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.


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...
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 hypercholesterolemia (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 heterozygous carriers.

A patient’s prognosis is worsened by early manifestations, particularly coronary manifestations, of atherosclerotic plaques. In HoFH in particular, supravalvular or valvular aortic stenosis with possible involvement of the coronary ostia can give rise to an unfavorable prognosis (28–30). Tendon and cutaneous xanthomas are typical outward signs of abnormal cholesterol storage (Figure 1). The most common locations 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 development of arcus corneae before the age of 45 (31). Arthropathies caused by precipitation of cholesterol crystals in the synovial fluid have been described (32–34).

**Prognosis**

In homozygous FH, fatal myocardial infarction is possible even in early childhood.

The age at which cardiovascular complications manifest in heterozygous FH can vary greatly. Early manifestation is possible from the age of 30, or even earlier, if other risk factors such as elevated lipoprotein(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 apparent (35, 36).

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**Table 1**

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

<table>
<thead>
<tr>
<th>Manifestation</th>
<th>Prevalence*2</th>
<th>Typical LDL cholesterol concentrations</th>
<th>Clinical characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heterozygous</td>
<td>1 in 500</td>
<td>190 to 450 mg/dL (4.9 to 11.6 mmol/L)</td>
<td>Familial clustering, tendon xanthomas of the extensor tendons of the joints of the fingers and Achilles tendons, xanthelasmata, arcus corneae, arthritis, manifestations of cardiovascular disease from early adulthood onwards possible</td>
</tr>
<tr>
<td>Homozygous or combined heterozygous</td>
<td>1 in 1 000 000</td>
<td>400 to &gt;1000 mg/dL (10 to &gt;26 mmol/L) and above possible</td>
<td>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</td>
</tr>
</tbody>
</table>

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* 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).
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 pathobiologically 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-
**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
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 to 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 surgery

TABLE 2

<table>
<thead>
<tr>
<th>Lipid-modifying treatment for familial hypercholesterolemia</th>
<th>Manifestation of heterozygous FH</th>
<th>Manifestation of homozygous FH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statins*1</td>
<td>Statins*1</td>
<td></td>
</tr>
<tr>
<td>Cholesterol resorption inhibitor (ezetimibe)*2</td>
<td>Cholesterol resorption inhibitor (ezetimibe)*2</td>
<td></td>
</tr>
<tr>
<td>Anion exchanger*3</td>
<td>Anion exchanger*3</td>
<td></td>
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<tr>
<td>LDL apheresis</td>
<td>LDL apheresis</td>
<td></td>
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<tr>
<td>Undergoing clinical development:</td>
<td>Undergoing clinical development:</td>
<td></td>
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<tr>
<td>– PCSK9 inhibitors</td>
<td>– PCSK9 inhibitors</td>
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<tr>
<td>– Apolipoprotein B antisense oligonucleotide</td>
<td>– Apolipoprotein B antisense oligonucleotide</td>
<td></td>
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<tr>
<td>MTP inhibition (lomitapide)*4</td>
<td></td>
<td></td>
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<tr>
<td>Undergoing clinical development:</td>
<td></td>
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<tr>
<td>– PCSK9 inhibitors</td>
<td>– PCSK9 inhibitors</td>
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<tr>
<td>– Apolipoprotein B antisense oligonucleotide</td>
<td>– Apolipoprotein B antisense oligonucleotide</td>
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</tbody>
</table>

*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 statin treatment in HoFH (e46, e47).

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

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

**REFERENCES**


For eReferences please refer to: www.aerzteblatt-international.de/ref3114
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eREFERENCES