REVIEW ARTICLE

# Familial Hypercholesterolemia: Developments in Diagnosis and Treatment

Gerald Klose, Ulrich Laufs, Winfried März, Eberhard Windler

## SUMMARY

Background: Familial hypercholesterolemia (FH) is a congenital disorder of lipid metabolism characterized by a marked elevation of the plasma concentration of LDL (low-density lipoprotein) cholesterol beginning in childhood and by the early onset of coronary heart disease. It is among the commonest genetic disorders, with an estimated prevalence in Germany of at least 1 per 500 persons.

Method: Review of pertinent literature retrieved by a selective search.

Results: FH is underdiagnosed and undertreated in Germany. It is clinically diagnosed on the basis of an elevated LDL cholesterol concentration (>190 mg/dL [4.9 mmol/L]), a family history of hypercholesterolemia, and early coronary heart disease, or the demonstration of xanthomas. The gold standard of diagnosis is the identification of the underlying genetic defect, which is possible in 80% of cases and enables the identification of affected relatives of the index patient. The recommended goals of treatment, based on the results of observational studies, are to lower the LDL cholesterol concentration by at least 50% or to less than 100 mg/dL (2.6 mmol/L) (for children: <135 mg/dL [3.5 mmol/L]). The target value is lower for patients with clinically overt atherosclerosis (<70 mg/dL [1.8 mmol/L]). Statins, combined with a health-promoting lifestyle, are the treatment of choice. Lipoprotein apheresis is used in very severe cases; its therapeutic effects on clinical endpoints and its side effect profile have not yet been documented in randomized controlled trials.

Conclusion: Familial hypercholesterolemia is a common disease that can be diagnosed simply and reliably on clinical grounds and by molecular genetic testing. Timely diagnosis and appropriate treatment can lower the risk of atherosclerosis in heterozygous patients to that of the general population.

Private practice for Internal Medicine, Gastroenterology, Cardiology and Preventional Medicine: Dres. T. Beckenbauer und S. Maierhof and joint practice Dres. K. W. Spieker and I van de Loo, Bremen: Prof. Dr. med. Klose

Department of Internal Medicine III—Cardiology, Angiology and Intensive Care Medicine, Saarland University Medical Center, Homburg/Saar: Prof. Dr. med. Laufs

Medical Clinic V (Nephrology, Hypertensiology, Endocrinology, Diabetology, Rheumatology), Department of Internal Medicine, Mannheim Medical Faculty, University of Heidelberg, Mannheim: Prof. Dr. med. März

Clinical Institute of Medical and Chemical Laboratory Diagnostics, Medical University Graz: Prof. Dr. med. März

Synlab Academy, Synlab Services GmbH, Mannheim: Prof. Dr. med. März

Preventive Medicine, Department of General and Interventional Cardiology, University Hospital Hamburg-Eppendorf, Hamburg: Prof. Dr. med. Windler

Familial hypercholesterolemia (FH) is characterized by congenital abnormalities in low-density lipoprotein (LDL) catabolism. Its main clinical consequences are premature atherosclerotic diseases. FH is an illustration of the causal relationship between elevated LDL cholesterol concentrations and vascular disease (1, 2). The extent, timing, and frequency of clinical complications vary and are related to the severity of the molecular defect and to additional risk factors (3). Research into FH led to the discovery of the LDL receptor (LDLR) and paved the way for the development of HMG-CoA reductase inhibitors (statins) (4–6).

In most European countries, and probably also in Germany, FH is diagnosed in only 15% of cases, typically not until after a heart attack has occurred at an early age or following multiple myocardial infarctions in a family (7, 8). There are no studies investigating the prevalence rate in a representative German sample. A frequency of 1 in 500 is assumed for heterozygous FH (HeFH) in the population of Germany *(Table 1)*. Danish and Norwegian data suggest an even higher prevalence rate of between 1 in 200 and 1 in 300 (9, 10). In some populations HeFH prevalence is extremely high as a result of founder effects (increased frequency of a genetic abnormality in an isolated population) (11–15).

Lowering LDL cholesterol concentrations can effectively reduce the particularly high risk that results from elevated LDL cholesterol concentrations and exposure from childhood onwards. This makes it essential to provide diagnosis and treatment as early as possible (16–19). An update is needed as a result of new findings concerning FH diagnosis and treatment, because primary, i.e. congenital, lipid metabolism disorders such as FH are not covered thoroughly even by recent guidelines (20–22). The current US guideline on cholesterol-lowering therapy makes no mention of genetic lipid metabolism disorders (23).

## Pathogenesis

FH is an autosomal dominant disorder of lipid metabolism. In 85% to 90% of cases it is caused by a mutation in the LDL receptor (LDLR) gene (1, 2). Reduced LDLR number or LDLR dysfunction inhibits the uptake and breakdown of LDL and subsequently increases hepatic cholesterol synthesis (4, 5, 25). This leads to considerable increases in plasma LDL cholesterol concentrations and to extra-plasmatic deposits. There are currently more than 1700 LDLR mutations

**TABLE 1**

Forms of manifestation, prevalence rates, and clinical characteristics of familial hypercholesterolemia
(autosomal dominant hypercholesterolemia[*1])

| Manifestation | Prevalence[*2] | Typical LDL cholesterol concentrations | Clinical characteristics |
|---|---|---|---|
| Heterozygous | 1 in 500 | 190 to 450 mg/dL (4.9 to 11.6 mmol/L) | Familial clustering, tendon xanthomas of the extensor tendons of the joints of the fingers and Achilles tendons, xanthelasmata, arcus corneae, arthritis, manifestations of cardio-vascular disease from early adulthood onwards possible |
| Homozygous or combined hete-rozygous | 1 in 1 000 000 | 400 to >1000 mg/dL (10 to >26 mmol/L) and above possible | Familial clustering, interdigital planar xanthomas, cutaneous xanthomas, tendon xanthomas of the extensor tendons of the joints of the fingers and Achilles tendons, xanthelasmata, arcus corneae, arthritis, severe cardiovascular atherosclerosis, and atherosclerosis of the aortic valve in early childhood possible |

[*1] Umbrella term for hypercholesterolemia caused by LDL receptor mutations (85 to 90%), apolipoprotein B-100 mutations (2 to 7%), or PSCK9 (proprotein convertase subtilisin/kexin type 9) gain-of-function mutations (less than 3%). Mutations of LDL receptor adapter protein 1 (LDLRAP1) are extremely rare; these cause autosomal recessive hypercholesterolemia (ARH) and lead to a phenotype corresponding to familial hypercholesterolemia.

[*2] Prevalence figures are based on assumptions made for Western populations. The prevalence rate of 1 in 500 is probably also an underestimate for Germany. Higher prevalence rates are found in some populations, e.g. 1 in 270 for HeFH in specific Canadian populations (11); a particularly high prevalence rate of 1 in 72 is found in South Africa (12). A HoFH prevalence rate of 1 in 860 000 is reported for Germany (e48), 1 in 640 000 for the Netherlands (13), 1 in 275 000 for Canada (11), and as high as 1 in 30 000 for South Africa (12).

**Figure 1:**
Broadening of the Achilles tendon in familial hypercho-lesterolemia, caused by tendon xanthomas



listed in databases of mutations (e.g. LDLR@www.ucl.ac.uk/ldlr/LOVDv.1.1.0/).

In addition to LDLR mutations, genetic defects in apolipoprotein B-100 and protease PCSK9 (proprotein convertase subtilisin/kexin type 9) can also cause elevated LDL cholesterol (25).

It is not possible to distinguish reliably between the three known causes of FH on a phenotypic, i.e. clinical, basis. The term "autosomal dominant hypercholeste-rolemia (ADH)" has therefore been coined (1, 2, 26). This review article uses the conventional, synonymous term "FH." This should not be confused with the rare condition autosomal recessive hypercholesterolemia, which is caused by two defective alleles of LDLR adapter protein 1 (LDLRAP1) (26).

### Clinical presentation

Heterozygous FH patients present elevated LDL cholesterol concentrations ranging from 190 mg/dL to over 450 mg/dL (4.9 mmol/L to over 10.3 mmol/L)

(Table 1) (27). Homozygous carriers may have an LDL cholesterol concentration of between 400 mg/dL (10.3 mmol/L) and more than 1000 mg/dL (>26 mmol/L). Dichotomous classification of FH as either heterozygous (HeFH) or homozygous (HoFH) is often inaccurate in molecular genetic terms, since usually two different mutations underlie a phenotypic 'homozygote'; these individuals are therefore hetero-zygous carriers.

A patient's prognosis is worsened by early manifes-tations, particularly coronary manifestations, of athe-rosclerotic plaques. In HoFH in particular, supra-valvular or valvular aortic stenosis with possible in-volvement of the coronary ostia can give rise to an un-favorable prognosis (28–30). Tendon and cutaneous xanthomas are typical outward signs of abnormal cholesterol storage (Figure 1). The most common lo-cations of tendon xanthomas are the Achilles tendon and extensor tendons of the joints of the fingers; xanthomas of the patellar and triceps tendons are less common. In homozygous individuals, cutaneous xanthomas in the gluteal (Figure 2), elbow, interdigital, or prepatellar regions are also typical.

More frequent but less specific are cholesterol deposits in the form of xanthelasmata and the develop-ment of arcus corneae before the age of 45 (31). Arthro-pathies caused by precipitation of cholesterol crystals in the synovial fluid have been described (32–34).

### Prognosis

In homozygous FH, fatal myocardial infarction is pos-sible even in early childhood.

The age at which cardiovascular complications manifest in heteroygous FH can vary greatly. Early manifestation is possible from the age of 30, or even earlier, if other risk factors such as elevated lipopro-tein(a) (Lp(a)) or low HDL cholesterol are present. However, they may not manifest until the age of 50 or above, or they may remain clinically inapparent (35, 36).

Genetic mutations in FH patients mean that they have a risk of coronary heart disease events eight times the risk of unaffected relatives (RR 8.54; 95% CI 5.29 to 13.8) (37). FH patients with xanthomas have three times the risk of coronary heart disease of those without xanthomas (38). It has been estimated that approximately 20% of FH patients do not develop symptomatic coronary heart disease at any point during their lives, possibly thanks to healthy lifestyles and/or genetically determined protective factors and due to other, competing causes of death (16).

## Diagnosis

In the past, data on the prevalence and prognosis of FH was often based on algorithms with clinical criteria such as the Simon Broome Register or the Dutch Lipid Clinic Network (27).

On the basis of these criteria, the following procedure for clinical practice has been tried and tested *(Figure 3):*

- Diagnosis is based on LDL cholesterol concentrations. FH should be suspected if LDL cholesterol is above 190 mg/dL (4.9 mmol/L), or above 155 mg/dL (4.0 mmol/L) in children under the age of 16. The additional presence of tendon xanthomas or arcus corneae before the age of 45 years makes FH even more likely.
- The second step is family history. If first-degree relatives with LDL cholesterol above 190 mg/dL (4.9 mmol/L) or early coronary heart disease (before the age of 60 for women or 55 for men) are identified or if first-degree relatives have xanthomas, the index patient can also be clinically diagnosed with FH, with no further clinical manifestation required.

Cascade screening can be used as an effective strategy to identify as many affected individuals as possible. Cascade screening is the testing of relatives of the index patient. This procedure is particularly effective for FH, because the dominant mode of inheritance means that half the index patient's relatives are affected. This strategy is also cost-effective if combined with genetic diagnostics (39, 40).

Abnormal cholesterol metabolism can be masked by concurrent statin treatment, which currently also seems to be reducing the frequency of xanthomas. This makes it even more important not to overlook familial clustering of cardiovascular events.

Because of the genetic heterogeneity of the clinical phenotype, it is advisable to include LDLR, the receptor-binding domain of apolipoprotein B-100, PCSK9, or in individual cases LDLRAP1 in molecular genetic diagnosis.

If FH is defined as the presence of at least one functionally significant mutation at one of these gene loci, the analytical sensitivity and specificity of genetic diagnosis are virtually 100% (e1). The positive predictive value of evidence of familial hypercholesterolemia for a manifestation of cardiovascular disease is age-dependent; the lifelong figure is approximately 60%.

With good clinical preselection based on the severity of the LDL cholesterol abnormality, familial manifestation, and potential stigmata, the pathobiochemically relevant mutations can be identified in up to 80% of suspected cases (7, 36, e2).
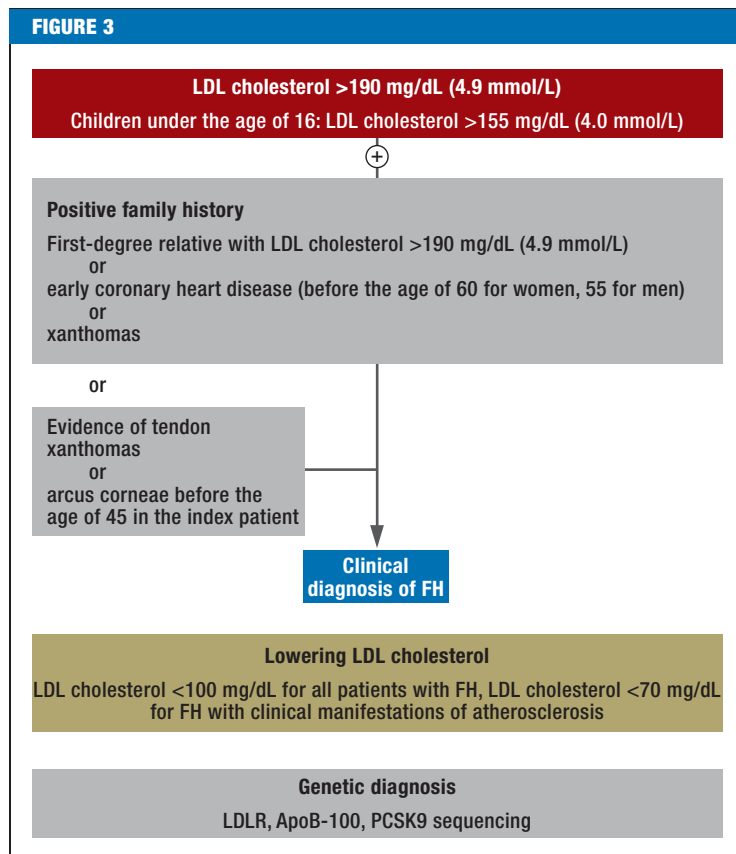
In other cases, either mutation occurs in genes that have not yet been identified as being relevant to FH or the cause of hypercholesterolemia is polygenic (e2). If there is no evidence of a disease-causing mutation, diagnosis is based on clinical characteristics (20–22). The costs of genetic diagnosis are only incurred in full once, for the index patient, because after a relevant mutation has been identified it can be the subject of a targeted search in relatives.

Legal issues, regarding insurance or employment behavior for example, are covered by the German Genetic Diagnostics Act (e3). Whether relatives benefit if significant risk factors for disease are discovered in a patient is the subject of ethical discussion (e4). The elderly and those already affected by atherosclerotic complications do not benefit from genetic diagnosis unless there are younger family members, as intensive statin therapy is indicated in any case. FH must be diagnosed according to guideline-based identification of clinical and subclinical manifestations of atherosclerosis (7, 21, 22).

In summary, molecular genetic diagnostics appears to be worthwhile in the following cases:

- More precise prognostic evaluation and justification of early, intensive treatment in younger hypercholesterolemia patients.
- Simpler cascade screening in the patient's relatives, including children and mutation carriers with a less marked phenotype, once one or more disease-causing mutations have been identified in an index patient (37, 40, e1).
- Because earlier detection in children of affected adults is possible, prompt treatment can be started, beginning with an appropriate lifestyle.
- Standard risk tables (SCORE, Framingham, PROCAM) underestimate the coronary heart dis-

## FIGURE 3

**LDL cholesterol >190 mg/dL (4.9 mmol/L)**

**Children under the age of 16: LDL cholesterol >155 mg/dL (4.0 mmol/L)**

⊕

**Positive family history**

First-degree relative with LDL cholesterol >190 mg/dL (4.9 mmol/L)
or
early coronary heart disease (before the age of 60 for women, 55 for men)
or
xanthomas

or

**Evidence of tendon xanthomas**
or
arcus corneae before the age of 45 in the index patient

**Clinical diagnosis of FH**

**Lowering LDL cholesterol**

LDL cholesterol <100 mg/dL for all patients with FH, LDL cholesterol <70 mg/dL for FH with clinical manifestations of atherosclerosis

**Genetic diagnosis**

LDLR, ApoB-100, PCSK9 sequencing

Procedure for identifying and treating patients with familial hypercholesterolemia in clinical practice

ease risk of FH patients, as they do not address lifetime risk (21); the need for treatment for elevated LDL cholesterol concentrations can be underestimated at younger ages (under 50) in particular.

- Specific diagnosis will improve compliance: both the thoroughness of treatment and patients' own treatment compliance (e4, 40).

### Differential diagnosis

Differential diagnosis must distinguish between familial hypercholesterolemia and polygenic hypercholesterolemia, familial combined hyperlipidemia, type 3 hyperlipoproteinemia, and severe forms of secondary hypercholesterolemia (hypothyroidism, cholestasis). In cases of massive hypertriglyceridemia, VLDL (very low density lipoproteins) and remnant particles as a proportion of cholesterol can contribute to a considerable increase in total cholesterol concentrations which is otherwise seen only in HoFH (29, e6). If cutaneous xanthomas occur in early childhood to adolescence, phytosterolemia (ABCG5/8 membrane transporter mutations) should be suspected; if there is a combination of xanthomas and neurological symptoms, cerebrotendinous xanthomatosis (sterol 27-hydroxylase mutations) should be suspected. Both diseases are detected by determining plasma non-cholesterol sterol concentrations (e7, e8).

### Treatment

There are no randomized controlled trials to enable evidence-based treatment recommendations for FH to be made; such trials do not seem to be ethically justifiable. Retrospective analyses and cohort studies show improved prognosis for FH patients who receive cholesterol-lowering therapy (e9, e10). For HoFH, relative risk is reduced to 0.34 for death and 0.49 for cardiovascular events, according to a retrospective comparison of lipid-modifying therapy available in the past and that available now (e9).

In a Dutch HeFH cohort (n = 2146), the risk of myocardial infarction, 6.7 per 1000 patient years, of FH patients given statin treatment fell to close to the figure for the general population of Rotterdam, 4.1 per 1000 patient years (e10). The absolute risk for untreated individuals was 60.5 per 1000 patient years. Guidelines recommend a target LDL cholesterol concentration of less than 100 mg/dL (2.6 mmol/L) for adults with FH (7, 21). For FH patients with clinical manifestations of atherosclerosis, the recommendation is to lower LDL cholesterol concentrations to less than 70 mg/dL (1.8 mmol/L). If these targets cannot be achieved, LDL cholesterol must be reduced by at least 50% using the strongest statin at the highest tolerated and authorized dose (7, 21, 22, 39, e12).

The findings of a systematic review and meta-analysis of seven studies indicate that there is insufficient evidence to support the target of 135 mg/dL (3.5 mmol/L) proposed for children over the age of 10 (e13). Before the age of 10 treatment is based on non-pharmacological measures, particularly diet.

### Lifestyle measures

Lifestyle measures focus on those that have been shown to be effective in reducing cardiovascular risk in general, particularly regular physical exercise and strict abstention from smoking. Cholesterol intake is also reduced by replacing animal fats, which are mostly saturated fatty acids, with plant oils, most of which are unsaturated fatty acids (e14). However, elevated LDL cholesterol in patients with FH cannot be sufficiently reduced through diet; statin treatment is always required. Given that there are numerous dietary recommendations insufficiently supported by evidence, it is possible that ineffective dietary recommendations may significantly compromise a patient's quality of life.

### Pharmacological treatment

The most important component of HeFH therapy is statin treatment. Meta-analyses of numerous randomized controlled trials are available on the general benefits of statin treatment (6).

Data on FH patients is limited to retrospective analyses and cohort comparisons (e9, e10). Even homozygous receptor-negative (mean 15% lower LDL cholesterol) and receptor-defective (mean 26% lower LDL cholesterol) FH patients have some response to statins (e15). The most common adverse effects of statins, which are not known to differ between FH

**TABLE 2**

**Lipid-modifying treatment for familial hypercholesterolemia**

| Manifestation of heterozygous FH | Manifestation of homozygous FH |
|---|---|
| Statins*[1] | Statins*[1] |
| Cholesterol resorption inhibitor (ezetimibe)*[2] | Cholesterol resorption inhibitor (ezetimibe)*[2] |
| Anion exchanger*[3] | Anion exchanger*[3] |
| | MTP inhibition (lomitapide)*[4] |
| LDL apheresis | LDL apheresis |
| | In selected cases: liver transplant (historically: portocaval shunt) |
| Undergoing clinical development:<br>– PCSK9 inhibitors<br>– Apolipoprotein B antisense oligonucleotide | Undergoing clinical development:<br>– PCSK9 inhibitors<br>– Apolipoprotein B antisense oligonucleotide |

*[1] Although statins are the first-line therapy for HeFH, HoFH patients have less or no response to this treatment because statins reduce cholesterol by increasing expression of LDL receptors that are absent in HoFH. Guidelines recommend use of the strongest statins at the highest authorized dose tolerated by the patient.

*[2] Restriction of enteral resorption of both dietary and biliary cholesterol by using ezetimibe to inhibit an intestinal cholesterol transporter, Niemann–Pick C1-like protein 1 (NPC1L1), increases the LDL-lowering effects of statins. This mechanism of action explains a therapeutic effect beyond that of stain treatment in HoFH (e46, e47).

*[3] Anion exchangers lead to lowered LDL cholesterol by inhibiting enterohepatic bile acid circulation. Use is restricted due to relatively poor tolerability, but this can be improved using the newer bile acid sequestrant colesevelam (e22).

*[4] Inhibition of synthesis of very-low-density lipoprotein (VLDL), the precursor of low-density lipoprotein (LDL)

patients and others, are muscular symptoms, increased liver enzyme activities, and a higher incidence of diabetes mellitus (OR: 1.09; 95% CI: 1.12 to 1.17).

For children, the severity of clinical manifestation, including vascular findings such as intima-media thickness (IMT) and the age at which relatives develop cardiovascular complications, are taken into account on an individual basis when deciding when to begin pharmacological treatment (e13).

A Cochrane analysis of nine placebo-controlled trials of statin treatment in childhood found no evidence of increased adverse drug effects for trial durations of up to 48 weeks (e16). The following statins have been approved in Germany:

- Pravastatin from the age of eight
- Fluvastatin from the age of nine
- Atorvastatin and rosuvastatin from the age of 10.

Lipid concentrations typically increase in pregnant women both with and without FH. No fetal malformations were observed in a study of statin exposure during pregnancy (e17–e19), but the terms of statin authorization themselves require treatment to be interrupted for the duration of pregnancy. Contraception must be used during statin treatment in fertile women.

If an HeFH patient's LDL cholesterol concentration is not sufficiently lowered using the highest tolerated dose of a powerful statin, combined therapy with the cholesterol resorption inhibitor ezetimibe and/or an anion exchanger (colesevelam, which has better tolerability than cholestyramine) is used *(Table 2)* (e20–e22).

### Lipid apheresis

Initial positive results of plasma exchange in HoFH patients led to the development of extracorporeal treatment methods for selective LDL elimination. As clinical experience increased, the treatment indication was extended to include HeFH patients and high-risk patients who had failed to achieve their target LDL cholesterol (e23–e29). There is no evidence from randomized controlled trials on the benefits of treatment. The plausible premise for the effectiveness of lipid apheresis is based on clinical observation and retrospective comparison of event rates before and after the beginning of regular apheresis therapy.

The requirement for cost reimbursement is more than 12 months of documented maximum dietary and pharmacological treatment without sufficient reduction of LDL cholesterol. Lipid apheresis is performed at least every two weeks, usually every week, and leads to a more than 50% decrease in LDL cholesterol and Lp(a) compared to baseline. Acute side effects can include a drop in blood pressure, headache, fatigue, edema, and dizziness; frequencies of up t o 3% are reported for these (e26). Complications at shunt sites and long-term iron-deficiency anemia are also possible. More serious adverse effects reported include allergic reactions, hemolysis, and shock. There is no systematically collated information on the frequency or severity of adverse events for these procedures; such information is expected from registry data (e29).

### Surgery

Before current treatment measures became available, ileal bypass was sometimes performed. This worked by interrupting enterohepatic bile acid circulation (e30). The evidence of the clinical benefit of this as found in the POSCH study is an early demonstration of the effectiveness of lowering LDL cholesterol (e31). Historically, a portocaval shunt was fitted (e32). Liver

transplantation to restore LDLR function in otherwise treatment-refractory HoFH has been described as successful in one patient (e33).

### New developments

Further treatment options are being sought as a result of failure to achieve target LDL cholesterol concentrations, lack of tolerability, and limited access to treatment (e34–e45). Such further options include lomitapide, a microsomal triglyceride transfer protein (MTP) inhibitor. Lomitapide is authorized by the EMA for HoFH only, among other reasons because it increases hepatocellular fat and transaminase activities (e35).

The antisense oligonucleotide mipomersen, which has been approved by the FDA but not the EMA, lowers LDL cholesterol by blocking messenger RNA for apolipoprotein B-100. This effect lowers LDL-cholesterol even in HoFH patients by 49% (e36–e38).

There are particularly high expectations for serine protease PCSK9 inhibition (e39, e41–e45). This is attractive because it has been observed that carriers of loss-of-function PCSK9 mutations have lower LDL cholesterol from birth onward and a significantly lower risk of cardiovascular events than the normal population (e40). The good tolerability and lipid modification of monoclonal antibodies specific for PCSK9 in patients with FH described in phase II trials are also being confirmed in ongoing phase III trials (e44, e45).

### KEY MESSAGES

- FH patients are at significantly increased risk of atherosclerosis as a result of both elevated LDL cholesterol concentrations and exposure from childhood onwards.

- Effective treatment for LDL cholesterol can reduce the risk to the same level as in the general population.

- Clinical diagnosis is based on LDL cholesterol concentrations above 190 mg/dL (4.9 mmol/L) together with a family history of hypercholesterolemia or early atherosclerosis, or evidence of xanthomas.

- Molecular genetic methods contribute to higher specificity of diagnosis, justification of intensity of treatment, and simpler screening of the patient's relatives.

- New treatment options to lower LDL cholesterol levels are being tested in randomized clinical trials.

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**Corresponding author:**
Prof. Dr. med. Gerald Klose
Center for Internal Medicine, Gastroenterology, Cardiology, and Preventive Medicine
Drs. T. Beckenbauer and S. Maierhof
Am Markt 11
28195 Bremen, Germany
klose.bremen@t-online.de

## REVIEW ARTICLE

# Familial Hypercholesterolemia: Developments in Diagnosis and Treatment

Gerald Klose, Ulrich Laufs, Winfried März, Eberhard Windler

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