

Diabetes mellitus is a risk factor so significant that the current guidelines consider its presence as already indicating high cardiovascular risk, even with more aggressive treatment aims. The study by Lloyd Jones *et al.*[74], assessing the life time risk of diabetics, showed that diabetic males present a 67% chance for developing a cardiovascular event along their life and females present a 57% chance[74]. Diabetes for FH population also has significant weight. The study by Kastelein *et al.*[75] showed 2.2 times higher risk for cardiovascular disease in diabetic FH patients. Arterial hypertension also confers higher risk in FH population (1.4 time higher risk for cardiovascular event) and must be correctly diagnosed and treated[75].

Familial history of early coronary disease (males < 55 years old and females < 65 years old) is a factor found more often in FH population and must be also valorized as risk factor.

Low HDL-c is considered as a significant risk factor in no FH population. There is evidence saying that low HDL-c can be also associated to higher CAD risk in FH patients[17,72]. Previous epidemiological studies had already shown the association between high cholesterol and cardiovascular disease. The raise in cholesterol in FH population basically occurs due to LDL-c; thus, very high LDL-c values must be also considered as significant risk factor in those subjects.

5.4. Recommendation

Classic risk factors also have a significant role in FH and must be actively researched (Class I, Evidence level B).

5.5. Role of other factors in cardiovascular risk of FG: Lp(a), Achilles tendon xanthoma, ultrasensitive C-reactive protein

Lipoprotein (a) or Lp(a) is a lipoprotein composed by the LDL particle with covalent bond with apolipoprotein (a) and apolipoprotein B-100. Apolipoprotein (a) presents strong homology with plasminogen. High Lp(a) levels can theoretically increase the cardiovascular risk due to the prothrombotic/antifibrinolytic effect of apolipoprotein (a) and Lp(a) deposition in subintimal space. Some studies and meta-analyses show association of Lp(a) and increase in cardiovascular risk in non FH population[76,77]. Other studies show association of high Lp(a) values and cardiovascular risk in FH, but there are methodology-related difficulties[78].

5.6. Recommendation

Routine Lp(a) dosage in FH can be considered (Class IIb, Evidence level C).

Achilles tendon xanthoma is a peculiar sign of familial hypercholesterolemia and is part of the diagnostic criterion for this disease. About 30% to 50% of heterozygous FH patients with genetic diagnosis present tendinous xanthoma. A study by Civeira *et al.*[79] had already shown that FH patients with xanthomas present higher prevalence of early cardiovascular disease compared to patients without xanthomas (36.7% versus 13.8%, p = 0.001)[79]. The meta-analysis by Oosterveer *et al.*[80] found a 3 times higher risk for FH patients presenting tendinous xanthoma to evolve with cardiovascular disease[80].

Achilles tendon xanthoma seems to be related to the higher cardiovascular risk in FH; and, as it is only based on physical exam, its research must be stimulated (Class IIA, Evidence level B).

The association of C-reactive protein and cardiovascular disease in FH is based on small studies on its association with subclinical atherosclerosis and controversial results[81,82].

There is no evidence for routine dosage for PCR in FH (Class IIB, Evidence level C).

5.7. Usual risk stratification is not valid for FH

The clinical risk scores widely used for stratification (such as Framingham score[83], PROCAM (Prospective Cardiovascular Münster Study)[84], Reynolds[85,86], among others) were not elaborated for patients presenting FH. The IV Brazilian Guideline for Dyslipidemia and Atherosclerosis Prevention[87] recommends the Framingham score for risk stratification and thus to guide on therapeutic aims. In FH, the Framingham score frequently underestimates the risk. For example, considering a 50-year-old FH-presenting male with total cholesterol of 390 mg/dL, LDL-c of 310 mg/dL, triglycerides of 150 mg/dL, HDL-c of 50 mg/dL, AP of 110 x 70 mm Hg, without antihypertensive drugs and non smoker, he presents a calculated risk of 8% in 10 years, that is, low risk[83]. We know that this patient subjected to that cholesterol level for long term cannot be approached as being of low cardiovascular risk.

5.8. Recommendation

Do not use Framingham score or other clinical risk scores in HF (Class IIb, Evidence level B).

5.9. How to do CV risk stratification in FH patients in clinical practice (Tables 2 and 3)

All patients presenting FH must be considered as being in high cardiovascular risk at least for long term (Class I, Evidence level B). The traditional risk factors also present impact on the evolution of that population and must be identified. We can consider as higher risk (Class I, Evidence level B) to only place < 55 and < 65 years old as cut age values for familial history of early CAD:

Table 2 - *Modified from Dutch MEDPED[1], adopting a criterion present in the proposal from Simon Broome Register Group[3]

Patients presenting FH with any of these features must be considered as being of very high risk	
Established coronary or cardiovascular disease	Previous history of acute myocardial infarction, stroke, peripheral arterial disease, myocardial revascularization, stable or unstable angina, transient ischemic attack, carotid stenosis higher than 50%, aorta aneurysm
Smokers	
Diabetes mellitus	
Familial history of early coronary disease	First- or second-degree relatives with disease onset before 45 years old in males and before 55 years old in females
2 or more risk factors	Table 3

Table 3 - Risk factors in subjects with FH

Risk factor	If more than 2 risk factors are present, treatment intensification is recommended
Age	Males older than 30 years old Females older than 40 years old
Baseline LDL-c	> 250 mg/dL
Gender	Male
Smoking	Current smoking
Familial history of early coronary artery disease	First-degree relatives: Males < 55 years old Females < 65 years old
Metabolic syndrome	Consider the criteria from International Diabetes Federation (IDF)
Low HDL-c	HDL-c < 40 mg/dL for males and 50 mg/dL for females
Systemic arterial hypertension	AP > 140 x 90 mm Hg or drug treatment of the SAH
Increase in lipoprotein (a)	Levels ≥ 60 mg/dL
Physical exam	Tendon xanthoma

5.10. Role of subclinical atherosclerosis in FH: intima-medium thickness of carotids (IMTC), coronary artery calcification (CAC), and coronary angiotomography (TCMD)

5.10.1. Coronary artery calcification (CAC)

Several studies have shown the correlation between CAC and coronary events in patients without previous cardiovascular events. Raggi *et al.*[89], following 632 asymptomatic patients for a period of 32 ± 7 months, report an occurrence of 19 CAD-related events and 8 deaths, and, among those events, 70% occurred in patients with CAC in the last quartile (> 400 Agatston). Absence of CAC was associated to a 0.11% event rate when compared to 4.8% per year with score > 400. In 2003, Kondos *et al.*[90] had demonstrated, following 8,855 patients for 37 ± 12 months, that CAC was a marker of heart events and that its presence provided additional information other than age and other risk factors in previously asymptomatic patients. There is evidence saying that CAC could aggregate value to traditional risk factors and even to Framingham score in risk stratification of primary prevention patients. Arad *et al.*[91] evaluated the calcium score in 4,613 asymptomatic patients between 50 and 70 years old and followed this population for 4.3 years. At that period, there were 119 cardiovascular events. The authors demonstrated that CAC was a risk predictor regardless of the traditional risk factors and was better than the Framingham score in predicting events (ROC [receiver operating characteristic] area under curve of 0.79 versus 0.69, p = 0.0006). A meta-analysis published in 2004 by Pletcher *et al.*[92] shows a linear relationship between CAC value and coronary event. The consensus on CAC by American Heart Association[93] of 2007 establishes that CAC can be used in medium-risk patients (risk of 10%-20% in 10 years) as a manner to improve their risk stratification.

CAC evaluation in FH population in Brazil was already been studied by Santos *et al.*[94] in females and by Martinez *et al.*[81] in males and females, both in studies showing higher CAC prevalence and severity in patients presenting FH referring to normolipidemic controls.

5.10.2. Coronary angiotomography (TCMD)

The capacity of TCMD to differentiate plates with different compositions can turn this method able to in detecting plate types associated to cardiovascular events[95-97]. An example of that analysis was done in a work by Pundziute *et al.*[98], where, while following 100 patients with known or suspected coronary disease subjected to TCMD for a mean of 16 months, the presence of mixed plates was one of the variables associated to cardiovascular event. Indeed, the information on plate composition provided by TCMD can aggregate value to the risk stratification for patients, considering the previous knowledge about less obstructive plates being the most related to an acute ischemic event[99-101] (due to the fact of being more frequent than the obstructive ones). The concept of "vulnerable plate" also originated from that information. This term was originally used by Little[102] while reporting that a plate responsible for an infarction or instable angina should not necessarily cause obstruction in the coronary lumen before causing the event. An atherosclerotic plate would present two significant features: first, it can be obstructive; second, it can be "vulnerable" as it can be thrombogenic if exposed to a triggering stimulus[102]. An injury would not need to be obstructive to be thrombogenic and also neither all obstructive injuries would be thrombogenic. Surgical myocardial revascularization and percutaneous angioplasty only treat obstructive injuries and, therefore, they would not be necessarily preventing an acute myocardial infarction and thus the treatment of the arterial disease should be done aiming the whole vascular territory.

Coronary angiotomography was evaluated in FH population in a study by Miname *et al.*[103]. The authors found a higher load of subclinical atherosclerosis compared to normolipidemic controls, represented by a higher number of patients with plates (48% versus 14%, p = 0.0005), with stenosis (19% versus 3%, p = 0.015), segments with plates (2.05 ± 2.85 versus 0.43 ± 1.33, p = 0.0016), and calcium score (55 ± 129 versus 38 ± 140, p = 0.0028)[103].

5.10.3. Intima-medium thickness of carotids (IMTC)

Currently, IMTC can be gauged by high-resolution ultrasound devices[104]. IMTC is associated to cardiovascular risk factors, cardiovascular disease prevalence, cardiovascular disease incidence, and atherosclerosis degree in different arterial sites. IMTC progression can be reverted or attenuated with intervention in risk factors, in association to a reduction in cardiovascular events[105]. These findings place IMTC as a potential substitute atherosclerosis marker.

IMTC was already studied in FH population in our population by Martinez *et al.*[81], showing a higher value of IMTC in FH group related to controls. IMTC was used in FH population as a substitute atherosclerosis marker to evaluate atherosclerosis progression with hypolipemiant medication[75,106].

5.11. Recommendation

There is evidence of higher prevalence of subclinical atherosclerosis severity in FH population. However, there is still no evidence for routine research on subclinical atherosclerosis in FH. This can aid in risk stratification (Class IIb, Evidence level C).

5.12. Role of ischemia test in FH

Consider the conduction of myocardial ischemia test (ergometric test) for asymptomatic FH patients with highest risk above 20 years old and lowest risk above 30 years old.

Prospective studies have shown that the main death causes in patients presenting FH are atherosclerosis-related disease[31,107].

Therefore, early identification of coronary artery disease has pivotal significance for preventing cardiovascular events or death, especially in subjects presenting highest-risk FH, especially the asymptomatic ones.

For that identification, myocardial ischemia-inducing tests such as ergometric test or cardiological stress tests evaluated by echocardiography or scintillography are a significant early diagnostic resource.

5.13. Recommendation

As FH is a disease that affects people since the birth and atherosclerosis can quickly develop in these subjects, the conduction of those myocardial ischemia tests (especially ergometric test, due to the fact of being of low cost and easy conduction) must be considered for highest-risk asymptomatic patients presenting FH older that 20 years old and males older than 30 years old and females older than 45 years old with lowest-risk classification, at every 3 to 5 years (Class IIb, Evidence level C)[17], sequentially as in figure 4.

6. Nutritional recommendation in treatment of familial hypercholesterolemia

Diet therapeutic measures and measures related to changes in life style must be always recommended for preventing cardiovascular disease[24]. Nevertheless, usually due to high LDL-c concentrations coming from the genetic defects that characterize familial hypercholesterolemia (FH), those measures have lower impact on lipids and possibly on the atherosclerosis development than on the general population. However, diet recommendations can produce benefits on cholesterolemia, triglycerides, vascular wall, weight adjustment, and control of other concurrent diseases such as *diabetes mellitus* and arterial hypertension, and must be stimulated for all patients presenting hypercholesterolemia, especially children[108].

6.1. Nutritional recommendations in treatment of hypercholesterolemia for children

It is recommended that a balanced alimentation is started after two years old[109]. This aims to reach the ideal lipid levels prescribed by the Brazilian Guideline on Dyslipidemias and Atherosclerosis Prevention[24]. Though the response to diet guiding is small in children and teenagers presenting the familial form of hypercholesterolemia, it is based on the adoption of proper feeding standards according to the presented lipid deviation, keeping the ingestion of vitamins and the quantity of calories needed for child or teenager development and growth. Therefore, individual and familial habits must be evaluated. The collaboration by a pediatrician and a nutritionist becomes worthy to perform the diet guiding better[110].

6.2. Nutritional recommendations in treatment of hypercholesterolemia for patients presenting hypercholesterolemia in general

6.3. Diet influences on the plasma concentration of plasma lipids

6.3.1. Alimentary cholesterol

In spite of the association between cholesterol intake and coronary disease in the treatment of hypercholesterolemia, it is known that alimentary cholesterol exerts little influence on the cholesterol plasma concentration and early atherosclerosis, as approximately 56% of diet cholesterol is absorbed[111]. Fatty acids (saturated and trans) exert higher influence on cholesterolemia[111,112].

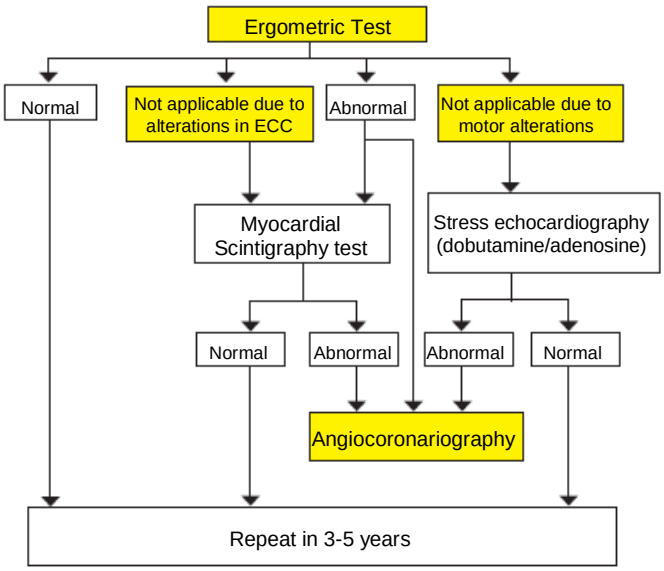


Fig. 4 - Recommendations for research tests for myocardial ischemia in patients presenting familial hypercholesterolemia.

Due to the controversy on the cholesterolemizing effect of the alimentary cholesterol, several guidelines[24,113] recommend restriction of total fat and cholesterol in diet, aiming to reduce and control plasma cholesterol and LDL-c.

6.3.2. Saturated fatty acids (SFA)

Among the several diet components, trans fatty acids are the ones that increase LDL-c more, followed by saturated fatty acids, which also increase HDL-c and do not change TC/HDL ratio if compared to the intake of carbohydrates. The intake of 1% of SFA TCV is associated to an increase from 1.3 to 1.7 mg/dL in LDL-c and from 0.4 to 0.5 mg/dL in HDL-c[111,114], with the inverse situation occurring when the ingestion of saturated fat is reduced.

Different SFA can have diverse effects in the lipid profile and cardiovascular risk factors. A recent meta-analysis[115] showed that, if compared to carbohydrates, the fatty acid (FA) lauric acid (C12:0) is the one which increases LDL-c more, followed by myristic acid (C14:0) and palmitic acid (C16:0). The stearic acid can cause a small reduction in LDL-c. Referring to HDL-c, in the same comparison with carbohydrates, FA lauric, myristic, and palmitic acids increase HDL-c in highest %, while stearic acid causes a small increase in HDL-c. The effect of fatty acids is compared to other nutrients, as carbohydrates in the referred case[115]. Therefore, when analyzing the effects of these FA, which nutrient was replaced with the referred FA must be verified.

6.3.3. Monounsaturated fatty acids (MUFA)

Monounsaturated fatty acids have one double bond at the carbon chain, and oleic acid (C18:1), ω-9 series, is the most common one found in nature, with higher concentration in olive oil.

The most accepted concept says the MUFA intake does not significantly affect total circulating cholesterol levels, while SFA intake increases cholesterol levels[116]. In a meta-analysis of 14 controlled studies between 1983 and 1994, diets rich in oils rich in MUFA versus PUFA showed similar effects on LDL-c and HDL-c, while PUFA provided a discrete reducing effect on triglycerides[117]. Thus, the SFA replacement with MUFA reduces LDL-c in a manner similar to the replacement with PUFA. Epidemiological data show that populations living in the Mediterranean area have lower risk for developing cardiovascular diseases due to the adopted food type, where the main fat source is olive oil associated to the high intake of cereals, vegetables, and fruits[118].

6.3.4. Polyunsaturated fatty acids

Polyunsaturated fatty acids are represented by omega-6 series and, in high quantities, can cause small reductions in HDL-c serum concentrations[119]. Omega-3 fatty acids can reduce triglyceride concentrations (effect secondary to reduction in VLDL-c synthesis), with the intake of two to three fish portions/week being recommended[120]. The most abundant polyunsaturated fatty acid, belonging to ω-6 series, is linoleic acid (C18:2), followed by arachidonic acid (C20:4), especially present in corn and sunflower oils. The main sources of linolenic acid, ω-3 series, are linseed, soybean, and canola. The fatty acids linoleic and linolenic acids are essential for humans, as mammal cells do not have capacity of inserting a double bond (unsaturated) before carbon 9 of the fatty acid chain. The fatty acids eicosapentaenoic (C20:5) and docosahexaenoic (C22:6) acids, ω-3 series, are found in fat of cold and deep water fish. They are not essential for humans, as they are synthesized from linoleic acid.

6.3.5. Trans fatty acids

Fatty acids are called trans when hydrogens bound to carbons in one unsaturation are in opposed sides[121]. They are present in diet, coming from partially hydrogenated fats, refined oils, and meat, milk and by-products from ruminant animals. According to Larqué *et al.*[122], food containing partially hydrogenated fat contributes with about 80% to 90% of the daily TFA intake. For food coming from ruminant animals, this contribution is very lower, being estimated in about 2% to 8%. Refined oils present reasonably low TFA levels (1.0%-1.5%), but their reuse, especially when preparing fried food, can turn their contribution significant in the daily TFA innestion[123,124].

A high intake of trans fatty acids from industrial food is associated to increase in coronary artery disease[125]. The most probable cause is their action on lipoproteins, in the same way as saturated fat, and then trans fat increase LDL-c concentration. A reduction in HDL-c represents a significant increase in LDL/HDL ratio. The main source of trans fat in diet is hydrogenated vegetal fat, industrially used for producing cookies, sandwich cookies, coated pastry, creamy ice creams, pies, and food commercialized in fast food restaurants. Though these fatty acids are abundant in hard margarines, they only represent 10% of the trans fat intake, with industrialized food being the largest source.

6.3.6. Alimentary fiber

The high alimentary fiber intake is associated to a significant decrease in prevalence rates of cardiovascular disease, stroke, and peripheral vascular disease; furthermore, the risk factors hypertension, diabetes, obesity, and dyslipidemia are less frequent in persons presenting high alimentary fiber intake[126]. A review done by Brown *et al.*[127] showed that soluble fibers decrease total cholesterol and LDL-c concentrations. The intake of approximately 3 g of soluble fiber is associated to a 5-mg/dL decrease in total cholesterol and LDL-c concentrations, which can predict a reduction of about 4% in cardiovascular disease incidence.

As a result of accumulated data, FDA authorized in 1997 the health claim for the association between soluble fibers from oats and psyllium and development of cardiovascular disease when ingested as part of a diet poor in cholesterol and saturated fat. Literature supports the use of psyllium for decreasing LDL-c levels. Doses > 7 to 8 g/day can reduce LDL levels in about 5%[128].

6.3.7. Phytosterol

Phytosterols are natural compounds with structure similar to cholesterol. The classic mechanism of action of phytosterols is the dislocation of cholesterol in micellar phase. In diet, mixed micelles have limited capacity for incorporating sterols. The competition between phytosterols and cholesterol reduces the cholesterol

content in micelles and thus decreases its transportation to the brush-border membrane in the intestine. Out of the micellar phase, cholesterol is not more soluble, forming cocrystals with phytosterols and then being excreted together with non absorbed phytosterols[129]. Therefore, effects are seen on decrease in cholesterol, especially LDL-c, caused by phytosterols[130]. The daily intake of two grams of phytosterols as enriched margarines reduces cholesterol absorption in approximately 30%-40%, causing a mean reduction in LDL-c of 8.8%[131]. However, this reduction in LDL-c concentrations may vary with the baseline LDL-c concentration of the subject, the medium where the phytosterol is inserted in (margarines, yogurts, milk), and the intake frequency (once or several times daily)[131]. Supplementation with phytosterols is an option for decreasing LDL-c in children with FH that still cannot receive pharmacological treatment[132].

6.3.8 Diets rich in carbohydrates

It is known for some years that a diet rich in carbohydrates increases the triglyceride plasma levels when compared to diets with high fat percentage. Those diets can reduce HDL-c concentrations and are little efficient on LDL-c[133].

6.3.9. Soybean

The effect of the intake of soybean-based food on LDL-c concentrations is controverted[128,134,135]. Controversies in results can be explained in part by the different methods used in studies, such as: different soybean doses are used in each study; the isoflavone concentration varies in supplements and the different studies; the replacement of animal protein with soybean can be biased, as animal products are rich in saturated fat, known to be atherogenic.

6.3.10 Egg

Egg is a low cost food and is an excellent source of several nutrients, such as folate, riboflavin, selenium, choline, and vitamins A, D, E, K, and B_{12}, besides mineral salts (iron, phosphorus, calcium, magnesium, sodium, potassium, chlorine, iodine, manganese, sulfur, copper, and zinc), high-quality protein, and lipid, which turn significant nutrients (such as lutein and zeaxanthin, associated to prevention of macular degeneration) bioavailable, besides being a source of saturated fat and cholesterol. It is noteworthy to remember that lipids, minerals, and vitamins are present almost totally in the yolk, with the white being especially constituted by proteins. An egg contains 50 to 250 mg of cholesterol, depending on its size. The impact of egg intake on the cholesterolemia depends on the capacity of the body to absorb cholesterol. It is believed that between 75%-85% of population are little sensitive to cholesterol concentrations in diet, that is, the impact of the intake of food rich in cholesterol (such as eggs) on LDL-c is very low[136]. Certainly, the high saturated fat intake by certain populations has a much higher impact on the cholesterolemia, and an egg will add little to the cardiovascular disease risk[137,138].

The way to prepare an egg must be careful: when fried or scrambled, there is addition of fat, increasing calories and, depending on the fat type, raising cholesterol.

6.3.11 Chocolate

Native of South America, chocolate is the product obtained from mixing cacao (*Theobroma cacao* L.) by-products, cocoa dough (or paste or liquor), cocoa, and/or cocoa butter with other ingredients. Chocolate fat, derived from cacao, is constituted by two saturated fatty acids (palmitic and stearic acids) and the monounsaturated oleic acid, in addition to a small quantity (less than 5%) of other fatty acids[139].

Though it is known that the saturated fat intake increases cholesterol levels, the regular intake of cocoa butter and chocolate rich in cocoa (dark chocolate) is not related to that increase[140]. The quantities of stearic fatty acid are responsible for the neutral effect on the cholesterol metabolism. However, there must be caution with chocolate manufactured with milk, as it can contain a large quantity of fatty acids myristic and lauric acids, known to be hypercholesterolemic.

6.3.12 Coconut and coconut oil

Coconut and coconut oil (*Coco nucifera*) are significant natural sources of saturated fat, especially of lauric acid (C12:0). Referring to dyslipidemia, it is known that saturated solid fat rich in lauric acid result in a more favorable lipidic profile than a solid fat rich in trans fatty acids[111,141]. However, compared to other types of saturated fat, especially myristic and palmitic acids, lauric acid presents higher power to raise both LDL-c and HDL-c[115]. In spite of that, this effect does not seem to be the cause of the increase in CVD prevalence according to studies conducted in Asia, where coconut oil represents up to 80% of the fat consumed in some regions[142,143].

In Brazil, a clinical trial conducted with normolipidemic females with low saturated fat intake during 12 weeks showed reduction in LDL:GDL ratio, increase in HDL-c, and reduction in abdominal circumference in the group that used coconut oil[144]. In spite of the potential benefits of coconut oil for HDL, the experimental studies prove the hypercholesterolemic effect of coconut and its by-products, such as the recent study with guinea pigs comparing coconut oil to olive oil and sunflower oil. The group treated with coconut oil presented significant increase in the non HDL fraction and triglycerides[145].

6.4. Recommendations

Recommendations	Recommendation degree	Evidence level
The intake of alimentary cholesterol must be < 300 mg/day to aid in cholesterolemia control.	I	A
The intake of saturated fatty acids must be < 7% of the total caloric value (TCV) for cholesterolemia control.	I	A
High intake of palmitic and myristic acids increases total cholesterol and LDL-cholesterol.	I	A
The adequacy of the intake of saturated fatty acids aids in controlling LDL-c.	I	A
The intake of monounsaturated fatty acids must be < 20% of TCV, together with a diet rich in fruits, vegetables, grains, and lean meat and skimmed dairy products, which are related to lower LDL-c plasma concentration.	I	A
The intake of polyunsaturated fatty acids must be < 10% of TCV.	II	B
The intake of trans fatty acids raises total cholesterol and LDL- c and reduces HDL-c.	I	A
The intake of chocolate rich in cocoa is not related to an increase in cholesterol.	II	A
Coconut and coconut oil are not recommended for treating hypercholesterolemia, with further studies being needed to guide their use in other metabolic alterations.	III	B
The intake of egg or other food rich in cholesterol has little influence on lipid plasma levels; however, a moderate intake of cholesterol source food is recommended.	II	A
A daily intake of 2 g of phytosterol is related to decrease in LDL-c.	I	A
A high soluble fiber intake is associated to reduction in LDL-c.	I	A
The intake of soybean protein replacing animal protein is related to higher control of lipid plasma levels.	III	B

7. Pharmacological treatment of heterozygous familial hypercholesterolemia

Several randomized studies have shown that reducing LDL-cholesterol (LDL-c) plasma concentration with statins results in decrease in the morbidity and mortality of atherosclerotic cardiovascular disease[146]. Data obtained from an authentic prospective meta-analysis conducted by Cholesterol Treatment Trialists (CTT) Collaborators are highlighted[147]. CTT included an analysis of 90,056 subjects from 14 randomized studies on the statin use in a five-year period. It was found that there was a proportional decrease in 19% in mortality by coronary cause in the analyzed five-year period for each 1 mmol/L of LDL-c reduction (39 mg/dL), projecting an expected reduction of 38% in ten years. This approximately means that we can obtain a decrease in 1% in atherosclerotic cardiovascular mortality in ten years for each 1 mg of LDL-c reduced with statin use.

Considering the potential benefit of higher reductions in LDL-c and making a growing decrease in morbidity and mortality possible, CTT conducted a new meta-analysis comparing the incidence of cardiovascular events between patient groups using higher statin doses versus patients with less intense doses[148]. Prospective data from 170 thousand participants with 26 large studies with minimum duration of two years were obtained. An additional reduction of 1.0 mmol/L in LDL-c (39 mg/dL) using more potent statins in high doses resulted in decrease of cardiovascular events compared to the group treated with lower intensity, at the same ratio found in studies on statin versus placebo, even in those with baseline LDL-c lower than 2 mmol/L (76 mg/dL) in less intense treatment. LDL-c reductions of 80 and 120 mg/dL resulted in decrease in major atherosclerotic events in 40% and 50%, respectively. Therefore, in spite of existing traditionally different aims for treating LDL-c in the Guidelines, CTT's data enable to conclude the significance of always trying a substantial reduction in LDL-c with the used hypolipemiant therapy.

In spite of not existing a specific controlled randomized study on cholesterolemia reduction in patients presenting FH, there is evidence in literature that those subjects are benefitted from an LDL-c reduction[32]. The FH cohort studied by Versmissen *at al.*[32], with more than two thousand patients followed for ten years, showed that the statin-treated group presented a 76% reduction in coronary disease risk (95% CI 0.18 to 0.30, $p < 0.001$) compared to the group without statin. This was associated to the relative 44% decrease in LDL-c, which corresponded to an absolute reduction of 124 mg/dL. In that study, the myocardial infarction rates at the follow-up end were similar to the ones in normal population. It is significant to emphasize that, due to the high risk of cardiovascular events in the population with familial hypercholesterolemia (FH), and considering all evidence of the benefit of LDL-c reduction for reducing morbidity and mortality by cardiovascular disease, it would not be ethical to conduct a study controlled by placebo in this population nowadays.

7.1. LDL-c aims in FH pharmacological treatment

Subjects presenting FH have risk of coronary disease along life, and can develop it early, in order that the pharmacological treatment must be initiated earlier and kept for long term to consistently reduce the incidence in cardiovascular events and mortality[149,150]. Thus, persons with FH require a regular and careful follow-up along their lives for controlling cholesterolemia.

The indication of pharmacological treatment occurs for LDL-c concentrations ≥ 190 mg/dL in an isolated was in subjects without previous manifestation of cardiovascular disease, after application of healthy life style measures. In the same way, subjects with LDL-c ≥ 160 mg/dL, but presenting other risk factors, must be also treated. Considering the high baseline cholesterolemia values present in FH, a weight reduction of at least 50% obtained with a drug treatment is deemed as having real therapeutic value[1]. Nevertheless, patients with FH in higher risk need intensification in treatment schedule to achieve higher LDL-c reductions.

These are considered as higher risk FH patients: those with clinical manifestation of cerebrovascular and/or peripheral coronary atherosclerosis or equivalent; diabetic patients with FH; smoking subjects with FH; presence of two or more FH-associated classic coronary risk factors (see Chapter 5 in this Guideline); antecedent of very early coronary artery disease (CAD) in first degree relatives (father or brother with CAD younger than 45 years old and mother or sister with CAD younger than 55 years old); and presence of high lipoprotein(s) (> 60 mg/dL). In patients presenting FH without such features, intensification in pharmacological treatment may be considered if LDL-c remains > 160 mg/dL or if the initial 50% reduction in LDL-c is not achieved.

7.2. Recommendation

Patients presenting FH must have reductions of at least 50% in LDL-c (Class I, Evidence level A). Major reductions may be needed depending on LDL-c values and cardiovascular event risk (Class I, Evidence level B).

7.3. Pharmacological treatment

7.3.1. Statins

Heterozygous FH is manifested with only 50% of LDL receptors working, usually presenting a good response to the use of statins, which significantly increase the expression of those receptors by determining the blockade of cholesterol intracellular synthesis. The used statins must be of high potency, such as atorvastatin (10-80 mg) and rosuvastatin (10-40 mg), titrated to obtain a reduction ≥ 50% from baseline levels[1,149,150], being difficult to reach such aim with the isolated use of simvastatin. Lower potency statins (such as fluvastatin, pravastatin, and lovastatin) are usually improper for patients presenting FH. In general, statins are well tolerated and present a good safety profile[151-153]. The potential adverse effects of statins referring to myopathy and raise in liver enzymes in patients presenting FH are evidently the same found in other patients more intensively treated. Less potent statins (such as fluvastatin and pravastatin) can have better tolerance and lower risk of severe myopathy, but present lower capacity to reduce high LDL-c levels[154-155]. Some patients do not tolerate statins. In those cases, other statin must be tried or reduced doses of those statins must be tried in combination with other hypolipemiants (such as ezetimibe, niacin, or cholestyramine)[150]. As last option for using statins in non tolerant patients, though there are few studies (usually short-term studies with small number of patients and that only evaluated tolerability or efficacy and not clinical results), their use may be tried every other day[156,157]. A combined therapy of niacin, ezetimibe, and/or cholestyramine is indicated for patients that cannot use statins.

7.3.2. Recommendation

Potent statins in proper doses are the first choice for reducing LDL-c in patients presenting FH (Class I, Evidence level A). In statin-intolerant patients, reduced doses in combination with other hypolipemiants (such as ezetimibe, niacin [or nicotinic acid], or cholestyramine) may be tried (Class I, Evidence level B). The combined therapy of niacin, ezetimibe, and/or cholestyramine is indicated for patients that cannot use statins (Class IIA, Evidence level B).

7.3.3. Adjuvant therapy to statins

Most patients presenting FH tolerate maximum doses of the most potent statins (atorvastatin and rosuvastatin) with safety and good tolerance. The fact is that, due to the very high LDL-c concentrations in FH, the addition of one or more hypolipemiants other than the statin is often needed to achieve the desired aims[25,158].

In the study by Lipid Research Clinics[159], cholestyramine reduced the incidence of myocardial infarction in 19%. Therefore, cholestyramine can be used as adjuvant to statins in FH. Cholestyramine is presented in 4-gram envelopes. The initial posology is 4 g daily, and a maximum of 24 g/day can be reached. Posologies higher than 16 g are difficultly tolerated. The main side effects are related to digestory system (gastric repleteness, nausea), interfering with intestinal motility and causing obstipation and tympanism, besides exacerbation of preexisting hemorrhoids. The drug decreases the absorption of liposoluble vitamins (A, D, K, E) and folic acid, with the supplementation of those elements being eventually necessary. Cholestyramine must be used one hour before or three hours after the ingestion of other medicines to not decrease their absorption. Cholestyramine is a useful drug for children under 8 years old that still cannot receive statins.

7.3.4. Recommendation

Cholestyramine can be used as an adjuvant therapy to statins for higher LDL-c reduction and when the latter are not sufficient in isolated use (Class I, Evidence level B).

By its turn, ezetimibe has a specific mechanism to inhibit cholesterol absorption at the enterocyte level and, therefore, it does not interfere with absorption of other agents[24,158]. The reduction in cholesterol inflow from the intestine to the liver results in a compensating increase in expression of liver LDL receptors and an increase in the uptake of circulating LDL-c particles. However, due to the increase in the cholesterol intracellular synthesis, which tries to compensate the decrease in its inflow to the hepatocyte, the final

cholesterolemia reduction using ezetimibe (isolated or associated to statin) is around 15% to 20%, but still having great significance in reducing cardiovascular events. The use of ezetimibe associated to simvastatin has shown efficacy in reducing cardiovascular events, besides safety in patients presenting non dialytic chronic kidney failure in SHARP study[160]. The reduction in major atherosclerotic events was proportional to the LDL-c decrease and was similar to the data obtained by the meta-analysis by CTT[147] with isolated statin use.

Ezetimibe can be used as an adjuvant therapy to statins for proper LDL-c reduction and prevention of cardiovascular disease in patients presenting FH (Class I, Evidence level B).

Niacin reduces the inflow of fatty acids to the liver and, consequently, leads to a lower production of VLDL-c, an LDL-c precursor, thus decreasing the concentration of those circulating particles. Its use has excellent scientific evidence level, started since approximately 20 days after the Coronary Drug Project study[161], where a 27% event reduction was verified after follow-up by 15 years. Combined with statins or in triple association with statins and absorption blockers, niacin reduced the anatomic atherosclerosis progression and the main cardiovascular results[162-165]. Tolerability is a limiting factor when using niacin, even at the prolonged release form, as its action in prostaglandin receptors in dermis results in a sometimes intense vasodilation and facial redness or pruritus. This frequent side effect stimulates a patient and progressive niacin titration, beginning in 500-mg doses in the first month, following progressive increases every four or eight weeks up to a possible tolerated maximum dose, not surpassing 2 g daily.

A single ingestion during the night aims to minimize the sensation of an eventual flushing that, in that way, could not be realized during sleep. The use of this schedule is recommended for patients using AAS 300 mg, one hour before the niacin, due to its potential benefit as prostaglandin inhibitor. Recently, its association with a specific prostaglandin inhibitor (laropiprant) improved the tolerance, making possible a highest use of such significant hypolipemiant drug[166]. In that case, titration may be tried more quickly, beginning with 1 g at night in the first month and increasing to a full dose of 2 g from the second month on, in case of good tolerance.

In the case of using a niacin/laropiprant combination, there is no need for using aspirin previously to the niacin ingestion. Other drugs such as monascus, omega-3 fatty acids, and antioxidant vitamins have not been testes in patients presenting FH, thus they are not indicated.

Niacin can be used as an adjuvant therapy to statins for a proper LDL-c reduction in patients presenting FH (Class I, Evidence level B). In order to control hypercholesterolemia and to reduce cardiovascular events in patients presenting FH, this Guideline contraindicates the use of fibrates, omega-3 fatty acids, monascus, and antioxidant vitamins due to the total lack of benefit evidence for those substances (Class III, Evidence level C).

8. Alternative therapies for treating familial hypercholesterolemia

Non pharmacological alternative therapies can be tried in cases of familial hypercholesterolemia (FH) refractory to drug treatment, such as ileal bypass surgery, plasmapheresis, and liver transplant.

8.1. Ileal bypass

A study using ileal bypass surgery decreased LDL-c in 38% and cardiovascular events in 30% in patients presenting severe hypercholesterolemia[167]. Referring to patients presenting FH, a study with only 11 patients showed LDL-c decrease in approximately 20%. These studies were conducted before the coming of statins and ezetimibe. The value of ileal bypass for treating FH and preventing cardiovascular disease during the current pharmacological therapy is unknown[168].

8.2. Recommendation

Though POSCH study has shown reduction in cardiovascular events with ileal bypass, that procedure is not routinely recommended for patients presenting FH refractory to pharmacological treatment (Class IIB, Evidence level C).

8.3. Plasmapheresis and LDL-apheresis

LDL-c can be intensely removed by plasma by plasmapheresis or LDL-apheresis. Currently, the techniques available for LDL-apheresis are:

- Immunoadsorption. Adsorption by dextran cellulose sulfate. Extracorporeal LDL precipitation system for heparin (HELP system).
- Direct lipoprotein adsorption using hemoperfusion filter (DALI).

Classically, apheresis may be performed in patients presenting homozygous FH; however, it can be also an alternative for patients with severe heterozygous FH refractory to pharmacological treatment. Small studies show regression of xanthomas and anatomic coronary injuries, besides LDL-c and Lp(a) reduction[169,170].

8.3.1. Indications for LDL-apheresis

1. LDL-apheresis is a medical therapy approved by the United States Food and Drug Administration[171] for patients that do not respond to treatment with LDL-c or that present chronic symptomatic diseases.
2. LDL-apheresis is indicated in patients that do not present a proper response to the optimized drug treatment after six months according to the these rules;

- patients with functional homozygous FH with LDL-cholesterol > 300 mg/dL (or non HDL-cholesterol > 330 mg/dL).
- patients with functional heterozygous FH with LDL-cholesterol > 300 mg/dL (or non HDL-cholesterol > 330 mg/dL) and zero or 1 risk factor.
- patients with functional heterozygous FH with LDL-

cholesterol > 200 mg/dL (or non HDL-cholesterol > 230 mg/dL) with two or more risk factors or lipoprotein (a) > 50 mg/dL.

- patients with functional heterozygous FH with LDL-cholesterol > 160 mg/dL (or non HDL-cholesterol > 190 mg/dL) with established DC and other cardiovascular diseases or diabetes.

8.3.2. Recommendations for using apheresis and preventing cardiovascular disease

Though plasmapheresis and LDL-apheresis are efficient in reducing LDL-c concentrations (and, in some small studies, they have shown regression of xanthomas and angiographic atherosclerosis), there is no evidence of controlled randomized studies saying that apheresis reduces the risk of cardiovascular events or prolongs life in patients presenting homozygous FH. Similarly, its cost-efficacy is debatable. Considering these facts, this Guideline places apheresis as treatment alternative for severe and refractory cases, but as Class IIB, Evidence level C.

8.4. Liver transplant

Liver transplant may be an alternative for FH patients refractory to pharmacological treatment[172]. This would be especially indicated in homozygous FH. However, this must be always discussed with patients and relatives, in order that procedure risks and benefits are explained.

8.5. Recommendation

Liver transplant may be an alternative for cases of FH refractory to pharmacological treatment, especially in patients presenting the homozygous form (Class IIB, Evidence level C).

9. Familial hypercholesterolemia - in children

9.1. Screening

At populational level, there must be a screening of the lipidic profile of children from 2 years old, following the criteria described below. Before that, the cases must be individually analyzed according to concurrent diseases, therapeutics, and familial history.

We must screen the lipidic profile in children between 2 and 10 years old when:

- They have parents or grandparents with history of ischemic artery disease in males younger than 55 years old and females younger than 65 years old.
- They have parents with total cholesterol higher than 240 mg/dL.
- They present other risk factors, such as systemic arterial hypertension, obesity, smoking, *diabetes mellitus*, being born small for their gestational age, and diet rich in saturated fat and/or trans fatty acids.
- They use drugs or present diseases that include dyslipidemia (human immunodeficiency syndrome, hypothryoidism, Cushing's disease, etc.).
- They present clinical manifestations of dyslipidemias (xanthomas, xanthelasma, corneal arch, recurring abdominal pains, pancreatitides).

Above 10 years old, every child must have dosed his/her total cholesterol at least once, regardless of the presence of risk factors (Class IIa, Level B).

9.2. Reference values

Reference values for lipids and lipoproteins in children and teenagers are described in table 41 (Class IIa, Level B).

Table 4 - Reference values for lipids and lipoproteins in children and teenagers[2]

Parameter	Acceptable	Borderline	High (p95)	Low (p5)
TC	< 170	170-199	> 200	
LDL-c	< 110	110-129	> 130	
n-HDL-c	123	123-143	> 144	
TG (0-9a)	< 75	75-99	> 100	
TG (10-19a)	< 90	90-129	> 130	
HDL-c	> 45	35-45		< 35
Apo A1	> 120	110-120		< 110
Apo B	< 90	90-109	> 110	

9.3. Screening of risk of familial hypercholesterolemia

For stratifying the risk in a child or teenager presenting monogenic FH, three aspects must be considered: LDL-c values of the child or teenager at the diagnosis; LDL-c values of the child or teenager after six months of diet; and if his/her parents use hypolipemiants or not. According to these three variables, the estimated risks of a subject presenting FH are described in Charts 1 and 2[173]:

Chart 1 - Estimated risk of presenting familial hypercholesterolemia in children and teenagers whose parents use hypolipemiants, according to LDL-c at the diagnosis and after six months of diet

	LDL-c after diet				
LDL-c at the diagnosis	mg/dL	< 140	140-169	170-229	> 230
	130-169	7%	14%	29%	49%
	170-209	27%	48%	68%	84%
	210-259	67%	83%	92%	97%
	≥ 260	92%	96%	98%	99%

Legend: possible %, probable %, definitive %

Chart 2 - Estimated risk of presenting familial hypercholesterolemia in children and teenagers whose parents do not use hypolipemiants, according to LDL-c at the diagnosis and after six months of diet

	LDL-c after diet				
LDL-c at the diagnosis	mg/dL	< 140	140-169	170-229	> 230
	130-169	1%	3%	7%	15%
	170-209	7%	14%	29%	49%
	210-259	28%	48%	69%	84%
	≥ 260	67%	83%	92%	97%

Legend: possible %, probable %, definitive %

When the LDL-c value is considered as isolated, the cut point with highest sensitivity and specificity for suspicion of familial hypercholesterolemia in childhood is 150 mg/d[174] (Class IIb, Level B).

9.4. Treatment

Rigorously following the criteria described below and after a change in life style, it is recommended that the hypolipemiant therapy is initiated after two years old, except in severe cases and with individualized evaluation. This aims to achieve the aim of values of 110 mg/dL of LDL-c (or at least 130 mg/dL) and to reduce xanthomatosis, to decrease pancreatitis risks, and to prevent the appearance of coronary artery disease (Class I, Level A).

9.4.1. Statins

The use of statins significantly decreases total cholesterol, LDL-c, and apolipoprotein B, apparently without a significant occurrence of adverse events related to sexual development or muscle or liver toxicity, and can be used from 8 years old[175]. Statins can decrease LDL-c in about 30% and increase HDL-c in 5% and consequently attenuate the intima-medium thickening and improve endothelial function[176-181] (Class I, Level A). Evaluating these considerations, there is no sufficient evidence for a consensus about when to begin with statins in childhood or which is the LDL-c aim to be achieved at that age range[182] (Class IIb, Level B).

The hypolipemiant doses usually used in children and teenagers are described in Chart 3:

Chart 3 - Hypolipemiant doses used in children and teenagers (Class IIa, Level B)

Drug	Doses (mg/d)
Lovastatin	10-40
Pravastatin	10-40
Simvastatin	10-40
Rosuvastatin	5-20
Atorvastatin	10-20
Cholestyramine	4-16*
Ezetimibe	10

** grams*

Doses higher than the described ones can be used after an individual risk analysis in children. In children and teenagers, the initial use of the lowest possible statin dose is suggested, preferentially associated to cholesterol absorption inhibitors (Class IIa, Level C).

9.4.2. Treatment monitoring

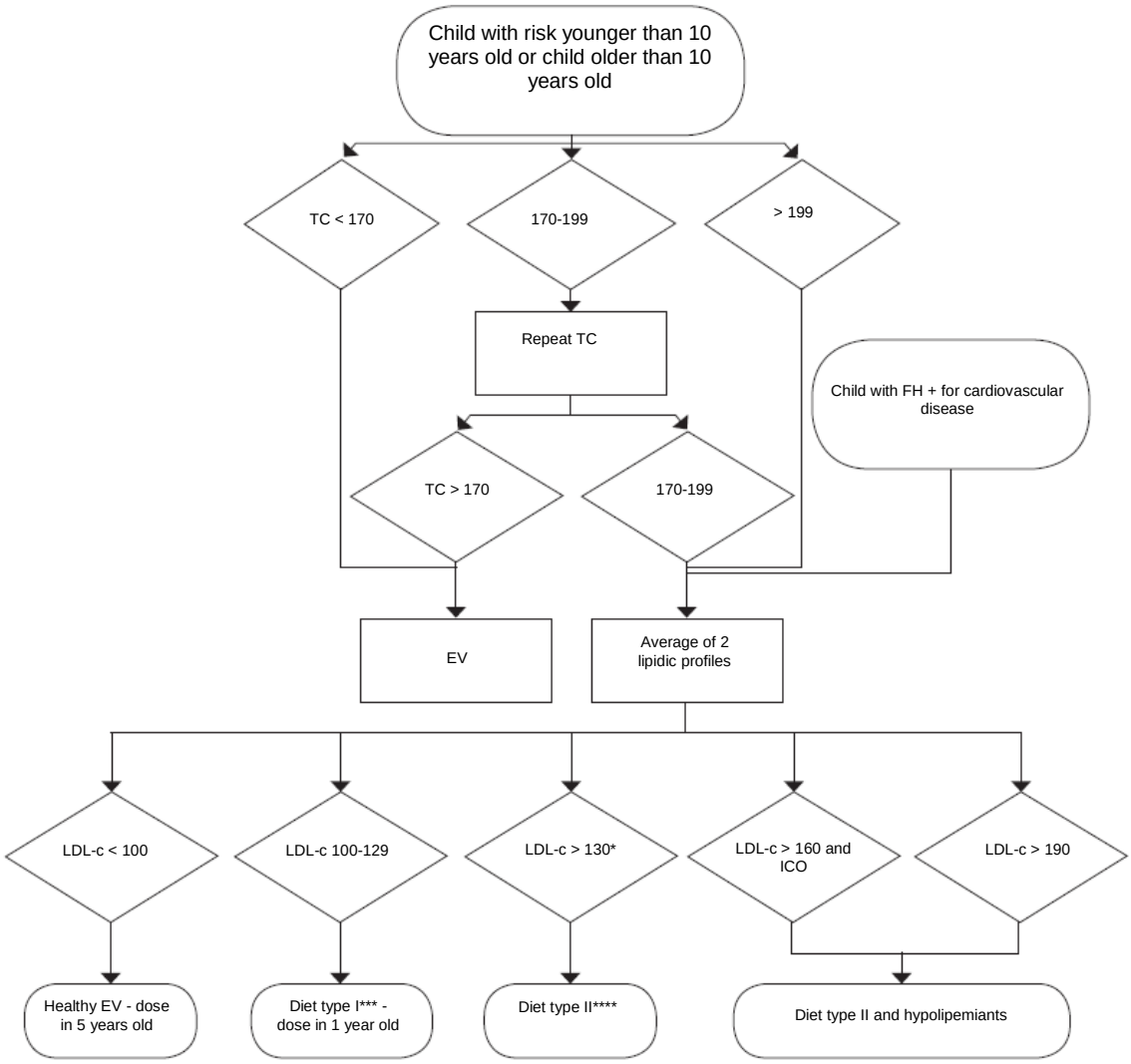
Figure 6 shows the monitoring algorithm for statin use in children and teenagers (Class IIa, Level C).

9.5. Cholesterol absorption inhibitors

The use of ezetimibe as monotherapy decreases LDL-c values in about 28% in children with heterozygous familial hypercholesterolemia. Its use as monotherapy is recommended from 5 years old and its use associated with statins is recommended above 8 years old, decreasing the side effects of the latter[185] (Class IIb, Level C).

9.6. Biliary acid sequestrants

Biliary acid sequestrants may be used at any age. As monotherapy, they decrease LDL-c levels in about 10%-15% in average. They can be also used associated to statins, in different administration hours. Due to the risk of malnutrition related to liposoluble vitamins, nutritional monitoring and supplementation are recommended, following objective deficiency criteria[186] (Class I, Level B).



Therapeutic Target

TC: total cholesterol, FH: familial history, LDL-c: LDL-cholesterol

Notes:

* In the presence of *diabetes mellitus*, infection by HIV, Kawasaki disease, nephrotic syndrome, and systemic lupus erythematosus, a drug treatment must be instituted with LDL-c values above 130 mg/dL, after changes in life style.

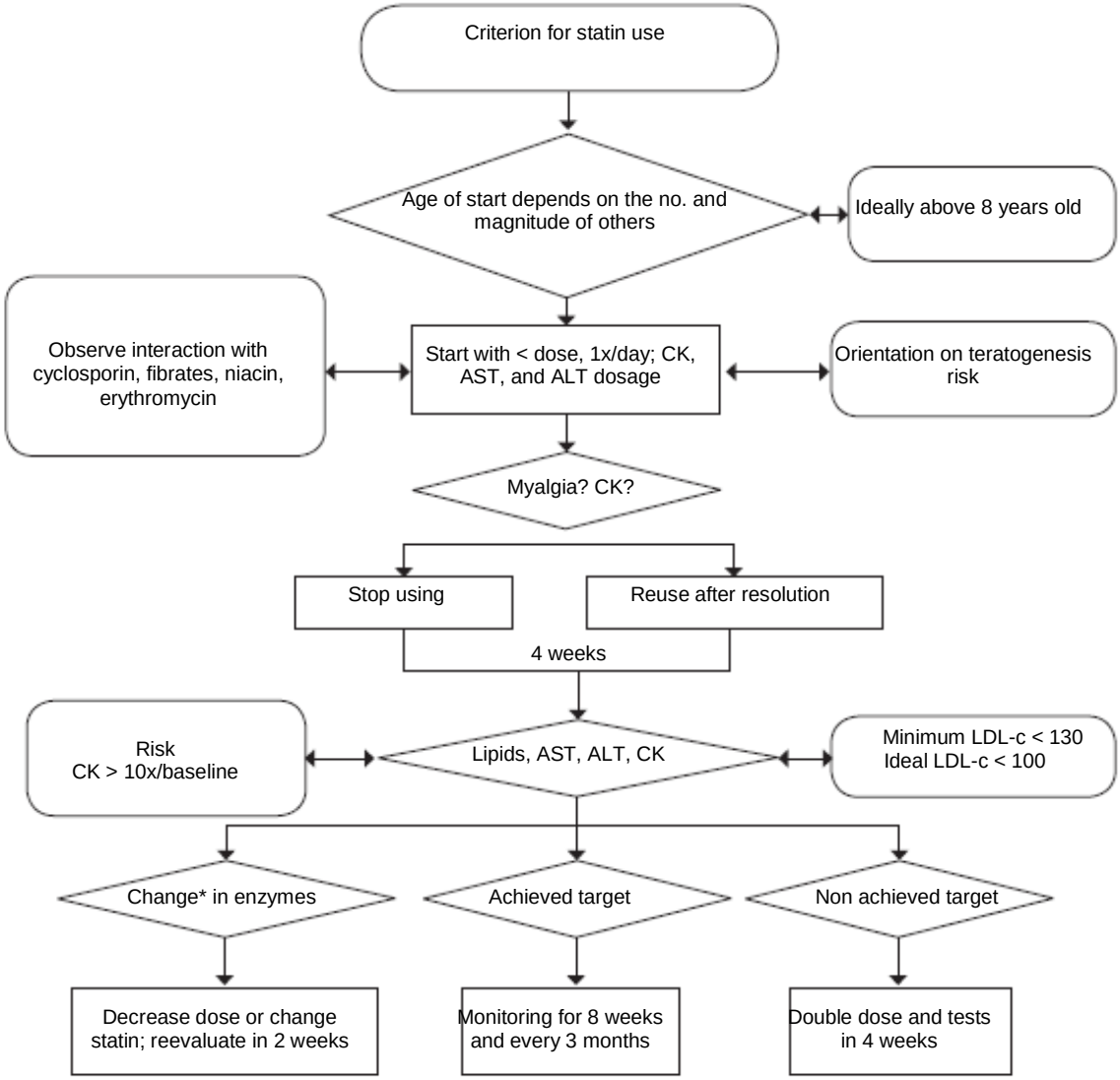
** The presence of emergent risk factors (high lipoprotein (a), homocysteine, and C-reactive protein values) is considered as determinant for the use of hypolipemiants in children with LDL-c levels above 160 mg/dL by some authors.

*** Diet type I: up to 30% of calories from fat; up to 10% of saturated fat; up to 100 mg/1000 cal of cholesterol; maximum of 300 mg/d.

**** Diet type II: up to 20% of calories from fat; up to 7% of saturated fat; up to 60 mg/1000 cal of cholesterol; maximum of 200 mg/d.

***** Every child with hypercholesterolemia diagnosis must have a secondary cause for the dyslipidemia discarded and/or lipid screening of his/her first degree relatives.

Fig. 5 *- Algorithm for diagnosis and conduct in dyslipidemia in childhood, based on risk factors and lipid levels (in mg/dL) (Adapted from Caramelli, B e Giuliano, I. Dislipidemia na infância e na adolescência. Pediatria (São Paulo) 2008;29(4):275-285.)*



* CPK: symptomatic: +3 to 10x

asymptomatic: > 10x

Fig. 6 *- Algorithm for monitoring statin use in children and teenagers. Adapted from Caramelli, B e Giuliano, I. Dislipidemia na infância e na adolescência. Pediatria (São Paulo) 2008;29(4):275-285.)*

9.7. Supplements

A supplementation of 1.2 to 1.5 g of phytosterols can decrease total cholesterol and LDL-c levels in about 10% in children presenting heterozygous familial hypercholesterolemia[26,187] (Class IIb, Level B).

9.8. Surgical indications

In teenagers with clinically manifested severe atherosclerosis, there is indication of myocardial revascularization[188,189]. In case of aortic disease coming from severe dyslipidemia, a replacement with lung homograft (Ross-Konno surgery) many become an interesting option for a teenager, due to its durability[190].

The most efficient treatment for monozygous FH is liver transplant, with good results[191,192] (Class IIb, Level C).

9.9. Psychological aspects

The pharmacological treatment seems to do not have impact on quality of live or anxiety of children presenting familial hypercholesterolemia. About 40% of children suffer from presenting the condition, but using hypolipemiants makes them feel safer in

about 60% of them. More than 50% of them are in diet and 79% of the parents suffer because their sons present familial hypercholesterolemia[193] (Class IIb, Level B).

10. Treatment of familial hypercholesterolemia in pregnancy

During pregnancy and lactation, therapeutic options for familial hypercholesterolemia (FH) are very limited, as statins, ezetimibe, and nicotinic acid must not be prescribed to prevent potential adverse effects in the fetus, associated to the use of those agents (respectively categories X, C, and C). This can be worrying, considering the increase in lipid plasma levels that usually occurs during pregnancy (increase of 25% to 50% in cholesterol levels, and increase of 150% to 300% in triglycerides), besides baseline cholesterol concentrations being already high due to the FH[194].

The use of other hypolipemiant medications, more specifically resins, is possible when there is clear need for maintaining the drug therapy with probable benefit. Resins, such as colesevelam and cholestyramine, are category B agents in pregnancy and lactation and, therefore, can be considered for FH treatment in those conditions, provided that there is medical supervision[15]. LDL-apheresis is a treatment modality that can be also used in special cases, where the cardiovascular risk of the patient is very high in lack of treatment, such as in patients with homozygous FH or heterozygous FH and severe atherosclerotic disease[195].

Females presenting FH at fertile age and that wish to become pregnant must receive pre-pregnancy advice and interrupt statins, ezetimibe, and nicotinic acid, at least four weeks before interrupting the used contraceptive method. It is significant to highlight that the use of an oral contraceptive is usually not contraindicated for most females with FH[196] and does not interfere with statin efficacy[197]. Females with increase risk of cardiovascular events must discuss other contraceptive methods besides the oral contraceptive[196].

Patients that became pregnant in a non programmed way must immediately interrupt those hypolipemiants and seek for obstetric follow-up. A few studies have evaluated females with familial hypercholesterolemia that became pregnant while using statins, with controverted results, referring to the incidence of fetal malformations. For example, Ofori *et al.*[198] did not see increase in the frequency of fetal abnormalities in females that conceived while using a statin in a study that included more than 100 thousand pregnant women, with 106 of them using statin[198]. However, a series of cases reported by FDA in 2004 evaluated 52 selected cases of gestational exposure to statins and found 20 cases of fetal structural defects, especially neurological and skeletal defects[199].

The relative scarcity of safe and efficient treatments for reducing cholesterol plasma levels in those patients is associated to the concern referring to adverse effects by the very hyperlipidemia. In fact, some works suggest an increased risk of prematurity in pregnant women with high cholesterol levels[200,201]. A recent work conducted in Norway, which evaluated 2,319 births from 1,093 females with FH, did not detect any difference referring to prematurity between females with genetic FH diagnosis and females from the general population[194]. For the low birth weight, in general, it seems that there is no significant difference between newborns from women with or without FH diagnosis. The frequency of congenital malformations in fetuses from females with FH also does not seem to be higher compared to females from the general population: 3.3% and 3.2%, respectively. Toleikyte *et al.*[194] also did not find differences in prematurity, low weight, and malformations according to different types of genetic mutation.

Though most available studies do not show significant fetal adverse events associated to the presence of familial hypercholesterolemia, a joint follow-up of pregnant women presenting familial hypercholesterolemia by an expert in lipids and an obstetrician is recommended. Attention must be paid to the possible presence of valve injuries (particularly of aortic valve stenosis) and premature coronary disease in those patients[202]. From the obstetric point of view, a survey for uteroplacental vascular failure is also significant[203,204].

10.1. Recommendations

Use of hypolipemiant medications in pregnant women with FH:

- Statins, ezetimibe, nicotinic acid, fibrates: Class III, Evidence level B.
- Resins: Class IIB, Evidence level B.
- Apheresis: Class IIB, Evidence level B.

10.2. Classification of agents for possible effects in fetus according to FDA

- Category A: Proper and controlled studies have not demonstrated risk to fetus in the first pregnancy trimester (and there is no evidence of risk in the following trimesters).
- Category B: Reproduction studies in animals have not demonstrated risk to fetus, and there is no proper and controlled study in pregnant females.
- Category C: Reproduction studies in animals have shown adverse effect in fetus, but there is no proper and controlled study in pregnant females.
- Category D: There is evidence of risk to human fetus based on adverse reaction data from study in humans or marketing or investigative experience. The benefits from the agent use in pregnant females may be higher than its risk in some situations.
- Category X: Studies in animals or humans have demonstrated fetal abnormalities and/or there is evidence of human fetal risk based on adverse effect data from marketing or investigative experience. The risks of agent use in pregnant females clearly surpass the potential benefits.

11. Future perspectives for treating familial hypercholesterolemia

In spite of the great advance in hypercholesterolemia treatment, particularly obtained with statins, a considerable number of subjects remain with LDL-c plasma levels above the aims. In patients with FH, this reality is still more expressive due to the severity of the hypercholesterolemia in those subjects. Besides statins, resins, and ezetimibe, new classes have been investigated aiming to develop a multiple therapy in out-of-aim patients, particularly those with FH. The classes in more advanced development stages are: (i) MTP inhibitor; (ii) squalene synthase inhibitor; (iii) PCSK9 inhibitor; (iv) thyroid hormone analogues; and (v) antisense oligonucleotides.

11.1. Microsomal transfer protein inhibitor

The triglyceride microsomal transfer protein (MTP) is responsible for transferring triglycerides to apolipoprotein B in hepatocytes during the VLDL synthesis. In MTP absence or dysfunction (such as in recessive abetalipoproteinemia), there is no VLDL production and thus there is no production of the other apolipoprotein B-containing lipoproteins, such as LDL, IDL, and Lp(a). Therefore, MTP pharmacological inhibition is a potential strategy as complementary therapy for hypercholesterolemia.

Lomitapide is an MTP inhibitor that, in a preliminary study in patients homozygote for FH, showed to be able to reduce LDL-c in up to 50.9% after four[4] treatment weeks[205]. In the recently concluded Long Term, Follow-on Study of Lomitapide in Patients With Homozygous Familial Hypercholesterolemia phase III study (ClinicalTrials.gov:NCT00943306), lomitapide was administered at a dose of up to 60 mg/day for 56 weeks to 29 patients, with an LDL-c average of 336 mg/dL in treatment with several hypolipemiants. A reduction of 50.2% in LDL-c and 56.1% in triglycerides was seen in 26 weeks. During that period, three patients left the study due to gastrointestinal adverse effects and three withdrew their consent.

Until now, there is no study with sample size and clinical results that determine safety and efficacy in reducing cardiovascular events.

11.2. Squalene synthase inhibitor

The cholesterol biosynthesis cascade has several restriction enzymes, with HMG CoA reductase being of the first ones and squalene synthase being the last one. Some squalene synthase inhibitors were discovered along time. Laropiprant was one of the inhibitors that proceeded to clinical studies, with a 23% reduction in LDL-c at the maximum dose of 100 mg/day[206]. In spite of being an inhibition of the same metabolic path, an additive effect was seen in the therapeutic combination of statins and lapaquistat in preliminary studies[207]. Lapaquistat has proceeded to phase III clinical trials, but studies with high dose (100 mg/kg) were interrupted due to the liver toxicity detected by the raise in transaminases. It is still unknown whether the adverse event was a drug class effect or a specific effect. Squalene synthase inhibition can accumulate squalene precursors, which could be responsible for hepatotoxicity.

11.3. Proprotein convertase subtilisin kexin inhibitor type 9 (PCSK9)

PCSK9 regulates plasma cholesterol concentrations by inhibiting the LDL uptake by its liver receptor. Subjects presenting mutations related to reduction in PCSK9 function present lower LDL-c concentrations and lower cardiovascular disease risk[208]. Antibodies and antisense molecules for PCSK9 are being developed and phase II and III studies are ongoing. PCSK9 inhibitors decrease LDL-c in 20% to 50%[208]. However, there is no evidence of clinical benefit or safety until now.

11.4. Thyroid hormone analogues

Thyroid hormone analogues reduce LDL-c and other lipoproteins by selective action on the liver LDL receptor, without the adverse effects of thyroid hormones on the cardiovascular system. For example, eprotirome is bound to the beta triiodothyronine receptor, facilitating the liver receptor expression for LDL. In a controlled randomized study with placebo in dyslipidemic patients using the maximum tolerated statin doses, eprotirome in 25-100 mcg/day for 12 weeks reduced LDL-c in 22% to 32%[209]. There were similar reductions in triglyceride, apo B100, and Lp(a) concentrations. This study still showed a 5% reduction in HDL-c with the maximum eprotirome dose. There was a reduction in free thyroxin concentrations with eprotirome use; however, these concentrations remained within the normalcy limits. There are no studies on this drug related to cardiovascular disease.

11.5. Antisense oligonucleotides (ASO)

Antisense oligonucleotides are small nucleotide sequences (DNA or RNA) that are especially bound to messenger RNA and inhibit protein synthesis by interfering with the translation of the message transmitted by the latter. Injected in the subcutaneous tissue, these molecules inhibit the apolipoprotein B100 synthesis in the liver and thus reduce VLDL, LDL, and Lp(a) plasma concentrations.

Mipomersen is a second generation ASO already in advanced development phase, and must be approved for homozygous FH soon. The medicine is administered by weekly subcutaneous injection at a 200-mg dose. There are phase III studies with follow-up of up to 104 weeks in patients presenting heterozygous and homozygous FH, besides patients presenting polygenic hypercholesterolemia refractory to conventional treatment.

At a dose of 200 mg/week, mipomersen decreased LDL-c in 25% in average in the studied populations, with responses varying from one patient to another (2%-80%)[210]. In most studies, the patients used the maximum tolerated doses of statins and/or ezetimibe. Apo B100 and Lp(a) reductions were also of 25%-30%. The main side effects of mipomersen are reactions at the injection site, flu-like symptoms, and accumulation of liver fat. Until now, there is no evidence of cardiovascular benefit.

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