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POSITION STATEMENT

Consensus document on diagnosis and management of familial hypercholesterolemia from the Italian Society for the Study of Atherosclerosis (SISA)

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KEYWORDS
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Abstract *Aims:* Familial Hypercholesterolemia (FH) is a genetic disorder of lipoprotein metabolism that causes an increased risk of premature atherosclerotic cardiovascular disease (ASCVD). Although early diagnosis and treatment of FH can significantly improve the cardiovascular prognosis, this disorder is underdiagnosed and undertreated. For these reasons the Italian Society for the Study of Atherosclerosis (SISA) assembled a Consensus Panel with the task to provide guidelines for FH diagnosis and treatment.
Data synthesis: Our guidelines include: i) an overview of the genetic complexity of FH and the role of candidate genes involved in LDL metabolism; ii) the prevalence of FH in the population; iii) the

Abbreviations: ADH, Autosomal Dominant Hypercholesterolemia; ApoB-100, Apolipoprotein B-100; APOE, Apolipoprotein E; ARH, Autosomal Recessive Hypercholesterolemia; ASCVD, Atherosclerotic cardiovascular disease; CAC, Coronary artery calcium; CAD, Coronary artery disease; CIMT, Intima-media thickening of common carotid arteries; CNV, Copy-number variants; CT, Computed tomography; CTCA, Computed tomography coronary angiography; DLCN, Dutch Lipid Clinic Network; FH, Familial Hypercholesterolemia; GOF, Gain of function; HDL-C, High Density Lipoprotein cholesterol; HeFH, heterozygous FH; HoFH, Homozygous FH; LA, Lipoprotein apheresis; LDL-C, Low-density lipoprotein cholesterol; LDLR, LDL receptor; LDLRAP1, LDL-Receptor Adaptor Protein 1; LOF, Loss of function; LIPA, Lysosomal Acid Lipase Deficiency; NGS, Next-generation sequencing; PCSK9, Proprotein Convertase Subtilisin/Kexin Type 9; TG, Triglycerides.

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Atherosclerotic cardiovascular disease; Cholesterol-lowering therapies

clinical criteria adopted for the diagnosis of FH; iv) the screening for ASCVD and the role of cardiovascular imaging techniques; v) the role of molecular diagnosis in establishing the genetic bases of the disorder; vi) the current therapeutic options in both heterozygous and homozygous FH. Treatment strategies and targets are currently based on low-density lipoprotein cholesterol (LDL-C) levels, as the prognosis of FH largely depends on the magnitude of LDL-C reduction achieved by lipid-lowering therapies. Statins with or without ezetimibe are the mainstay of treatment. Addition of novel medications like PCSK9 inhibitors, ANGPTL3 inhibitors or lomitapide in homozygous FH results in a further reduction of LDL-C levels. LDL apheresis is indicated in FH patients with inadequate response to cholesterol-lowering therapies.

Conclusion: FH is a common, treatable genetic disorder and, although our understanding of this disease has improved, many challenges still remain with regard to its identification and management.

1. Introduction

The definition of Familial Hypercholesterolemia (FH) includes disorders with a semi-dominant or recessive pattern of inheritance, which were formerly defined as Autosomal Dominant Hypercholesterolemia (ADH) and Autosomal Recessive Hypercholesterolemia (ARH). Regardless of the type of transmission, these disorders are characterized by elevated plasma levels of low-density lipoprotein cholesterol (LDL-C) from birth, resulting from defects in the mechanism responsible for the receptor-mediated hepatic removal of LDL particles from plasma [1–4].

The genes involved in ADH include: 1) *LDLR* encoding the LDL receptor (LDLR) (ADH-1); 2) *APOB*, encoding the apolipoprotein B-100 (apoB-100), the major protein component of LDL, responsible for the binding of LDL particles to LDLR (ADH-2); and 3) *PCSK9*, encoding Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9), a protein that promotes the intracellular degradation of the LDLR (ADH-3). ADH is caused by loss of function (LOF) variants of *LDLR* and *APOB* genes or gain of function (GOF) variants of *PCSK9* gene (Table 1 and Fig. 1) [1,5].

ARH is due to LOF variants of *LDLRAP1* gene which encodes the LDL-Receptor Adaptor Protein 1, involved in the recruitment of the LDLR in clatrin coated pits on the cell membrane of hepatocytes and its cellular internalization (Table 1 and Fig. 1) [6].

The molecular complexity of FH derives from the fact that the causative variants in candidate genes can be present in 1 allele (heterozygous genotype) or in 2 alleles (homozygous genotype). Furthermore, the homozygous genotype can involve only one candidate gene (monogenic) or two different genes (digenic).

The molecular characterization of a large number of ADH patients has shown that >90% of them have a LOF variant of *LDLR* gene. More than 2500 variants of this gene have been annotated in the available data-bases. LOF variants of *APOB* gene which block the binding of LDL to LDLR have been found in 3–8% of FH patients. Fewer than 1% of patients have been found to carry a GOF variant of *PCSK9* gene, resulting in an increased lysosomal degradation of LDLR and in defective receptor-mediated hepatic uptake of plasma LDL [1,5]. Several pathogenic LOF variants of *LDLRAP1* gene were reported in the rare patients with ARH [6,7].

There are other genetic disorders of lipid metabolism mimicking the FH phenotype such as: Sitosterolemia (*ABCG5* or *ABCG8* gene variants) [8–10] and Lysosomal Acid Lipase Deficiency (*LIPA* gene variants) that are due to

Table 1 Genes associated with primary monogenic cause of high plasma levels of LDL cholesterol.

	Genes	Chr.	Pathogenic variants	Variant type	Inheritance	Prevalence of gene variants in FH patients
Classic FH	***LDLR***	19p13.2	>2500	LOF	AD (ADH-1)	92–94%
	APOB	2p24.1	~16	LOF	AD (ADH-2)	<5%
	PCSK9	1p32.3	~32	GOF	AD (ADH-3)	<0.5%
	LDLRAP1	1p36.11	~25	LOF	AR (ARH)	<1%
FH phenocopies	***APOE***	19q13.32	2	LOF	AD	<<<0.1%
	ABCG5	2p21	~45	LOF	AR (Sitosterolemia)	<<<1%
	ABCG8	2p21	~60	LOF	AR (Sitosterolemia)	<<1%
	LIPA	10q23.31	~100	LOF	AR (Lysosomal Acid Lipase Deficiency)	<1%

Chr: Chromosome, AD: Autosomal dominant, ADH: Autosomal dominant hypercholesterolemia, AR: Autosomal recessive; ARH: Autosomal recessive hypercholesterolemia, LOF: loss of function, GOF: gain of function.

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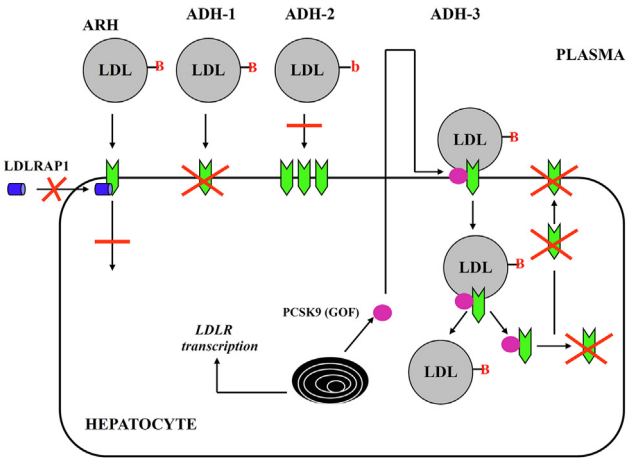

Figure 1 Effect of pathogenic variants of major candidate genes in Autosomal Dominant Hypercholesterolemia (ADH) and Autosomal Recessive Hypercholesterolemia (ARH).
ADH-1 is due to loss of function variants in *LDLR* gene that disrupt the activity of the LDL receptor (LDLR). ADH-2 is due to loss of function variants in the *APOB* gene that reduce the binding of LDL to the LDLR. ADH-3 is due to gain of function (GOF) variants in *PCSK9* gene which increase the capacity of PCSK9 to induce the lysosomal degradation of the internalized LDLR. ARH is due to loss of function variants in *LDLRAP1* gene that disrupt the activity of an adaptor protein involved in the positioning of the LDLR on the coated pits of the plasma membrane.

defects of cholesterol metabolism not primarily related to the LDLR pathway [11]. Only few patients are affected by these conditions as the lipid phenotype is present only in homozygotes. Recently, patients with FH-like phenotype with dominant transmission have been found to carry two extremely rare LOF variants of *APOE* gene [12,13].

Finally, it should be emphasized that a large percentage of adult subjects with primary hypercholesterolemia do not have a readily identifiable defect in the known candidate genes (they are designated phenotype positive/genotype negative subjects) [1,5]. It has been reported that a variable proportion of these subjects has inherited a combination of common genetic variants raising LDL-C (polygenic inheritance) whose additive effect would result in a "phenocopy" of FH [14–16].

Another genetic condition of hypercholesterolemia may be related to the elevation of lipoprotein (a) [Lp(a)], an LDL sized particle covalently linked to the unique glycoprotein apo(a) [17–19].

2. Epidemiology of familial hypercholesterolemia

Historically, the prevalence of heterozygous FH (HeFH) was considered to be 1 in 500 persons, as mathematically derived by the prevalence of the rarer homozygous form of FH detected in the London population [20]. In the past decade, this estimate has been refined mainly by the evidence from Danish population studies becoming higher than previously thought [21,22]. Later on, these findings were confirmed in other populations and large meta-analyses have determined that the global prevalence of HeFH is 1 in ~250–300 in most populations [23–25].

Prevalence data in Italy are scarce, mainly due to the lack of systematic screening programmes in the general population. Some local experiences, respectively using a cut-off of LDL-C ≥190 mg/dL or the Dutch Lipid Clinic Network (DLCN) criteria, reported estimates that range from 1.46% to 0.18% in the general population [26–28] and from 2.3% to 3.5% among statin-treated patients [26,29].

Meta-analyses clearly show how this prevalence is higher in subgroups of subjects with premature ASCVD. Indeed, a recent study showed that HeFH prevalence is 20-fold higher among those with premature ASCVD, and 23-fold higher among those with severe hypercholesterolemia [25]. Accordingly, data from the POSTER study on patients with a recent ASCVD or a planned revascularization procedure [30], and from the START Registry on patients with stable coronary artery disease (CAD) reported a prevalence of 1 in 20–40 [31].

The prevalence in the paediatric population is also poorly documented. Estimates from meta-analyses are comparable to those in adults (0.28%–0.36%) [23]. Experiences from some systematic screening programs report a prevalence of 0.1–0.3% [32,33]. An Italian experience of a screening program suggested that 17.2% of a cohort of unrelated hypercholesterolemic children (TC > 90° percentile), on the basis of familial phenotype, could have been classified as probable HeFH, with genetic confirmation obtained in about half of these children [34].

The homozygous form of FH (HoFH), on the other hand, is much rarer. Estimates on the Italian population suggested a prevalence between 1:350,000 and 1:450,000 [8,35]. In Italy, we found a high prevalence, about 1:40,000, of the ARH in the island of Sardinia [36], likely caused by a combination of genetic drift, consanguinity, and geographic isolation [37].

Meta-analyses also show a high variability of prevalence estimates, partly due to the different geographical and ethnic origin of the populations included, but mostly related to the criterion for defining the disease, which can be diagnosed either on a clinical or genetic basis. Since the presence of a pathogenic variant has been described in 30–80% of clinically diagnosed individuals [38] and since

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knowledge of the genetic basis of the disease is still evolving [39], it is not surprising that estimates of HeFH in the general population vary from 0.12% to 1.2% (overall pooled prevalence 0.40%) (BOX 1) [24].

In Italy, FH shows a highly heterogeneous genetic background. However, several pathogenic variants were recurrent in unrelated patients, leading to the identification of more than ten *LDLR* clusters, as for example that represented by carriers of the c.1646G > A, p. (G549D) (FH Palermo-1) mutation, including 78 families mainly distributed in the southern regions of mainland Italy and in Sicily, c.662 A > G, p. (D221G) (FH Padua-1) mutation, including 97 apparently unrelated families mostly distributed in the north-east areas of Italy, the c.1415_1418dupACAT, p. (Q474Hfs*63) (FH Savona-1) mutation, including 52 families in the Liguria region [40], the c.1775G > A, p. (G592E) (FH Foggia-1) mutation, described in 40 families in Southern Italy [41], and the c.2312-3C > A, p. (A771_I796del) (FH Naples-8) mutation, described in 39 families of the Campania region [42].

3. Screening approaches

In HeFH and HoFH the exposure to high and very high LDL-C levels respectively starts at birth and clinicians can calculate for each FH patient the LDL-C burden (years of exposure multiplied by average LDL-C) [43]. The clinical consequences of a such high LDL-C burden are: i) the acceleration of atherogenesis and the anticipation of the clinical cardiovascular events in comparison with the non-FH subjects; ii) the need to identify the FH patients, especially the FH children, in order to start, as early as possible, the therapeutical interventions [44].

The effectiveness of cardiovascular prevention in individuals with FH is strictly dependent on the timing of diagnosis: the earlier the patient is diagnosed the earlier treatment can be started and a better the clinical prognosis is expected. For this reason, various screening approaches have been proposed and implemented [45,46]. The simplest, and least expensive [47], is the cascade screening, i.e. the investigation of first-degree relatives of a person diagnosed with FH, especially when the diagnosis is confirmed by genetic testing. This approach plays a key role especially in pediatric age, as in this age group the clinical features of the disease are often still poorly manifested [48]. In most cases, FH subjects are identified through opportunistic screening, often starting with the finding of elevated cholesterol levels or following the development of a cardiovascular event at an early age, especially if accompanied by a family history of hypercholesterolemia or cardiovascular events. The main limitation for this approach is the strict dependence on the sensitivity and awareness of the clinician, whether general practitioner, pediatrician, endocrinologist, cardiologist or others [49,50]. Electronic extraction tools and clinical alert systems, integrated into digital health information systems, could be useful in the identification of index cases [26]. Finally, one possible approach is systematic screening at pre-school or school age. It is certainly more demanding in terms of resources, but has been proven to be cost-effective [51], as demonstrated by the example of Slovenia in Europe [52]. Results from the implementation of different strategies in different countries suggest that a combination of different approaches is probably the most effective way to enhance FH diagnosis. However, screening modalities need to be tailored to fit different economic, social and health system contexts.

BOX 1
Epidemiology of FH

FH is not a rare disease. It is important for doctors, paediatricians and specialists to be aware that HeFH can affect:

- 1 in ~250–300 of adult patients
- 1 in 20–40 of adult patients with hypercholesterolaemia (LDL-C >5.0 mmol/L, >190 mg/dL) or with coronary artery disease
- 1 in 6 of pediatric patients with hypercholesterolaemia (total cholesterol >90° percentile, 4.9 mmol/L, 190 mg/dL)

4. Molecular diagnosis of FH patients

4.1. Molecular analysis

Despite clinical diagnosis may identify FH patients allowing for an immediate treatment, molecular diagnosis is mandatory to: 1) confirm the diagnosis; 2) define the genetic status; 3) start the cascade screening.

Next-generation sequencing (NGS) improved the genetic analysis of FH patients allowing to analyze several genes at the same time. Two NGS approaches are possible: one based on a FH-specific gene panel and another one based on exome sequencing enabling the sequence of coding regions of all genes while focusing the variant analysis on causative genes [53]. NGS should be set-up with a high coverage allowing the detection of copy-number variants (CNV) at least in the *LDLR* gene, although in very rare cases CNVs in the other causative genes can be the FH pathogenic cause, such as in the case of the whole *PCSK9* gene duplication [54]. The genetic analysis of FH and methodological limitations are reported in Fig. 2.

Due to the partial phenotypic overlap between HeFH and HoFH, the genetic status of patients should be accurately defined by the status of variants as follows: 1) in case of presence of 2 different variants in the same gene, the analysis of variant segregation should be performed to determine if the 2 variants are present on the same allele (heterozygous variant) or on different alleles (bi-allelic also known as “compound heterozygous variants”); 2) in

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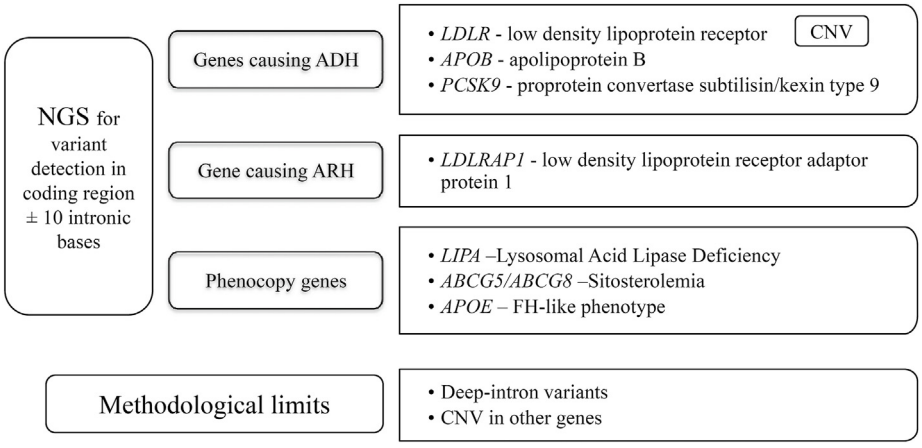

Figure 2 Genes and analytical approach for the genetic screening of FH.
Next-generation sequencing (NGS) should be set-up to detect small variants in the coding region and exon-intron boundaries (at least 10 intronic bases) of indicated genes and the copy number variants (CNVs) at least in the *LDLR* gene. CNV of *LDLR* gene could be eventually evaluated by Multiplex Ligation-dependent Probe Amplification (MLPA) (ADH, Autosomal Dominant Hypercholesterolemia; ARH, Autosomal Recessive Hypercholesterolemia.

case of detection of 2 copies of the identical variant ("true" or "simple" HoFH), the homozygous status cannot be directly established; in fact, it should be verified the absence of CNVs including the region of the variant to exclude a possible hemizygous/compound heterozygous status. If this is not possible by the methods employed, a segregation study should be performed to verify that the variant is present in both patient's parents.

The polygenic score for high LDL-C should be calculated in patients without rare variants in causative genes because it could represent a genetic basis of the hypercholesterolemia in a large number of patients [55].

4.2. Pathogenicity evaluation

An accurate pathogenicity evaluation is mandatory to correctly define the patient's genotype, in order to claim the variant pathogenicity only in case of scientific evidences. Variants should be evaluated according to the American College of Medical Genetics (ACMG) guidelines considering the FH-specific suggestions by Chora et al. [56]. The ClinGen consortium also improved the pathogenicity evaluation of *LDLR* variants [57]. As example, assigning the pathogenicity criterion related to the variant presence in databases it is not only based on the absence of the variant, but also on its presence with a low frequency, because of the high frequency of FH.

Databases containing pathogenic variants (HGMD professional, ClinVar and LOVD) with related scientific evidence (specific functional studies, co-segregation of variant with phenotype, etc.) should be consulted in order to correctly evaluate. Recently, a database of *LDLR* variants with a pathogenicity classification approved by the ClinGen FH Variant Curation Expert Panel was created; all included variants were revised by the experts and have been marked as FDA-approved (https://www.clinicalgenome.org/affiliation/50004/#heading_documents).

4.3. Genetic report

Genetic reports should clearly indicate the methodology used, the results obtained as well as specific comments on each single case. Table 2 lists the main aspects to be taken into account when drawing up the genetic report of a patient with FH.

4.4. Genotype-phenotype correlations

The identification of a pathogenic variant helps to estimate the cardiovascular risk assessment because among patients with the same LDL-C level, cardiovascular risk was found to be higher in carriers of a pathogenic variant than in non-carriers [58]. The identification of the variant type and the correct definition of the genetic status (HeFH or HoFH) can also improve risk stratification [59]. The different aspects of FH genetics and of their correlation with phenotype are reported in Table 3 [40,41,58,60–66,70].

5. Clinical diagnosis of familial hypercholesterolemia

Several clinical diagnostic criteria exist to define the probability that a given subject is affected by FH. In particular, the age of first detection of high LDL-C levels (>5.0 mmol/L in adults and >3.5 mmol/L in children; >190 mg/dL and >135 mg/dL, respectively), the presence of tendon xanthoma and premature ASCVD manifestations, and positive family history have to be considered key to the diagnosis [1]. All the information of clinical history is useful to build up a score (e.g. DLCN score), which gives an overview of the cardiovascular risk condition of the patient. Other diagnostic indexes may be used for the clinical diagnosis of FH beside the DLCN criteria, Simon Broome system [67], and World Health Organization (WHO) [68]. According to 2019 ESC/EAS Guidelines for the management of dyslipidaemias [63], the use of DLCN

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Table 2 Aspects relevant to patient diagnosis to be highlighted in the genetic report.

Section	Notes	Potential implications for physicians/ laboratory
Methods	Used methodology should be described in order to infer the procedure limits i.e. not analyzed genes, low coverage preventing CNV detection, etc. Method limits should also be specified in the genetic report.	It allows to establish if the genetic screening should be extended.
Results	Variants should be reported according to the current official nomenclature of the Human Genome Variation Society (HGVS -http://varnomen.hgvs.org/).	It allows to correctly identify the variant for cascade screening and for variant analysis in databases.
	Pathogenicity assessment should be reported in order to understand the variant role in the disease development.	It allows to correctly define the genetic status of the patient.
	Variant of uncertain significance (VUS) should be reported because several variants are classified as VUS due to lack of evidences and future studies could reveal their pathogenicity.	Patients with VUS could be easily reclassified as patients with pathogenic variants.
	In case of detection of two different variants, if no segregation study was performed, a precautionary sentence should report that the identified variants could be present both on the same allele or on the two different alleles, preventing the correct definition of the HeFH or HoFH status.	It allows to correctly define the patient's genotype as HeFH or HoFH.
	In case of detection of a variant at homozygous status, if the method not allowed to verify the absence of CNV or if no segregation study was performed, a precautionary sentence should report that the patient could be both a homozygote or a compound heterozygote due to an eventual CNV including the region of the variant.	The identification of an allele with a deletion is important for performing cascade screening.
Conclusions/additional comments	In case of detection of a pathogenic variant, the screening of patient's relatives should be recommended. In case of biallelic variants (homozygous or compound heterozygous status), it should be clearly indicated that all patient's children will be obligate HeFH.	The genetic report may induce the patient or the patient's doctor to perform the molecular analysis of relatives, thus identifying additional FH patients.
	In case of patients without pathogenic variants, the report should clearly indicate that additional causative variants could be present in relation to the method limits.	It allows to establish if the genetic screening should be extended.

score for the clinical diagnosis of FH is recommended. Patients with definite clinical diagnosis of FH early deserve intensive lipid lowering therapy because high LDL-C levels are the driver of an increased cardiovascular risk despite a genetic diagnosis.

It has been reported that 60–80% of patients with clinically-defined "definite" FH, are found to be positive at the molecular diagnosis, whereas in patients with "probable" FH only 21–44% are found to be positive. Additionally, the LDL-C level is "crucial", as the probability of finding a causative variant in FH-candidate genes is higher in the presence of extremely elevated plasma LDL-C levels [1]. It should be emphasized that an FH phenotype as defined by the currently used clinical diagnostic criteria (e.g. DLCN, Simon Broome) can have different genetic causes (monogenic/digenic, polygenic or multifactorial). To take into account this heterogeneity the term "FH syndrome" has been proposed [69].

6. Recommendations for diagnosis and clinical evaluation of heterozygous familial hypercholesterolemia

6.1. Clinical evaluation

There are several clinical data that can be useful to raise suspicion of FH. They are listed in BOX 2 and must be always part of the clinical screening in a patient with suspected FH. Nevertheless, the presence of other major cardiovascular risk factors (diabetes mellitus, smoking habits, arterial hypertension) as well as the exclusion of secondary hyperlipidemias should be performed. Routine biochemistry results would be useful in this context. Plasma triglycerides (TG), high density lipoprotein cholesterol (HDL-C), apoB and Lp(a) concentration measurements should be included in the baseline lipid panel of a FH patient.

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Table 3 Features of FH genetics which impact on the diagnosis and management of the FH patients.

Genotype-phenotype correlations	Clinical consequences
Presence of a pathogenic variant: 1) confers increased cardiovascular risk [58,70]; 2) is associated with higher LDL-C levels in adults and children [60–62].	Patients with a FH-causative variant should be considered at high cardiovascular risk according to the EAS guidelines [63].
Patients with 2 pathogenic variants (HoFH) show a worse phenotype than HeFH [60]. However, an overlap of LDL-C levels can be observed among patients with 2 variants and patients with one variant.	Based only on the LDL-C levels an accurate differentiation between HeFH and HoFH cannot be made. Molecular analysis enables to determine the genetic status, allowing to identify HoFH needing stronger therapies.
Among different variant types, patients with null variants show a worse phenotype than patients with defective alleles. In some cases, HeFH patients with a null allele show a phenotype similar to HoFH patients [58].	The identification of the causative variant and of the associated degree of protein impairment allows for a prognostic evaluation of patient cardiovascular risk.
Patients with pathogenic variants in the *LDLR* gene show a worse phenotype than patients with pathogenic variants in other genes [62].	
Patients with FH-causative variants (monogenic FH) and heterozygote for variants in FH-phenocopy genes (oligogenic FH) show a worse phenotype than monogenic FH [64].	The search for variants in FH-phenocopies can help to identify patients predisposed to develop more severe hypercholesterolemia than monogenic FH patients.
A large variability of phenotypes was observed among patients sharing the same variant/variant type [41,60].	The presence of a variant could lead to different LDL-C levels among patients sharing the same variant in a family
Incomplete penetrance was observed among HeFH carrying *APOB* variants functionally proved to cause decreased LDL binding to LDLR [65].	Within a family, not all members with the pathogenic variant in the *APOB* gene will develop hypercholesterolemia
Presence of a founder effect in specific geographic areas lead to a high prevalence of specific genetic variants, also explaining a high frequency of FH [40,66].	There is a high probability of genetically determined FH in regions with a founder effect of FH-causative variants, implying the need of a wider approach of molecular screening.

To better define the exposure of the patient to high LDL-C concentrations, it is useful to collect information on the degree of control of hypercholesterolemia in the past years in relation to drug interventions and lifestyle changes.

Further investigation should involve patient's relatives to establish: i) LDL-C levels; ii) presence of xanthoma and ASCVD events. The age of occurrence of first clinical manifestations of cardiovascular disease should also be recorded (BOX 2).

The presence of xanthoma should be systematically searched in patients with suspected FH. Also the type (tendons, cutaneous planar or tuberous) and sites (Achilles tendons, hand extensors tendons, interdigital, knees, elbows, other sites) of xanthoma need to be described. The thickness of Achilles tendons should be evaluated by palpation, with the awareness of the availability of echographic methods that are very sensitive for detection and useful for the follow up of local cholesterol accumulation. Corneal arcus is of diagnostic interest in younger patients, while in older ages (>70 years) it represents a nonspecific clinical finding, not necessarily associated with hypercholesterolemia (BOX 2).

Blood pressure measurement should be necessarily part of cardiovascular assessment of FH patient. Standard electrocardiogram (ECG) should be performed to detect signs of suspect myocardial ischemia, although a stress ECG is expected to be more sensitive for ischemia. Carotid ultrasound investigation has become very popular because of its non-invasiveness, relatively low cost and established predictive power for cardiovascular events. Bilateral carotid scan can be performed according to a standardized procedure, which allows measurement of intima-media thickening of common carotid arteries (CIMT), bifurcation and internal carotid

BOX 2
Clinical work-up in FH patients

Clinical History

- LDL-C levels (patients and relatives, first degree) – Age of detection of high LDL-C and time of exposure (patients)
- History of high LDL-C (patients) - History of drug management
- Cigarette smoking, Blood Pressure, Diabetes mellitus
- Exclusion of secondary hypercholesterolemia – Routine biochemistry – TG, HDL-C, ApoB, Lp(a)
- Xanthoma (type, sites, age of detection) and Corneal arcus (patients and relatives)
- Clinical Cardiovascular disease (MI, Stroke, PVD, Aortic aneurism) – Age of first event
- Use of DLCN criteria

Clinical examination

- Xanthoma (type and site) and Corneal arcus (age of first detection)
- Blood Pressure, ECG, Echocardiography, Carotid ultrasound (intima media thickening, plaque)
- Instrumental investigations, upon indication of the cardiologist

ApoB: apolipoprotein B; DLCN: Dutch Lipid Clinic Network; ECG: electrocardiogram; HDL-C: HDL cholesterol; LDL-C: LDL-cholesterol; Lp(a): Lipoprotein (a); MI: myocardial infarction; PVD: peripheral vascular disease; TG: triglycerides.

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arteries. The identification of carotid plaques is critical (areas of localized thickening >2.0 mm, with loss of parallelism of ultrasound interfaces). The presence of plaque calcification suggests relatively stable plaque, while echolucent plaques are those more prone to thrombotic complications. Echocardiography is part of the cardiologic assessment of FH patient. Aortic valve abnormalities are more specifically related to hypercholesterolemia. In general, the extension and severity of cardiovascular damage are directly related to hypercholesterolemia (severity and years of exposure) and to the type of causative pathogenic variant: negative allele (null allele) or allele with residual functional activity (defective allele) (see below) [70].

6.2. Management

FH patients should undergo at least one visit a year, even if clinical signs of cardiovascular disease are absent. Symptomatic FH patients should be evaluated and followed up by a clinical cardiologist. Early diagnosis and clinical control of cardiovascular complications imply communication and discussion with a cardiologist, who will also give advice on type and frequency of instrumental investigations. Lifestyle (diet, physical exercise, smoking habits) should be monitored. In this regard, non-medical support would be of great value, if available.

The lifestyle counseling including the change of dietary habits and the implementation of physical activity should be initiated as early as possible. Clinicians should be aware that the LDL-C lowering effects of dietary interventions aimed at reducing the intake of saturated fatty acids and increasing the intake of soluble fiber is relatively modest in patients with HeFH. The caloric restriction is useful in reducing body weight and triglyceride plasma levels. Evidence supporting the role of the Mediterranean diet in FH are limited but seem to suggest a favorable effect in reducing the LDL-C, apoB and C reactive protein levels. Moreover, when supplemented with plant sterols Mediterranean diet may reduce LDL-C, especially in FH children [71,72]. Limitations in physical exercise and working activity should be discussed with the patient, considering the issue of possible rehabilitative interventions. During follow-up visits, drug response should be investigated and possible treatment side effects identified and discussed with the patient.

7. Recommendations for diagnosis and clinical evaluation of homozygous familial hypercholesterolemia

7.1. Diagnosis of HoFH

Homozygous form of FH is a rare genetic disorder characterized by severely elevated levels of LDL-C and the occurrence of premature ASCVD very early in life. It is caused by bi-allelic pathogenic variants [73] affecting key proteins in the LDLR pathway [6].

According to the 2023 Consensus Panel on FH of the European Atherosclerosis Society (EAS) the diagnosis of HoFH can be made based on genetic or clinical criteria [74]. The Panel suggested that HoFH should be suspected if untreated LDL-C levels are >10 mmol/L (>~400 mg/dL), requiring further evaluation, including a detailed medical and family history and/or genetic testing.

Recently published data have confirmed that LDL-C levels in HoFH patients can overlap with those usually seen in HeFH. In two studies, patients with genetically confirmed HoFH had untreated LDL-C levels <12.9 mmol/L (<500 mg/dL) [75] with LDL-C ranging from 4.4 to 27.2 mmol/L (170–1053 mg/dL). Among the 125 homozygous ADH and 66 ARH patients characterized in Italy [6], 56 ADH (45%) and 22 ARH (33%) did not meet the classic diagnostic criteria for HoFH. Furthermore, patients with genetically confirmed HoFH treated with traditional lipid-lowering agents may exhibit treated LDL-C levels <8 mmol/L (<300 mg/dL). Thus, the diagnosis of HoFH should not be excluded based solely on LDL-C levels but must also include other supportive findings such as family history, early occurrence of ASCVD, lack of response to cholesterol-lowering treatments or genetic evidence. Even if there is not genetic evidence for the presence of two pathogenic variants, subjects with high LDL-C in the range of HoFH showing tendon and cutaneous xanthomata before the age of 10 years should be diagnosed as HoFH. It is worth to remember that xanthomas also occur in Sitosterolemia [76], which may be a phenocopy of HoFH as well as in Lysosomal Acid Lipase Deficiency, although this latter disorder has other distinguishing features.

All suspected HoFH patients should undergo molecular diagnosis, if available. This is crucial to tailor therapeutic management (see below) and for cascade screening to identify additional siblings with HoFH and HeFH.

7.2. Clinical management and proposed screening for ASCVD in HoFH

Once a diagnosis of HoFH is suspected, a consultation between lipid specialist and patients should be arranged and the patients should be managed under the long-term supervision of a lipidologist. At diagnosis, additional cardiovascular risk factors (i.e. blood pressure, weight, diet, exercise, smoking and alcohol use) should be assessed and re-evaluated at least twice a year together with the evaluation of treatment response.

HoFH is characterized by accelerated atherosclerosis, typically located at the aortic root and coronary ostia, even though other vessels (carotid arteries, descending aorta, and ileo-femoral and renal arteries) may be affected [77,78]. Therefore, all HoFH patients at diagnosis should be referred for the assessment of coronary and carotid arterial disease with full investigation as appropriate (see below).

Very recently, a large registry (HoFH International Clinical Collaborators –HICC) confirmed that the occurrence of major manifestations of ASCVD or aortic stenosis at diagnosis was as high as 36% in patients with HoFH. Moreover, one third of patients had supra-valvular aortic stenosis, which frequently required surgical intervention. These results confirm the need of early diagnosis and early

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evaluation of subclinical and overt ASCVD in all HoFH patients immediately after diagnosis.

In first place, non-invasive testing for asymptomatic cardiac ischemia should be considered in HoFH. If available, computed tomography coronary angiography (CTCA) every 5 years, or more frequently if clinically indicated, should be considered. Nevertheless, invasive coronary angiography is indicated in patients with clinical symptoms suggestive of ischemia or valve disfunction, or in the presence of findings of ischemia from non-invasive cardiac evaluation. Although stress echocardiography may not be considered as preferred first line test [79], it could be useful when CTCA is not available or not possible for clinical reasons. Aortic valve and aortic root should be evaluated by echocardiography at presentation and annually.

8. Diagnosis and clinical management in special FH populations

8.1. FH in fertile women

Three important issues for women with FH need to be addressed: a) contraception; b) pregnancy; c) breastfeeding.

Contraception is recommended for women who are taking any LDL-C lowering drugs (except for bile acid sequestrants) employed for FH treatment because their potential teratogenic effect [80]. However, risks and benefits of contraception need to be balanced individually. The thrombotic risk associated with hormonal contraceptive methods should be carefully assessed and combined formulations, particularly those of third generation should be avoided [81,82]. Thus, non-hormonal techniques for contraception are recommended (namely a non-hormonal intrauterine device) or if this is not feasible, oral contraceptives with the lowest thrombotic risk should be selected, preferring progesterone-only based contraceptives [80].

Regarding pregnancy, a preliminary counseling must be considered as a crucial clinical step for both HoFH and HeFH women. This counseling should be oriented to increase the awareness about risks and expectations of pregnancy, considering also the side effects of lipid-lowering drugs. Moreover, counseling for women with HoFH must include the information that their children will have HeFH and, if their partner has HeFH, the risk of newborn child with HoFH is 50%. To this regard, the partner of a FH woman should always be tested for FH if the desire to become pregnant has been expressed.

For these reasons, FH women should be advised that pregnancy need to be discussed at multidisciplinary level and closely monitored. In fact, pregnancy, particularly in HoFH, is associated with further increase in LDL-C and lipid-lowering therapies are usually discontinued with possible consequences on cardiovascular morbidity and mortality. If a FH woman is planning to conceive, it is generally recommended to discontinue statins and ezetimibe therapy from one to three months before conception [83].

The lipid-lowering therapeutic attitude towards pregnant FH women must take into account several general considerations. In the first place, clinician should assess the severity of FH and verify the presence of a preexisting cardiovascular disease that could be exacerbated during pregnancy. Another consideration arises from the fact that several evidence has reassured on the safety of statins during pregnancy [84]. A statin-based therapy should be proposed to selected HoFH or severe HeFH women during pregnancy [85,86] mainly in those women with an established ASCVD. The discontinuation of statin therapy during pregnancy should be considered especially for FH women who have been optimally managed earlier in life, as a continuous, prolonged adherence to lipid-lowering therapy before pregnancy could prevent pregnancy-related complications such as acute coronary syndrome [80]. At this regard, HeFH women could be more easily eligible to treatment discontinuation than HoFH women due to less severe phenotypic features of the disease.

In HoFH female during pregnancy lipoprotein apheresis (LA) may be considered as the treatment of choice [85,86]. In view of the well-known changes in volemia during pregnancy, the pressure gradient across the aortic valve and root should be assessed by echocardiography in all pre-conception HoFH women and monitored during pregnancy.

Regarding breastfeeding, lipid-lowering therapies, with the exception of bile-acid sequestrants, must be discontinued during lactation. No definitive guidelines on the management of FH women during breastfeeding are available, although a duplex management strategy is possible: maintain lactation for breastfeeding deferring FH treatment or resume lipid-lowering therapy giving up breastfeeding. In every case, it is desirable that the decision should be shared between the woman and the physician.

8.2. FH in children

In the pediatric population, FH diagnosis is based on laboratory values, patients' family history, clinical and genetic criteria (BOX 3). Early identification of FH children represents a crucial factor to achieve a normal life expectancy, as well as to diminish risk of early events and mortality [52,87]. However, the finding of FH-typical clinical manifestations represents a critical issue in young HeFH, due to the limited timeframe exposure to high LDL-C levels, leading to delayed cardiovascular involvement. In fact, the main biochemical and clinical parameters employed in phenotype-based diagnosis, such as elevated LDL-C levels or detection of premature coronary heart disease, tendon xanthoma, and/or corneal arch, show a poorly clinical usefulness in very young children [88]. Xanthomas and corneal arch are rarely observed in childhood, except from the most severe HoFH forms. Furthermore, LDL-C levels typically display relevant fluctuations, thus hindering the identification of cut-offs specific for a timely diagnosis [88,89]. The diagnosis based upon the DLCN criteria has not been validated in children and adolescents [90]. In

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BOX 3
When FH should be suspected in children and what to do.

1.1 If one parent has an ascertained HeFH, all of the proband's seemingly healthy children should be addressed to proper screening to ascertain/exclude HeFH

1.2 In a child with repeated abnormal LDL-C levels (>3.5 mmol/L; >135 mg/dL) after exclusion of secondary causes of hypercholesterolemia,
- i) perform clinical and laboratory investigation in parents
- ii) reconstruct history of ascendents,
- iii) pay attention to the unfrequent scenario of a "de novo mutation" if parents are mutation-negative, or the particular case of adopted child

1.3 In children with repeated abnormal LDL-C levels (>10.3 mmol/L; >400 mg/dL) and eventual evidence of cutaneous and/or tendon xantomatosis
- i) suspect the presence of HoFH
- ii) analyze the biochemical phenotype in parents to confirm a dominant transmission (ADH) or recessive transmission (ARH) or phenocopies (Sitosterolemia or Lysosomal Acid Lipase Deficiency).
- iii) perform genetic analysis of the genes responsible for ADH, ARH, Sitosterolemia and Lysosomal Acid Lipase Deficiency.

presence of elevated LDL-C levels secondary causes should be excluded, including hypothyroidism, nephrotic syndrome, obstructive liver disease, obesity, anorexia nervosa or drug-induced dyslipidemia. One way to improve the low diagnostic rates of FH in most of European populations consists in implementation of FH screening in childhood. The FH pediatric screening was recognized by the European Commission Public Health Best Practice Portal as one of the best practices in non-communicable disease prevention. Imaging of increased CIMT and abnormal flow-mediated dilation have been reported in young HeFH patients, and several studies documented an improvement in these preclinical markers of atherosclerosis upon lipid-lowering treatment. The reduction of LDL-C level is the main goal of therapy to prevent worsening of ASCVD.

The pediatric FH patients should be encouraged to maintain adherence to lifestyle modifications even after pharmacological treatment initiation. A healthy diet rich in vegetables, fruits, whole grains, fish and low-fat products should be suggested, together with systematic physical activity.

Children and adolescents with HoFH should receive a consultation by a pediatric cardiologist for clinical and instrumental evaluation of the atherosclerosis burden using non-invasive imaging, such as CTCA and carotid ultrasonography, as well as exercise testing or functional cardiac imaging, as clinically indicated. Non-invasive cardiac and vascular imaging techniques may be also used during follow-up of FH children and adolescents to assess the impact of lipid-lowering treatment.

Prenatal diagnosis on chorionic villi samples is possible, upon family's specific request, in those cases when the causative mutation has been previously identified in both parents at heterozygous state [91,92].

9. Imaging techniques for evaluating subclinical atherosclerosis in HeFH and HoFH patients

Patients with FH carry a higher risk of premature ASCVD [23,93]. In untreated patients with HoFH, development of ASCVD and/or aortic disease (valvular and supravalvular) is expected as early as in the first decade of life [77]. In fact, it has been reported that in patients <16 years old, 10% have clinical ASCVD, 40% subclinical evidence of ASCVD, and 40% aortic valve disease (regurgitation or stenosis). In those between 16 and 30 years old, 90% show clinical ASCVD. Yet, a systematic investigation of the cost effectiveness of traditional and advanced cardiovascular imaging techniques to detect subclinical ASCVD is lacking in patients with either HoFH or HeFH, and therefore recommendations can be made only based on a consensus agreement. Previous studies [77,94] suggest the utility of the ultrasound of carotid intima-media thickness, computed tomography (CT)-based coronary artery calcium (CAC) quantification, and magnetic resonance based aortic atherosclerosis evaluation in vascular assessment in patients affected by FH. More recently, CTCA has emerged as the most accurate non-invasive imaging modality to assess coronary artery atherosclerosis in symptomatic and asymptomatic patients. CAC has been shown to be a surrogate marker for atherosclerosis, with the calcium score 'Agatston score' being proportional to atherosclerosis plaque burden and cardiovascular risk [93]. However, further prognostic studies are needed to evaluate the value of cardiac CT for stratification of subjects who may have a baseline risk higher than the general population, such as FH patients, and no recommendations about the use of advanced non-invasive imaging in asymptomatic FH patients are reported in the current guidelines.

Current guidelines classify HeFH patients without other cardiovascular risk factors at high ASCVD risk and target LDL-C value to be achieved with therapy is < 70 mg/dL. Patients with HeFH who have at least one other cardiovascular risk factor or who have already had a cardiovascular event or have subclinical atherosclerosis, are at very high cardiovascular risk and the target LDL-C value is < 55 mg/dL [95,96]. As a consequence, detection of

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subclinical atherosclerosis has gained increasing relevance in order to perform accurate ASCVD risk stratification and to guide therapy, and should be considered especially in asymptomatic HeFH patients with a history of premature familial ASCVD events.

In conclusion, patients with HoFH should be investigated at diagnosis, even if asymptomatic, for ASCVD, aortic valvular disease and aortic supravalvular stenosis using CTCA and echocardiography, whereas functional tests (e.g. stress imaging techniques) or preferably anatomic CTCA techniques are to be considered for assessing ASCVD in HeFH. Initial Coronary (CT) Angiography is recommended for HoFH as per the EAS recent guidance [74].

10. Treatment of familial hypercholesterolemia

10.1. Drug treatment of HeFH

The aim of the drug therapy of HeFH is to lower LDL-C levels to decrease cardiovascular risk. The greater the absolute LDL-C reduction, the greater the cardiovascular risk reduction [97]. Treatment goals should be identified after the assessment of total ASCVD risk.

As indicated above, patients with HeFH and ASCVD or with another major risk factor are classified to be at very-high-risk, and an LDL-C reduction of >50% from baseline and an LDL-C goal of <1.4 mmol/L (<55 mg/dL) are recommended; <1.0 mmol/L (<40 mg/dL) if the patient experienced a second vascular event within 2 years. Patients with HeFH without known ASCVD and without other risk factors are classified to be at high-risk, and an LDL-C reduction of >50% from baseline and an LDL-C goal of <1.8 mmol/L (<70 mg/dL) are recommended [63].

Cholesterol-lowering medications should be taken regularly and initiated as soon as possible after the diagnosis of HeFH. Statins in addition to dietary and lifestyle modifications are the first-line drugs. Other drugs include ezetimibe, bempedoic acid, PCSK9 inhibitors, bile acids sequestrants and inclisiran. The average LDL-C reduction ranges from ≈30% with moderate intensity statins to ≈50% with high intensity statins and ≈85% with association therapy with PCSK9 inhibitor plus high intensity statin plus ezetimibe (Table 4). The intensity of therapy should be selected to achieve the recommended reduction in LDL-C based on the person's estimated risk of ASCVD.

Treatment should be initiated with high-intensity statin therapy (atorvastatin 40/80 mg, rosuvastatin 20/40 mg). In most cases statins should be taken in combination with ezetimibe [98]. PCSK9 inhibitors (alirocumab [99] and evolocumab [100]), taken subcutaneously every two weeks and inclisiran [101] every six months, are recommended in very-high-risk patients with HeFH when the treatment goal is not achieved on maximal tolerated statin plus ezetimibe (BOX 4). PCSK9 inhibitors are also recommended in patients who cannot tolerate statins.

Bempedoic acid is a novel non-statin drug that inhibits cholesterol biosynthesis in the same pathway as statins [102]. It is administered as a prodrug and is only converted to active drug in the liver and not muscles. Bempedoic acid, alone or in combination with ezetimibe and PCSK9 inhibitors, may represent a valid alternative in patients intolerant to statins.

Bile acid sequestrants (colestiramine [103] and colesevelam) can be used as third-line agents in patients not at target for LDL-C and in those with statin intolerance. However, they are poorly tolerated and have limited efficacy on LDL-C reduction [104].

Inclisiran, a small interfering RNA which reduces the intrahepatic expression of PCSK9, is now available for the treatment of patients not at target for LDL-C [105]. After an initial dose, the drug will be given again subcutaneously after three months, and then twice a year.

High intensity statin treatment may be associated with several side effects. In particular muscle adverse events (myalgias, muscle weakness, myositis) are the most commonly reported. However, most statin intolerant patients can tolerate them when reinitiated at a later time and possibly with a different statin [106]. True statin-intolerant patients can be managed with alternative therapies including bempedoic acid and PCSK9 inhibitors.

Cholesterol-lowering treatment should be carefully monitored to improve compliance. Given the very high baseline LDL-C plasma levels few patients reach LDL-C goals [107]. Patient and physician should regularly reassess tolerance to medication and share benefits of treatment, and therapeutic plan.

10.2. Drug treatment of HoFH

Lifestyle intervention and maximal tolerated dose of a high efficacy statin plus ezetimibe, are the mainstays of

Table 4 Percent LDL-C reduction with different cholesterol-lowering treatments.

Drug treatment	% LDL-C reduction
Moderate intensity statins (*atorvastatin* 10–20 mg; *rosuvastatin* 5–10 mg; *simvastatin* 20–40 mg; *pravastatin* 40–80 mg)	30%
High intensity statins (*atorvastatin* 40–80 mg; *rosuvastatin* 20–40 mg)	50%
High intensity statins + ezetimibe 10 mg	65%
PCSK9 inhibitors (*alirocumab*, *evolocumab*, subcutaneously every two weeks)	60%
High intensity statins + PCSK9 inhibitors	75%
High intensity statins + PCSK9 inhibitors + ezetimibe 10 mg	80%
Bempedoic acid 180 mg	20%
Bempedoic acid 180 mg + ezetimibe 10 mg	40%

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BOX 4
Highlights of lipid-lowering treatment of HeFH

1. Assess total ASCVD risk (*high or very high*)
2. Identify LDL-C treatment goals (*<70/<55/ <40* mg/dL *and 50% reduction*)
3. Share the goals, benefits and possible side effects of therapy with the patient and involve him in the therapeutic decision-making process
4. Encourage a healthy lifestyle (*healthy diet, smoking cessation, physical activity*)
5. Start therapy with high intensity statins (*atorvastatin* 40/80 mg or *rosuvastatin* 20/40 mg) plus ezetimibe 10 mg
6. Add PCSK9 inhibitor (*alirocumab* or *evolocumab* taken subcutaneously every two weeks) if treatment goal is not achieved on maximal tolerated statin plus ezetimibe
7. Regularly reassess tolerance to medication and evaluate treatment adherence
8. Discuss the results and give positive feedbacks for successfully reaching the treatment goals

SCVD: atherosclerotic cardiovascular event; LDL-C: LDL cholesterol.

treatment [108,109]. Under those circumstances LDL-C reduction largely depends on the residual LDLR activity and statins, alone and in combination with ezetimibe, have been proved to reduce ASCVD risk in HoFH and should be started at diagnosis [48,110].

Bile acid sequestrants are largely ineffective and are not recommend in HoFH [111].

Liver transplant often coupled with heart transplantation, has been an option to treat HoFH. Most patients still require post-transplant lipid-lowering therapies and the need of long-term immunosuppressant therapy [112]. Moreover, progression of aortic valve disease has been observed despite the surgical procedure [113]. Therefore, liver transplant should be considered only as last option when conventional or innovative drugs are not available.

Lipoprotein apheresis (LA) is recommended to be started by age 3 and no later than 8 years. LA is effective in acutely reducing LDL-C (55–70%) [114] with a mean long-term reduction ranging from 21% to 36% [115]. Major limitations include limited availability worldwide and costs together with the high impact on social and emotional burden (i.e., educational attainment, employment related issues) in HoFH treated patients [116,117]. Although mitigated, aortic valve stenosis and ASCVD still progress in a consistent number of LA treated patients [118]. Despite this, when available, LA should be offered to HoFH patients, particularly in the pediatric population and in pregnancy, possibly with a weekly frequency.

The management of HoFH has rapidly progressed over the last decade with the availability of several innovative drugs.

PCSK9 inhibitors (monoclonal antibodies, PCSK9 mAb) administered every other week or monthly may be used in HoFH. The response to PCSK9 inhibitors depends largely on the LDLR residual activity with no or poor effectiveness in those patients carrying two null alleles (LDLR-NEG alleles) or ARH [119,120]. Overall, these drugs are generally safe and are associated with an LDL-C percent reduction up to 30% [100,121,122]. On the other hand, the treatment with inclisiran, a small interfering RNA (siRNA) against PCSK9, did not reduce LDL-C levels in patients with HoFH despite substantial lowering of PCSK9 levels [123]. The use of PCSK9 inhibitors on top of statins and ezetimibe tailoring depends on the molecular diagnosis. If the lipid phenotype or molecular diagnosis suggests LDLR-NEG or ARH, the use of PCSK9 inhibitors will be ineffective.

Lomitapide is a small molecule inhibiting the microsomal triglyceride transfer protein (MTTP) to reduce production of very low-density lipoprotein (VLDL) and LDL thus acting independently of LDLR residual activity. Lomitapide inhibits also intestinal MTTP, thereby reducing chylomicrons and determining fat malabsorption. Results from clinical trials have showed that it reduces LDL-C by 40–70% in HoFH with an acceptable safety and tolerance profile [124] and therefore, since 2013 lomitapide can be used in Italy to treat HoFH [125]. These results have been confirmed by real world-data [126–130] confirming the efficacy data and reassuring on the medium-term safety. Despite this, the major limitations associated with this drug are the high cost and the potential warning on the long-term liver-safety. The use of lomitapide in all HoFH as III-line therapy or as II-line therapy in LDLR-NEG HoFH and ARH patients is recommended. This drug should be used with the support of an expert dietician to reduce the side effects associated with steatorrhea. In agreement with the Italian Medicines Agency (AIFA) disposition [131], the liver function as well as regular screening for steatohepatitis/fibrosis or progressive liver disease should be strictly monitored.

The angiopoietin-like 3 (ANGPTL3) protein has emerged in the last years as a very attractive therapeutic target since homozygous carriers of LOF mutations of *ANGPTL3* are characterized by a marked reduction of ApoB and ApoA1 containing lipoproteins and reduced ASCVD risk [132–134]. Evinacumab is a monoclonal antibody that inhibits ANGPTL3 [135] whose use was recently tested in a Phase III trial (ELIPSE trial) showing that the infusion of 15 mg/kg of body weight once every 4 weeks was associated with a 47% reduction of LDL-C independently from the background HoFH genotype. No clinically relevant side effects were registered during the trial. Considering the outbreaking results of the ELIPSE trial, the use of evinacumab was approved for treating HoFH patients from the age of 12 by EMA and FDA, and, more recently from AIFA. The use of evinacumab is recommended in all HoFH as III-line therapy or as II-line therapy in LDLR-NEG HoFH or ARH patients as an alternative to lomitapide or in combination with it. The choice to use lomitapide or evinacumab

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Table 5 LDL cholesterol-lowering treatments, their efficacy and side effects in HoFH.

	Name	Mechanism of action	Administration route	Dosage	LDL-C lowering effect	Adverse event	References
LDLR dependent	**Statins**	Reduction of cholesterol biosynthesis through HMG-CoA reductase inhibition ↑ LDLR activity	Oral	Variables dosage daily	Variable LDL-C-lowering effect depending on the residual LDLR activity	•Myalgia •Myopathy •Liver toxicity	[136,137]
	Ezetimibe	↓ Cholesterol absorption ↑ LDLR activity	Oral	10 mg daily	Plus 10%−15% on top of statins	•Liver toxicity	[141−143]
	Alirocumab-Evolocumab	↓ LDLR degradation (monoclonal antibodies)	Subcutaneous	75/150 mg−140 mg bi-monthly	21%−35%	•Injection site reactions •Flu like symptoms	[100,121,122,138−140,144]
LDLR independent	**Lomitapide**	↓ Microsomal triglyceride transfer protein activity Inhibition of LDL production	Oral	Variables dosage daily	LDL-C (50%) ApoB (49%)	•Hepatic steatosis •Gastrointestinal disorders •Impaired liver function	[124,126−128,130,145−150]
	Evinacumab	Inhibition of ANGPTL3 ↑ lipoprotein lipase activity ↓ VLDL secretion	Subcutaneous	15 mg/kg monthly	LDL-C (43.4% −49.1%)	•Flu-like symptoms	[134,135,151−156]
	Lipoprotein Apheresis	Physical removal of LDL by selective and non-selective methods	Extracorporeal treatment of whole-blood or plasma	Weekly or biweekly	LDL-C (acutely 55−70%; long-term 21−36%) Lp(a): acutely 55 −70%	•Hypotension •Iron deficiency anemia (long-term)	[114,115]

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may be related to patient preferences (oral vs. intravenous injection) and reimbursement policies especially for combined treatment as well as the tolerability of the treatment.

HICC registry data highlighted that HoFH patients that do not receive adequate combination of lipid-lowering therapies, have higher on-treatment LDL-C levels and shorter survival free from cardiovascular events [78]. A combination of all the available therapeutic tools to achieve LDL-C targets in HoFH and reduce the associated cardiovascular disease burden is recommended. Table 5 provides an overview of the lipid-lowering therapies available to treat FH categorized in two groups based on the mechanism of action: LDLR dependent and LDLR independent drugs [100,114,115,121–124,126–128,130,134–140,141,143–156].

10.3. Treatment of HeFH and HoFH patients during pediatric age

The cornerstone of pharmacotherapy in HeFH children and adolescents is represented by the use of statins [48] maximally tolerated/age-appropriate dose [157,158]. Pharmacological treatment in HeFH is approved for the age ≥6 years. Pravastatin and rosuvastatin are approved for use in children aged 8 and 6 years, respectively. As statin use is contraindicated in pregnancy and lactation, suitable contraception is necessary to all post-pubertal young girls on lipid-lowering treatment. A second drug to use is ezetimibe, which has been shown to reduce LDL-C by additionally 15–20%, when added to statins and is well tolerated. Lipoprotein apheresis is the main recommended treatment for HoFH children, usually low responders to pharmacotherapy. LA should be initiated as soon as possible, starting even before the age of 8 years (in very severe cases, as soon as 3 years of age). A single treatment can lower LDL-C by 55–70%, while the long-term therapy has proved to result in the regression of xanthomas and atherosclerotic plaques and optimize the prognosis of cardiovascular events [90,159]. In the most severe cases, weekly treatment frequency is recommended.

Other viable pharmacological options may be taken into account before considering LA. The phase 3, part B, open-label study with evinacumab in pediatric patients with HoFH, showed that this pharmacological option is effective and safe in reducing LDL-C level in this difficult clinical setting [160]. Recently, the Italian Medicines Agency (AIFA) has approved the use of evinacumab for adolescent subjects (>12 years) with HoFH. Lomitapide may represent another opportunity for HoFH children. The ongoing APH-19 (NCT04681170) phase 3 trial, lomitapide significantly reduced LDL-C levels in pediatric HoFH patients and safety was consistent with the known profile of drug, with no new signals identified [161].

Conclusions

In Italy, as in other European countries, FH is still underdiagnosed and/or identified late in life when ASCVD already developed. This updated SISA Consensus document provides a pragmatic guidance to improve early diagnosis and to plan appropriate LDL-C lowering therapies in this condition. This document is addressed not only to lipidologists but also to other physicians (i.e. general practitioners, cardiologists, pediatricians) to promote a better care and to improve the cardiovascular health of FH patients.

Contribution statement

Francesco Angelico, Sebastiano Calandra, Manuela Casula, Angelo B. Cefalù, Laura D'Erasmo, Giuliana Fortunato, Pasquale Perrone-Filardi, Paolo Rubba, Patrizia Suppressa, equally contributed to the manuscript.

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Declaration of competing interest

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