

## Guidelines for Diagnosis and Treatment of Familial Hypercholesterolemia 2017

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### Statement

1. Familial hypercholesterolemia (FH) is an autosomal hereditary disease with the 3 major clinical features of hyper-LDL-cholesterolemia, premature coronary artery disease and tendon and skin xanthomas. As there is a considerably high risk of coronary artery disease (CAD), in addition to early diagnosis and intensive treatment, family screening (cascade screening) is required (**Recommendation level A**)

2. For a diagnosis of FH, at least 2 of the following criteria should be satisfied:

① LDL-C  $\geq 180$  mg/dL, ② Tendon/skin xanthomas, ③ History of FH or premature CAD within 2nd degree blood relatives (**Recommendation level A**)

3. Intensive lipid-lowering therapy is necessary for the treatment of FH. First-line drug should be statins. (**Recommendation level A, Evidence level 3**)

4. Screening for CAD as well as asymptomatic atherosclerosis should be conducted periodically in FH patients. (**Recommendation level A**)

5. For homozygous FH, consider LDL apheresis and treatment with PCSK9 inhibitors or MTP inhibitors. (**Recommendation level A**)

6. For severe forms of heterozygous FH who have resistant to drug therapy, consider PCSK9 inhibitors and LDL apheresis. (**Recommendation level A**)

7. Refer FH homozygotes as well as heterozygotes who are resistant to drug therapy, who are children or are pregnant or have the desire to bear children to a specialist. (**Recommendation level A**)

**Key words:** Adult, Familial hypercholesterolemia, Homozygote, Heterozygote, Diagnosis criteria, Treatment guidelines, Lifestyle habits, Drug therapy, LDL apheresis

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## 1. Introduction

Familial hypercholesterolemia (FH) is an autosomal hereditary disease with the 3 major clinical features of 1) hyper-LDL-cholesterolemia, 2) premature CAD and 3) tendon and skin xanthomas. FH is dominantly inherited except autosomal recessive hypercholesterolemia (ARH), a very rare form.

FH patients have hyper-LDL-cholesterolemia from their birth and atherosclerosis progresses from a young age, resulting in having a high risk of CAD. Untreated heterozygous FH (HeFH) men 30 to 50 years of age and women 50 to 70 years of age, respectively, are likely to develop CAD such as myocardial infarction and angina pectoris<sup>1)</sup>. Actually, it has been reported that the risk of CAD is 13 times higher in untreated HeFH than non-FH<sup>2)</sup>. In medical practice for FH patients, conducting early diagnosis and appropriate treatment as well as family screening (cascade screening) is very important to prevent premature death as hyper-LDL-cholesterolemia itself is asymptomatic. HeFH patients in Japan are observed in one in 200–500 of the general population, similar to those in other countries, suggesting that there are over 300,000 patients. Accordingly, FH is the most frequently encountered genetic disease in daily practice. Although there has been no accurate study on FH diagnosis rates in Japan, they are assumed to be low. Therefore, there is an urgent need to raise them.

Furthermore, a diagnosis of FH in a single patient makes it possible to discover new FH patients in the same family and initiate early treatment. Thus, clinicians should be aware that FH is an autosomal dominant inheritance disease, and should conduct early diagnosis and appropriate treatment not only for the patient but also his/her family.

### 1.1 FH Causative Genes

As stated in the diagnostic criteria, it is not necessary for a diagnosis of FH to perform genetic analysis. However, in addition to hyper-LDL-cholesterolemia, the presence of mutation in LDL receptor or other genes involved in LDL receptor pathway gives a definitive diagnosis of FH. Unfortunately, the number of facilities capable of genetic analysis is limited. On the other hand, if a proband is genetically diagnosed as FH, this constitutes a definite diagnosis of FH in the family.

FH is caused by pathogenic mutations in genes of the LDL receptor, apolipoprotein B-100 (Apo-B100) and proprotein convertase subtilisin/kexin type 9 (PCSK9) which play an important role in LDL receptor pathway. Mutations in causative genes are found in 60–80% of clinically diagnosed HeFH<sup>3, 4)</sup>. FH homozy-

gotes (HoFH) are defined as having 2 pathogenic mutations in the 2 alleles of the causative genes (Fig. 1).

#### 1.1.1 LDL Receptor

LDL receptor gene mutations are the cause of the disease in much of genetically diagnosed FH (80% or more). To date, over 1,000 mutations in LDL receptor gene have been reported as the cause of FH worldwide (<http://www.ucl.ac.uk/fh/>). Even in Japan alone, over 100 mutations have been reported.

#### 1.1.2 Apo B-100

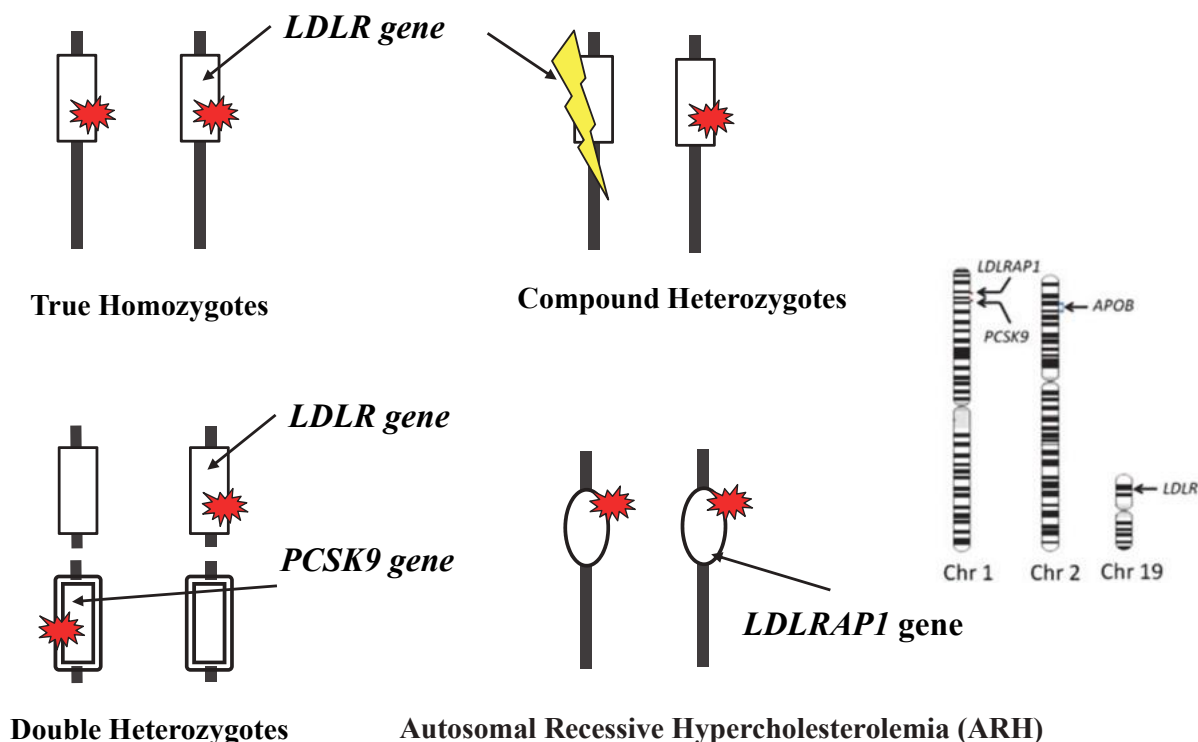
Since apolipoprotein B-100 (apo B-100) is a ligand for the LDL receptor, patients with apo B-100 mutations, which is called familial defective apolipoprotein B-100 (FDB), have a similar clinical manifestation to classical FH with LDL receptor mutations. Although prevalence is high in white western populations, it is low in other ethnic groups. Interestingly, no case has been reported in Japan. Serum lipid levels are usually lower in FDB patients than in those with LDL receptor mutations.

#### 1.1.3 PCSK9

As PCSK9 is involved in the degradation of the LDL receptor, a gain-of-function mutation will decrease LDL receptors and cause hyper-LDL-cholesterolemia. Clinically, there is no distinction between homozygotes for PCSK9 gain-of-function mutations with serious disease and LDL receptor mutation homozygotes<sup>5, 6)</sup>. In Japan, the E32K mutation was reported as a PCSK9 gain-of-function mutation. Since this is a mild gain-of-function mutation, LDL-C elevation is relatively mild. This mutation is observed in 1–2% of the general population but has a high prevalence of 6% in clinically diagnosed FH. If the E32K mutation is also present in FH patients heterozygous for LDL receptor mutations, the clinical picture is similar to that for HoFH but the response to drug therapy is better<sup>7)</sup>. The V4I mutation also occurs in 6% of FH and if it is present together with LDL receptor mutations, the clinical picture is similar to that for HoFH<sup>3)</sup>. Clinically, it may be difficult to distinguish from HoFH and in the case that an LDL receptor and a PCSK9 mutation are present in both alleles, genetically speaking, this is not an FH homozygote but a double heterozygote. To determine whether a PCSK9 mutation is the cause of FH, the assessment in a specialist facility is required.

#### 1.1.4 LDL Receptor Adapter Protein 1 (LDLRAP1)

LDLRAP1 is involved in the endocytosis of the LDL receptor. Mutations in the LDLRAP1 gene inherited from both parents cause autosomal recessive hyper-



**Fig. 1.** Combination of genetic mutation showing a clinical phenotype of FH homozygote.

cholesterolemia (ARH), an extremely rare disease. As ARH patients have huge xanthomas and hyper-LDL-cholesterolemia, HoFH would be suspected. An important difference between HoFH and ARH is that hyper-LDL-cholesterolemia is not observed in their parents<sup>8)</sup>.

### 1.2 Epidemiology of FH

It is difficult to estimate the prevalence of FH in Japan because of under-diagnosis. HoFH patients with LDL receptor mutations, who are presenting a clear clinical features of FH, are found to be around one in 1 million. Thus, the prevalence of HeFH patients with LDL receptor mutations has been calculated as 1 in 500 of the general population using the Hardy-Weinberg equilibrium equation. With advances in genetic diagnosis technology in recent years, the number of cases of definitively diagnosed HoFH has been increasing and Mabuchi *et al* have reported that based on their analysis of LDL receptor and PCSK gain-of-function mutations in Japan's Hokuriku region, the prevalence of HeFH calculated from the prevalence of HoFH is 1 in 208 of the general population so they estimated it was higher than previously thought<sup>4)</sup>. Thus, the frequency of HeFH is estimated at 1 in 200–500 people.

Similarly, worldwide HeFH prevalence has been reported to be 1 in 200–500 individuals excluding some high prevalence populations (Christian Lebanese in

Lebanon, French Canadians in Quebec, Afrikaners in South Africa, Ashkenazi Jews). It has also been reported that FH is not a rare disease and that patients being treated for hyper-LDL-cholesterolemia account for around 8.5% of FH<sup>9)</sup>.

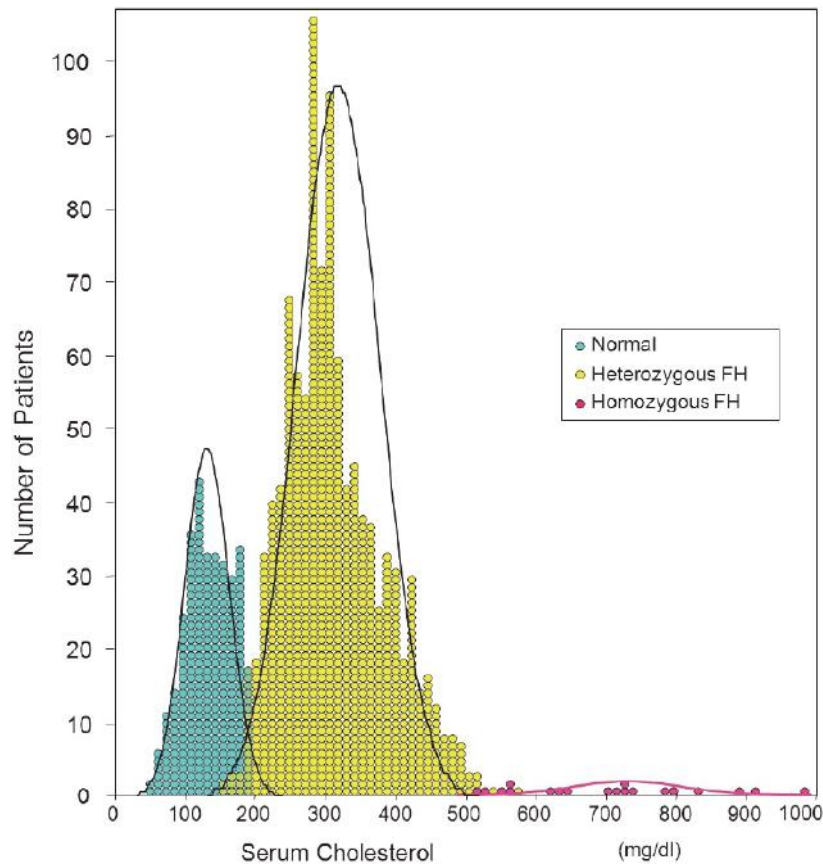
### 1.3 Clinical Features of FH

FH is an autosomal dominant hereditary disease with the 3 major features of hyper-LDL-cholesterolemia, premature CAD and tendon and skin xanthomas.

#### 1.3.1 Hyper-LDL-Cholesterolemia

In the report of the Research Team Investigating Primary Hyperlipidemia under the Japanese Ministry of Health Labour and Welfare's Health and Labour Sciences Project to Overcome Intractable Diseases for fiscal 1996–1997, Bujo *et al* reported that average untreated LDL-C levels were 248 mg/dL (296 males, 345 females, mean age 51 years) in 641 Japanese HeFH and there was no gender difference<sup>10)</sup>.

There is a trimodal distribution of serum total cholesterol (TC) levels in FH patients and their families, with levels of  $179 \pm 26$  in normal individuals,  $338 \pm 63$  in HeFH and  $713 \pm 122$  in HoFH (all mean  $\pm$  SD (mg/dL)). Thus, the concentrations in HoFH are twice as high as in HeFH, and four times in normal individuals, respectively<sup>11)</sup>. However, there is an over-



**Fig. 2.** Distribution of serum total cholesterol levels in normal subjects, and heterozygous and homozygous patients with FH (modified by adding patients of Reference 11).

lap between normal individuals and HeFH as well as between HeFH and HoFH so it may be difficult to make a distinction based on serum lipid levels alone (**Fig. 2**).

In the case of a poor response to LDL-C lowering with statins and other treatment, FH should be suspected actively<sup>12</sup>.

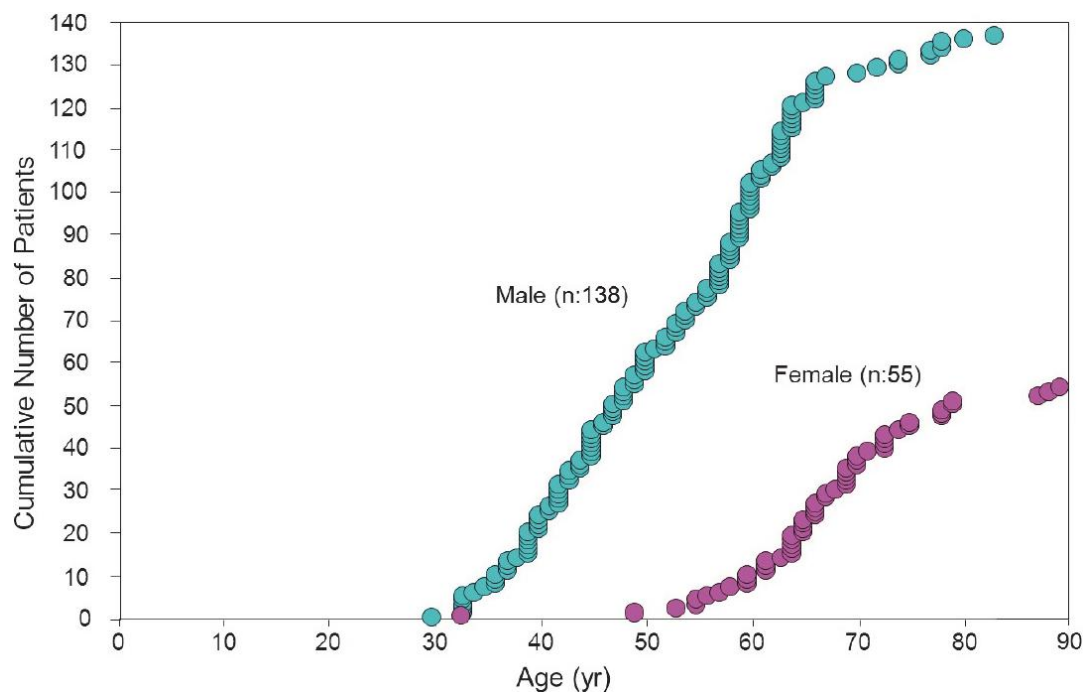
### 1.3.2 Premature Coronary Artery Disease

If LDL-C is high in patients with premature CAD patients, FH should be suspected. As hyper-LDL-cholesterolemia causes atherosclerosis especially in coronary arteries, the leading cause of deaths in FH has been reportedly CAD as high as 60% of frequency. Although hyper-LDL-cholesterolemia is also considered to be associated with cerebrovascular disease, the prevalence in HeFH is only 5–10%<sup>11, 13</sup>. Although the rate of myocardial infarction increases constantly from the 30s in male FH, it is rare before the 50s in female FH, showing a clear gender difference (**Fig. 3**). However, it is possible to delay the onset of CAD and improve the prognosis of HeFH through early diagnosis and inten-

sive lipid lowering therapy mainly with statins<sup>2</sup>.

### 1.3.3 Tendon and Skin Xanthomas

Physical findings such as tendon/skin xanthoma are important signs for clinical diagnosis of FH. Compared to HeFH, xanthomas are even more prominent in HoFH (**Fig. 4**). Skin xanthomas frequently develop at sites under regular mechanical stimuli, such as the extensor sides of the elbows/knees and wrist/gluteal regions. Xanthelasma has low specificity and diagnostic value because it is frequently observed in conditions other than FH, but it is still a finding for suspecting FH. Tendon xanthomas frequently appear as thickening of the Achilles tendon making palpation important in diagnosis. However, FH cannot be ruled out when xanthomas are not present and, in fact, they are not observed in 20–30% of definitively diagnosed FH by genetic testing<sup>14</sup>. Generally, xanthomas are absent or slight before adulthood and become more prominent with age. On the other hand, some cases of elderly patients lack tendon xanthomas. It should be noted that evaluation of xanthoma is difficult in the Achilles ten-



**Fig. 3.** Cumulative number of patients with myocardial infarction by age in male and female heterozygous FH patients (patients were add to Reference 11, and the form of indication was modified).

don after its rupture. Therefore, when xanthomas are lacking, a family survey and genetic diagnosis are necessary. In addition, FH patients may complain of Achilles tendon pain due to Achilles tendonitis.

#### 1.3.4 Corneal Arcus

The corneal arcus shown in **Fig. 5** is a characteristic finding for FH and its prevalence is approximately 30% in FH patients under the age of 50<sup>10, 15</sup>. In the elderly, it may be difficult to distinguish from arcus senilis, as it is common in the aged. However, when observed in patients under 50 years, corneal arcus has high diagnostic value.

#### 1.3.5 Other Risk Factors in FH

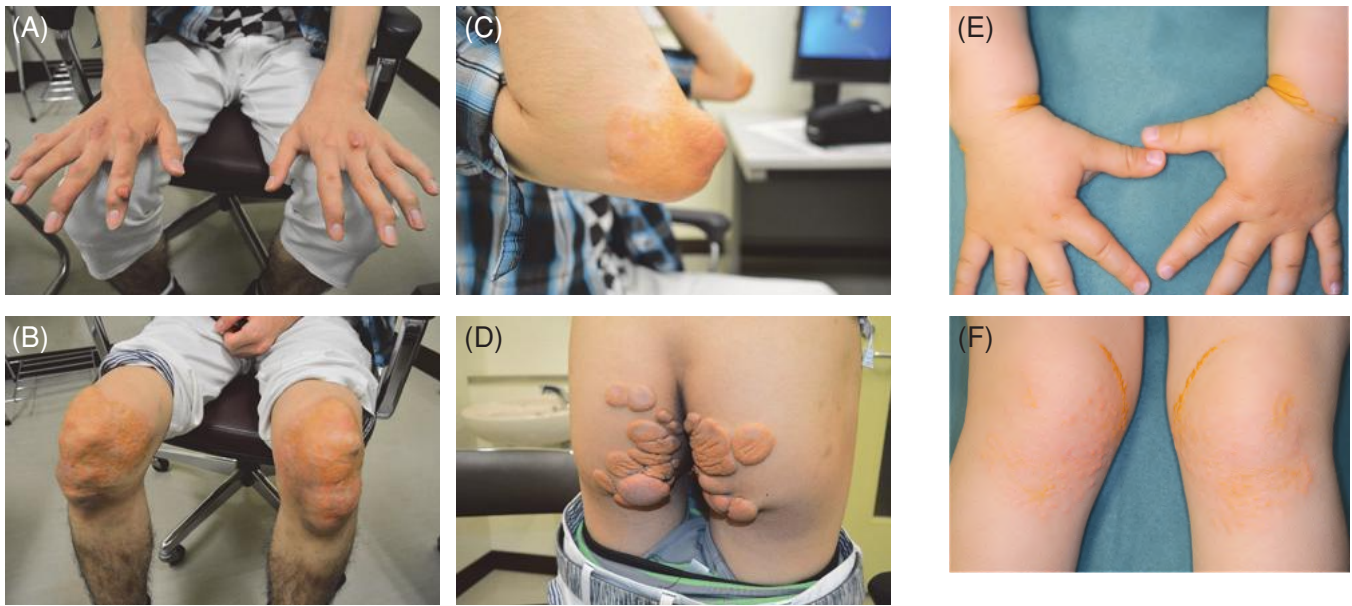
It has been reported that there is a wide variation in age of onset and speed of progression in CAD among patients. Several studies stated below have reported that other risk factors also affect the variation in clinical courses. In a study on 117 HeFH in the Hokuriku region, Yagi *et al* determined diabetes and low HDL-C levels to be significant risk factors<sup>16</sup> and Harada-Shiba *et al*,<sup>17</sup> in an analysis of HeFH in the Kinki region, determined smoking, family history of CAD, Achilles tendon thickening, high LDL-C levels, low HDL-C levels, high TG levels, diabetes and hypertension to be risk factors. Hirobe *et al* also noted the involvement of low HDL-C levels in CAD onset in HeFH<sup>18</sup>, Yanagi

*et al* noted the involvement of diabetes and impaired glucose tolerance<sup>19</sup>, Nakamura *et al* noted the importance of visceral fat<sup>20</sup> and Ogura *et al* noted that hypertension and low HDL-C levels (as well as impaired cholesterol efflux capacity) were residual risks in HeFH patients treated with statins<sup>15</sup>. Also, the Research Team Investigating Primary Hyperlipidemia reported that in FH patients with CAD, high TG levels and low HDL-C levels were frequently present as complications<sup>21</sup>. In addition, some studies conducted in other countries found that high Lp(a) level was a risk factor for CAD in HeFH patients<sup>22-25</sup>. Furthermore, it has been reported that among clinically diagnosed FH patients, the risk of CAD is high in those with mutations in FH related genes<sup>26</sup>.

### 1.4 Differential Diagnosis

Sitosterolemia is an autosomal recessive hereditary disease with prominent skin and tendon xanthomas from a young age and is diagnosed based on elevated blood levels of plant sterols (sitosterol, campesterol, etc.). In many cases serum cholesterol is normal, but when it is elevated to moderate or higher levels, a differential diagnosis from either FH or ARH is necessary. The causative gene is ATP-binding cassette transporter G5 (ABCG5) or ATP-binding cassette transporter G8 (ABCG8)<sup>27, 28</sup>. Cerebrotendinous xanthomatosis (CTX) is an autosomal recessive hereditary dis-





**Fig. 4.** Skin and tuberous xanthomas in a 22-year-old man (A) Finger tuberous xanthomas, (B) Xanthoma planum on the knees, (C) Xanthoma planum on the elbows, (D) Xanthoma planum on the buttocks. Skin xanthomas in a 3-year-old boy (E, F).

ease diagnosed from such symptoms as tendon xanthomas, typically Achilles tendon xanthomas, reduced intelligence, ataxia, speech impediments, cataract and cerebellar symptoms as well as high blood cholestanol levels. The essential feature of the disease is impaired bile acid synthesis due to  $27\alpha$ -hydroxylase deficiency<sup>29</sup>.

While the genetics are unclear, pseudohomozygous type 2 hypercholesterolemia presents a similar pathology to FH. The parents do not usually show definite hypercholesterolemia and the patient show good response to dietary therapy and bile acid adsorbing resins<sup>30, 31</sup>.

### 1.5 Diagnosis of FH

FH is diagnosed from high LDL-C levels, Achilles tendon thickening, skin xanthomas and familial history. Achilles tendon thickening is determined by a visual examination or palpation (Fig. 6). When thickening is suspected, conduct a radiographic examination and measure the maximum thickness of the Achilles tendon. If it is  $\geq 9$  mm, the tendon is determined as thickened (Fig. 7). Skin and tendon xanthomas frequently occur on the extensor sides of the hands, elbows, or knees. Also, due to the mode of inheritance, the onset of premature CAD (age of onset: males younger than 55 years, women younger than 65 years, respectively) in the family is frequent. Therefore, careful enquiring about family history is very important in making a correct diagnosis. When FH is diagnosed, be sure to conduct screening for blood relatives (cascade screening).

The features of HoFH are serum TC  $\geq 600$  mg/

dL as well as xanthomas and atherosclerotic diseases from childhood, and parents are HeFH. Xanthomas from childhood are characteristic and the initial consultation regarding them may be in a dermatology department. It may be difficult to distinguish from serious cases of HeFH so in order to make a definitive diagnosis of HoFH, genetic analysis is required. In recent years, diagnosis based on decreased LDL receptor activity (20% or less than normal)<sup>32</sup> in fibroblasts and lymphocytes has hardly been conducted.

#### 1.5.1 FH Diagnosis Criteria

The diagnosis criteria for FH are the same as in the previous guidelines “Guidelines for the Prevention of Atherosclerotic Diseases 2012<sup>33</sup>”, and are shown in Table 1.

As a point for attention, there may be a transient drop in LDL-C when serious diseases such as acute myocardial infarction are also present. Therefore, when examining a patient with acute myocardial infarction, the Achilles tendon should be palpated and a family survey conducted. This requires particular attention if the patient is young in age.

#### 1.5.2 Achilles Tendon Radiography

Achilles tendon thickness is evaluated by means of radiography. The angle between the lower leg bone and sole should be 90 degrees. An angle of incidence should be established involving the fibular lateral malleus from the lateral side. For a digital system, the imaging distance is 120 cm and the following imaging



**Fig. 5.** Corneal arcus in FH patients.

conditions should be employed: 50 kV, 5.0 mAs (e.g.  $100 \text{ mA} \times 0.05 \text{ sec}$ ,  $50 \text{ mA} \times 0.1 \text{ sec}$ ). When the maximum diameter is  $\geq 9 \text{ mm}$  a diagnosis of thickening is made. Evaluation by means of ultrasound is also possible but has yet to be standardized.

### 1.5.3 Differential Diagnosis (Secondary Hyperlipidemia)

The major diseases requiring differentiation from FH are secondary hyperlipidemia characterized by hyper-LDL-cholesterolemia (due to diabetes, hypothyroidism, nephrotic syndrome, cholestatic liver disease, or drug-induced hyperlipidemia (by steroids, etc.)) and the similar disease familial combined hyperlipidemia (FCHL). FCHL can be distinguished from FH based on absence of tendon xanthomas, presence of small dense LDL and presence of other types of dyslipidemia within the family (type IIa, type IIb, type IV) and in the case of children, LDL-C does not rise as high as in FH. The points for distinguishing FCHL from FH are listed in [Table 2](#).

For diseases similar to FH with tendon xanthomas, refer to 1.4.

## 1.6 Screening and Follow-Up for Atherosclerotic Diseases in FH

HeFH develop systemic atherosclerotic diseases including CAD in the early stage of life. Therefore, early screening and treatment for atherosclerotic diseases are required. Endeavor to conduct patient interviews, auscultation (heart sounds and bruit in carotid artery, subclavian artery, renal artery and femoral artery areas) and palpation on a regular basis. For the diagnosis of CAD, history taking, electrocardiography, exercise electrocardiography (treadmill, ergometer), echocardiography and drug loading or exercise stress myocardial scintigraphy are to be performed. When CAD

is suspected in these examinations, clarify the location of the coronary artery stenosis through coronary artery CT or coronary angiography. However, FH patients frequently show calcification, which sometimes makes it difficult to make a diagnosis. Characteristic coronary angiography findings in HeFH include marked stenotic lesions at the origin and dilative lesions downstream (coronary aneurysms).

In evaluating carotid atherosclerosis in HeFH, in addition to listening to bruit in the physical examination, carry out carotid ultrasonography and if stenosis is suspected, MR angiography, CT angiography or vascular angiography should be performed. To evaluate the presence of cerebral infarction, MRI and CT should be carried out if necessary.

In elderly HeFH, aortic aneurysms are frequently present. Conduct chest X-ray and CT exams to evaluate thoracic aortic aneurysms, and abdominal ultrasonography and CT to evaluate abdominal aortic aneurysms. The treatment needs cooperation with cardiovascular surgeons.

In some HeFH patients, peripheral artery disease (PAD) develops concomitantly; therefore the presence of cold sensation in the feet and intermittent claudication should be investigated by history taking and dorsalis pedis artery and posterior tibial artery should be palpated. In order to evaluate the arteriosclerosis of the femoral artery, ankle-brachial blood pressure index (ABI) should be measured. When stenosis is suspected, femoral artery ultrasonography (Doppler method), CT angiography and MR angiography should be performed.

To assess valvular disorders, such as aortic valve stenosis (AS), echocardiography should be conducted and if required, cardiac catheterization should be performed. In severe cases having a decrease in the aortic valve orifice area with marked differences in the aortic valve pressure, aortic valve replacement surgery or trans-

catheter aortic valve implantation (TAVI) is performed.

## 2. Treatment of HeFH

### 2.1 Target LDL-C Levels for Management in HeFH

Because FH is a disease associated with a very high risk of CAD, FH should be considered to correspond to secondary prevention, and it is desirable to set a management target for the LDL-C level at  $<100$  mg/dL. However, in many cases, it is difficult to achieve the target in clinical practice. The ASAP study<sup>34)</sup> showed that there was a decrease in intima-media thickness (IMT) in carotid ultrasonography in patients in whom a reduction of  $\geq 50\%$  in LDL-C was achieved with high dose statin for 2 years. Therefore, it is also acceptable to aim for  $<50\%$  of the pretreatment level if the management target for LDL-C is not achieved (Fig. 8).

In HeFH patients for secondary prevention, the LDL-C management target level is set at  $<70$  mg/dL because they can be considered to be at even higher risk.

However, there is no clear evidence for the validity of these numerical targets because clinical studies on FH without lipid-lowering therapy are ethically not permissible. The achievement of the management target does not always assure the absence of future cardiovascular events. In addition, it should be noted that risk charts issued by the Japan Atherosclerosis Society cannot be applied for risk assessment in the treatment of FH.

### 2.2 Dietary Therapy in HeFH

Dietary therapy should be conducted in HeFH and the procedure should be the same as that for other dyslipidemia. Specifically, patients should be instructed to observe the points for attention in dietary therapy for hypercholesterolemic patients drawn up by the Japan Atherosclerosis Society which are: ① Saturated fats 4.5% to 7%, ② Reduce trans-fat intake, ③ Cholesterol  $\leq 200$  mg/day.

### 2.3 Exercise Therapy in HeFH

Exercise therapy is necessary for HeFH patients, however due to the high risk of CAD, screening for CAD before administering exercise therapy is essential. CAD should be evaluated by patient interviews to determine the presence or absence of effort angina, and exercise electrocardiography and echocardiography should be performed. If the existence of CAD is suspected, administering treatment for CAD before initiating exercise therapy is thus preferred. For specifics on conducting exercise therapy, refer to the section entitled "Exercise therapy".



Fig. 6. Achilles tendon thickening in an FH patient.

### 2.4 Drug Therapy in HeFH

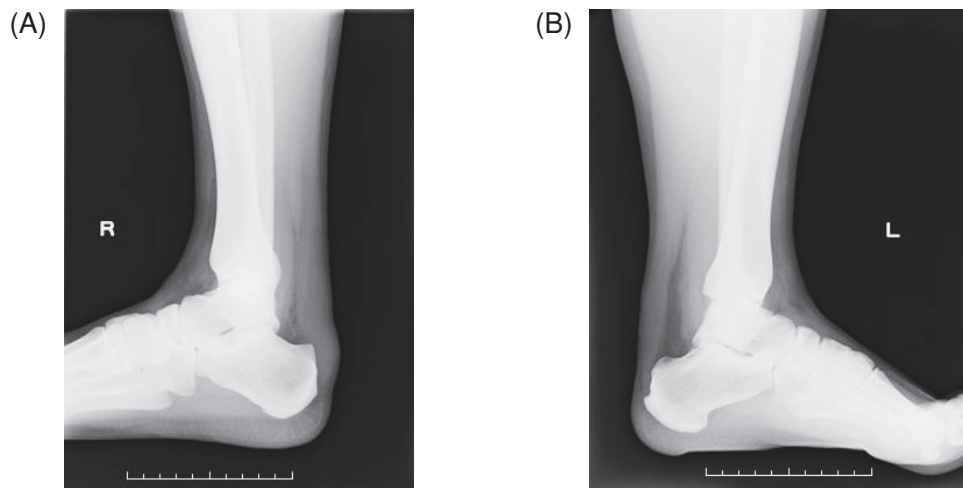
In many HeFH patients, adequate lipid management cannot be achieved through lifestyle habit interventions such as dietary therapy, exercise therapy, smoking cessation and anti-obesity measures alone, so drug therapy is usually combined with them. Statins are the first-line drugs for FH treatment. In this regard, a retrospective analysis of 329 HeFH patients conducted in Japan revealed that statin use significantly delayed the onset of CAD<sup>35)</sup>. Also with the focus on LDL-C lowering rate, current treatment is performed mainly with high-intensity statins.

Start statins at the initial dose and then increase it while observing efficacy and monitoring for adverse events. Although the LDL-C lowering effect of statins increases dose dependently, care is necessary because the frequency and severity of adverse events may also increase. For patients with statin intolerance, try a different statin or different dosing intervals (every other day, twice weekly, etc.) with the aim of increasing to the maximum tolerated dose<sup>36)</sup>.

When sufficient efficacy is not obtained with statin alone, it may be possible to increase the LDL-C lowering effect through combination with other lipid lowering drugs. Drugs that may be combined with statin include small intestine-specific cholesterol transporter inhibitors (ezetimibe), PCSK9 inhibitors, bile acid adsorbing resins (cholestyramine and colestimide), probucol, fibrates and nicotinic acid formulations.

The ENHANCE study<sup>37)</sup> reported that the addition of ezetimibe to statin in FH patients achieved a further LDL-C lowering effect. Also, it has been reported that the addition of therapy with the PCSK9 inhibitor evolocumab (Rutherford-II study<sup>38)</sup> or alirocumab (Odyssey FHI and FHII studies<sup>39)</sup>) in HeFH





**Fig. 7.** Radiograms of the Achilles tendon in FH patients. (A) Achilles tendon in a 40-year-old man (maximum thickness: 22 mm), (B) Achilles tendon in a 29-year-old man (maximum thickness: 19 mm).

patients already being treated with statin (and ezetimibe) achieved further lowering of LDL-C (approx. 60%) and Lp (a) relatively safely. However, it remains unclear whether such combination therapies, rather than statin alone, are more effective in preventing cardiovascular events among FH patients so it will be necessary to clarify this in the future. When combining PCSK9 inhibitors with LDL apheresis, they should be administered afterwards because they will be eliminated by apheresis.

For patients with statin intolerance due to side effects such as myalgia (including CK elevation) and liver dysfunction, monotherapy or combination therapy with the above lipid lowering agents should be performed to avoid or reduce the dose of statins but their atherosclerosis preventing effect has not been sufficiently established. A retrospective study conducted in Japan suggested that probucol delays the onset of recurrent CAD in HeFH patients<sup>40)</sup>, but the possibility of adverse events with probucol such as QT prolongation needs to be kept in mind.

### 2.5 LDL Apheresis in HeFH

The number of HeFH undergoing LDL apheresis has been decreasing in recent years due to the development of statins, ezetimibe, PCSK9 inhibitors and other cholesterol lowering drugs. However, as apheresis allows many patients to achieve LDL-C management target levels, there is no reason to hesitate in using it in the case of patients with drug resistance and advanced CAD. Apheresis is covered by public health insurance for HeFH when TC exceeds 400 mg/dL in a steady state (weight and serum albumin stable) under dietary therapy and does not decrease to 250 mg/dL

or less by drug therapy in the presence of coronary artery lesions in addition to xanthomas.

## 3. Treatment of HoFH

### 3.1 LDL Cholesterol Management Target Levels in HoFH

In HoFH, treatment should be proactively conducted because it is essential to lower LDL-C as early as possible. In HoFH, ideal LDL-C management target levels are also <100 mg/dL for primary prevention patients and <70 mg/dL for secondary prevention patients, but in many cases they are difficult to achieve (Fig. 9).

### 3.2 Lifestyle Habit Interventions in HoFH

Similar to HeFH patients, fundamental treatment for HoFH patients consists of lifestyle habit interventions such as dietary therapy, exercise therapy, smoking cessation and anti-obesity measures. As atherosclerosis progresses more quickly than in heterozygotes, before giving guidance in exercise therapy and initiating it, patients should be carefully evaluated for CAD as well as valvular disease (particularly aortic valve stenosis, supraaortic stenosis) and aortic aneurysms.

### 3.3 Drug Therapy in HoFH

In HoFH, management is not possible with the above lifestyle habit interventions alone and powerful LDL-C lowering therapy is required from a young age to prevent the onset and progression of CAD. The major mechanisms of action of statins, bile acid adsorbing resins and PCSK9 inhibitors all involve enhancing LDL receptor expression. For the defective type, in

**Table 1.** Diagnostic criteria for heterozygous FH in Adults (15 years of age or older)

<ul style="list-style-type: none"> <li>•Hyper-LDL-cholesterolemia (an untreated LDL-C level <math>\geq 180</math> mg/dL)</li> <li>•Tendon xanthomas (thickening of tendons on dorsal side of the hands, elbows, knees or Achilles tendon hypertrophy) or xanthoma tuberosum</li> <li>•Family history of FH or premature CAD (within the patient's second-degree relatives)</li> </ul>
<ul style="list-style-type: none"> <li>•The diagnosis should be made after excluding secondary dyslipidemia.</li> <li>•If a patient meets two or more of the above-mentioned criteria, the condition should be diagnosed as FH. In case of suspected heterozygous FH, making a diagnosis using genetic testing is desirable.</li> <li>•Xanthelasma is not included in xanthoma tuberosum.</li> <li>•Achilles tendon hypertrophy is diagnosed if the Achilles tendon thickness is <math>\geq 9</math> mm on X-ray imaging. (See Appendix)</li> <li>•An LDL-C level of <math>\geq 250</math> mg/dL strongly suggests FH.</li> <li>•If a patient is already receiving drug therapy, the lipid level before treatment should be used as the reference for diagnosis.</li> <li>•Premature CAD is defined as the occurrence of CAD in men <math>&lt;55</math> years of age or women <math>&lt;65</math> years of age, respectively.</li> <li>•If FH is diagnosed, it is preferable to also examine the patient's family members.</li> <li>•These diagnostic criteria also apply to HoFH.</li> </ul>

which only a small amount of LDL receptor activity remains, slight efficacy is observed, however in the negative type in which LDL receptor activity is completely absent, no LDL-C lowering effect is observed<sup>41, 42)</sup>. Based on this as well as from the viewpoint of medical economics, administration of PCSK9 inhibitors should be ceased if there is no decrease in LDL-C. However, a retrospective study found that the administration of statin and other drugs was effective in reducing mortality rates in HoFH<sup>43)</sup>. In addition, it has been reported that a microsomal triglyceride transfer protein (MTP) inhibitor, which was developed for HoFH patients, lowered LDL-C by approximately 50%<sup>44)</sup>. A study in HoFH patients was conducted in Japan<sup>45)</sup> and it is now on the market. However, as the frequencies of the adverse events of fatty liver and diarrhea are high with MTP inhibitor, it is essential to control the fat and alcohol intake strictly. Probucol reportedly exerts a certain LDL-C lowering effect in HoFH and may cause the regression or disappearance of xanthoma in the skin, Achilles tendon<sup>46)</sup>. Nevertheless, for LDL-C control, LDL apheresis therapy once every 1-2 weeks is still required in many cases. When patients are resistant to all of the above treatments or show intolerance, liver transplantation may be considered.

### 3.4 LDL Apheresis

#### 3.4.1 Use of LDL Apheresis

In patients with HoFH, as it is difficult to decrease the LDL-C level sufficiently using existing drug therapies, continued LDL apheresis therapy is required from childhood in many cases. LDL apheresis therapy uses an extracorporeal circulation device to eliminate LDL from blood and was developed for HoFH with this purpose in mind.

#### 3.4.2 Benefits of LDL Apheresis

LDL apheresis may be safely performed in children. Also, it has been reported that it has no adverse effect on their development or growth and not only achieves reduction or disappearance of xanthomas, but also inhibits the progression of or mitigates aortic valve stenosis and supralvalvular aortic stenosis as well as coronary artery and other atherosclerotic lesions<sup>47-49)</sup>. It has also been reported that, besides lowering LDL-C, LDL apheresis inhibits expression of cell adhesion molecules (ICAM-1, ELAM-1, etc.), suppresses thrombus formation by decreasing fibrinogen and coagulation factors, that LDL is not readily oxidized after LDL apheresis and that it has an anti-atherosclerotic action via improvement of LDL subtypes<sup>50)</sup>.

#### 3.4.3 Time of Initiating LDL Apheresis Therapy

Considering the prevention of the progression of atherosclerotic diseases, LDL apheresis therapy should be initiated at the youngest possible age. However, it is difficult to perform until child patients can be kept still during it. While a realistic time for commencement is from the age of 4–6 years when extracorporeal circulation with them lying still on a bed is possible, a case of commencing apheresis at the age of 3.5 years was reported<sup>51)</sup>. It has also been reported that in some cases, coronary artery stenosis and complete occlusion, coronary valve stenosis and supralvalvular aortic stenosis are already present in infancy, and if LDL apheresis is initiated from the age 10 years onwards the prognosis is poor<sup>52)</sup>, and it has been recommended to start treatment as early as possible<sup>47)</sup>. In childhood, it should be conducted using plasma exchange in view of its small extracorporeal circulation volume, but if existing LDL adsorption methods are used, ways of

**Table 2.** Differential diagnosis point of FH and familial combined hyperlipidemia (FCHL)

	FH Heterozygotes	FCHL
Gene	Monogenic causes LDL receptor ( <i>LDLR</i> ) Apolipoprotein B-100 ( <i>APOB</i> ) Proprotein convertase subtilisin-like kexin type 9 ( <i>PCSK9</i> ) LDLR adaptor protein 1 ( <i>LDLRAP1</i> )	Complex genetic causes Upstream transcription factor 1 ( <i>USF-1</i> ), Lipoprotein lipase ( <i>LPL</i> ), etc.
Prevalence	1 in 200 -500	1 in almost 100
lipid profile	Mostly type IIa, often type IIb	In family and individual, variable phenotype of type IIa and/or type IIb and/or type IV
Tendon and skin xanthomas	Often observed	Not observed
Premature corneal limbus	Often observed	Not usually observed
Small dense LDL	Rare	Characteristic feature of FCHL
Insulin resistance	Rare	Often observed

reducing extracorporeal circulation should be devised.

#### 3.4.4 Setting of LDL Apheresis Plasma Treatment Volumes and Blood Access

Volumes of plasma to be treated in LDL apheresis are determined from pretreatment LDL-C levels and individual patient plasma volumes (proportional to body weight). Normally, treatment of 3–6 L of plasma can reduce LDL-C by 60–80%. However, LDL-C starts rising soon after treatment and continues rising until the next treatment. The effectiveness of LDL apheresis may depend on time-averaged concentrations ( $C_{AVG}$ ) and that it can be estimated using  $C_{AVG} = C_{MIN} + 0.73 (C_{MAX} - C_{MIN})$ . In order to decrease the time averaged concentrations, plasma treatment volumes, treatment frequency and concomitant medication need to be determined.

Blood access in LDL apheresis is commonly via the cubital vein or brachial vein. Unlike hemodialysis in renal failure, as the blood flow rate is 50–150 mL/min, a shunt only has to be made for certain patients. Unlike the case of renal failure patients, hematocrit is normal in FH, so shunt occlusion readily occurs and care is needed.

#### 3.4.5 LDL Apheresis Methods

##### 3.4.5.1 Plasma Exchange

This was the first apheresis method and was initially conducted by Thompson *et al* in 1975. They reported a clear improvement in clinical symptoms in FH patients including a drop in cholesterol, decreased angina pain with reduction in coronary artery stenosis and disappearance of xanthomas<sup>53</sup>. However, as this method reduces cholesterol by removing the patient's

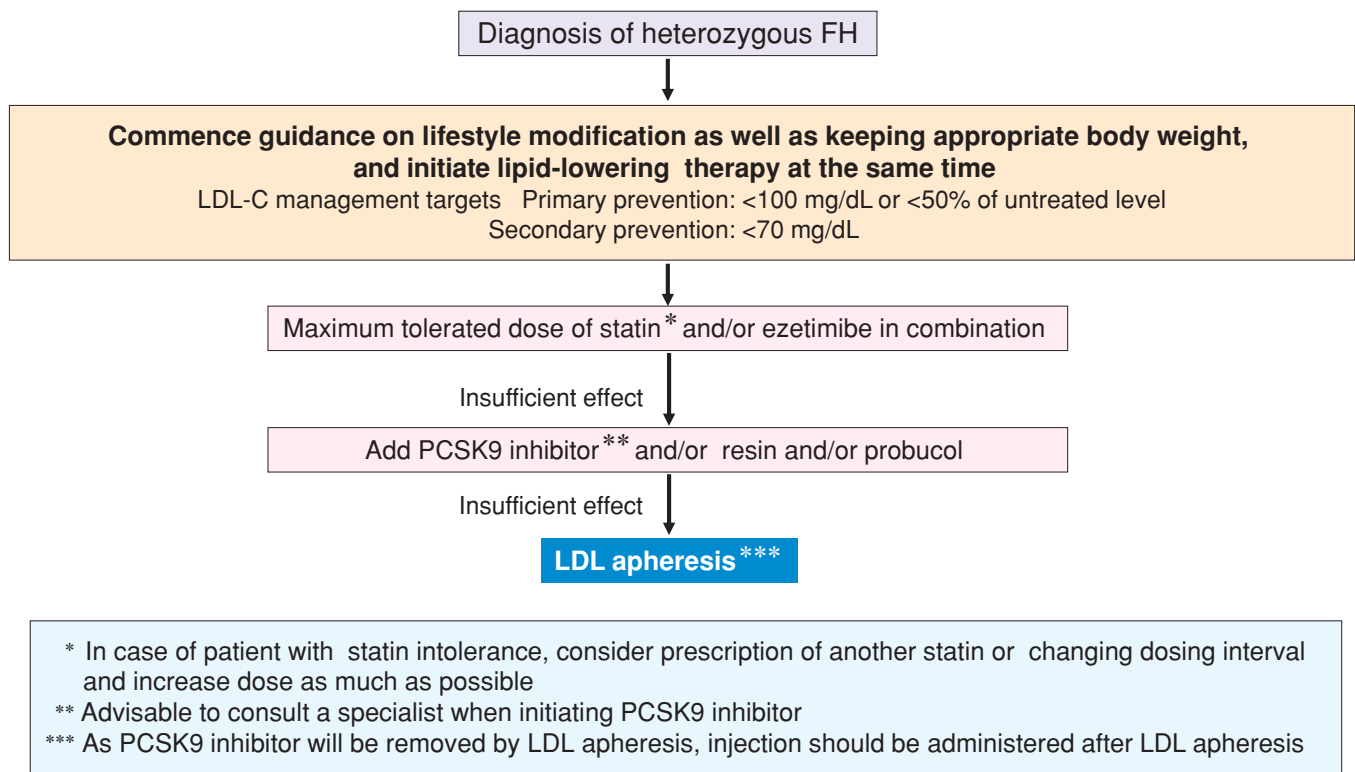
plasma and replacing it with a human albumin preparation, it also non-selectively removes immunoglobulin and other substances needed by the body. For this reason, at present, it is only used in HoFH children of less than 10 years old with the purpose of reducing the extracorporeal circulation volume.

##### 3.4.5.2 Double Filtration

This method uses double filtration membranes of different pore sizes developed by Yoshikawa and Kishino *et al* in Japan. The primary membrane separates blood cells and plasma and the secondary membrane removes LDL and VLDL, which have larger particle sizes than other plasma components. It selectively removes VLDL and LDL and the HDL removal rate is lower than that for plasma exchange. However, disadvantages include the additional removal of albumin (10%) and globulin (30–60%) by the secondary membrane, a limitation on the plasma treatment volume due to clogging of secondary membrane pores and an increase in membrane pressure due to this.

##### 3.4.5.3 LDL Adsorption (Liposorber System)

The LDL adsorption method was developed based on the selective binding of LDL and dextran sulfate. After separating the blood into blood cell components and plasma components, plasma is passed through columns containing dextran sulfate, the negatively charged ligand, in porous beads and the positively charged apo B containing lipoproteins (VLDL, LDL, Lipoprotein (a)) are selectively removed<sup>54</sup>. Two small volume columns (LA15, 150 mL) are used. The LDL adsorbed in the columns is eluted alternately using high concentration NaCl (5%). As the LDL adsorbing columns



**Fig. 8.** Treatment flow chart for adult (15 years or over) heterozygous FH.

are negatively charged, the blood coagulation system will be activated and result in a rise in bradykinin levels. Therefore, combination therapy with angiotensin converting enzyme (ACE) inhibitors may cause anaphylaxis symptoms and is contraindicated.

#### 3.4.6 LDL Apheresis Adverse Events, Cautions

Owing to a decrease in effective circulating blood volume in apheresis, hypotension may frequently occur, so great care is needed, particularly in the case of patients with aortic valve disease and CAD. Iron deficiency anemia is a common adverse event, but patients recover by taking iron preparations.

### 3.5 Criteria for Having HoFH Authorized for Treatment as Designated Intractable Disease

HoFH is a designated intractable disease and patients can be authorized to receive financial support for its treatment. The criteria for authorization include a definitive diagnosis based on genetic analysis of genes involved in the LDL receptor pathway or measurement of LDL receptor activity and close to definitive diagnosis based on marked hypercholesterolemia or skin xanthomas since childhood and resistance to drug therapy. Details of designated intractable diseases are given on the Ministry of Health Labour and Welfare's In-

tractable Disease Information Center website:

<http://www.mhlw.go.jp/stf/seisakunitsuite/bunya/0000084783.html>

The procedures for authorization may be completed at the patient's nearest health center.

## 4. Pediatric FH

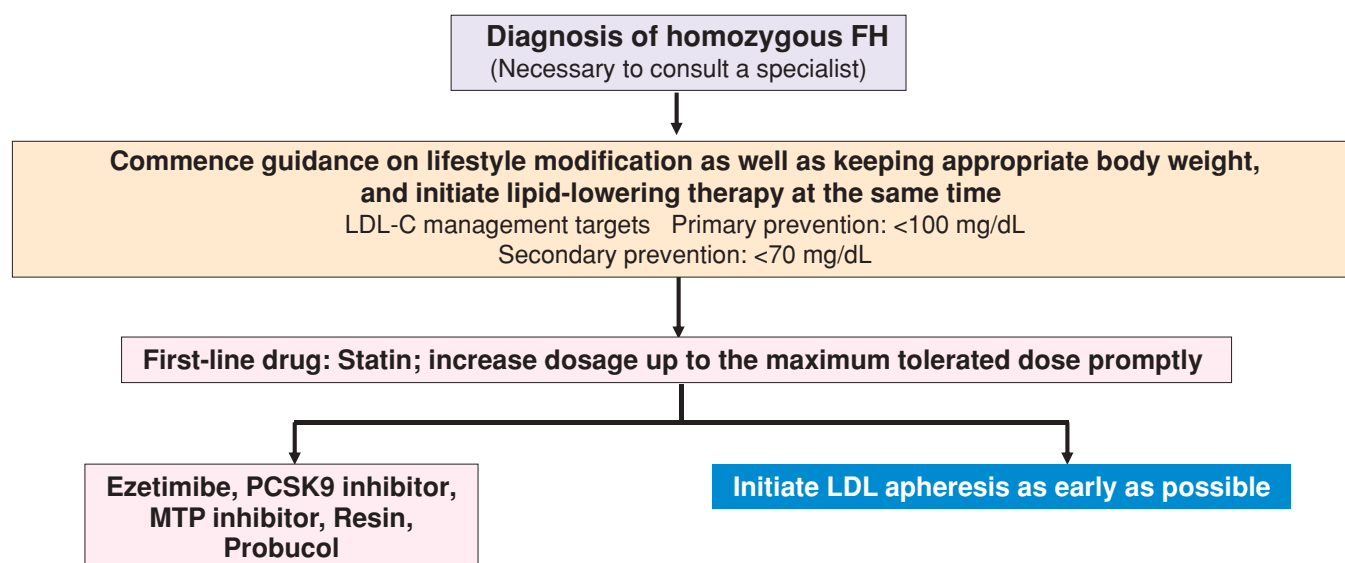
For HeFH, CAD and other atherosclerotic diseases will not be a clinical problem in childhood. However, based on autopsy findings, the Bogalusa Heart Study<sup>55)</sup> and Pathological Determinants of Atherosclerosis in Youth (PDAY)<sup>56)</sup> reported that atherosclerotic changes were already present in FH child patients, so early diagnosis and atherosclerosis prevention measures are considered to be very important in childhood.

### 4.1 Diagnosis of Pediatric FH

In 2012, the Japan Atherosclerosis Society drew up diagnosis criteria for pediatric HeFH<sup>33)</sup>. The present diagnostic criteria for pediatric FH (Table 3) are essentially the same as those established by the Society. However, as these criteria enable not only HeFH but also HoFH to be diagnosed, the title of the criteria was amended.

FH has mainly an autosomal dominant inheri-





**Fig. 9.** Treatment flow chart for adult (15 years or over) homozygous FH.

tance pattern and as there are usually no physical manifestations, such as xanthomas and corneal arcus, in pediatric HeFH, the emphasis is on family history. Thus, the presence of FH in either parent is important in diagnosis. While hyper-LDL-cholesterolemia ( $\geq 140$  mg/dL) is also important, as many children are referred due to total cholesterol (TC), the 95th percentile<sup>57)</sup>, i.e. TC  $\geq 220$  mg/dL, is added as a criterion. In the case of having high TC, a fasting blood sample is taken and LDL-C should be calculated by the Friedewald formula. The hyper-LDL-cholesterolemia criteria also use the 95th percentile<sup>57)</sup> for healthy children.

## 4.2 Screening for Pediatric FH

It is advisable for all children to be assessed for presence of dyslipidemia once up to the age of 10 through measurement of serum lipids<sup>58)</sup>. If this guideline could take hold among pediatricians, early discovery of FH would increase.

From the viewpoint of medical economics, a realistic, effective method of screening would involve analysis of families in which pediatric or adult FH patients had already been diagnosed (cascade screening) to discover other patients with FH. Even in the absence of a specialized FH screening system, analysis of such families would exponentially increase diagnosis rates for both pediatric and adult FH.

It should be noted that financial assistance is available for pediatric HeFH under grant-in-aid program for specific chronic diseases in childhood.

## 4.3 Evaluation of Atherosclerosis in Children

For assessment of atherosclerosis in pediatric HeFH,

non-invasive methods are mainly used. IMT measured by carotid ultrasonography is a good indicator for assessing the progress of atherosclerosis and determining the effectiveness of treatment. Detailed exams are then conducted as required.

## 4.4 Treatment of Pediatric HeFH

### 4.4.1 Improvement of Lifestyle Habits Through Guidance

When FH is diagnosed, patients should be provided with guidance regarding lifestyle habits, including diet, as quickly as possible. This is the same for both HoFH and HeFH. However, even with lifestyle habit improvement, it is often difficult to reduce LDL-C to the target level. In such cases, drug therapy is added and in more serious cases, LDL apheresis should be considered. Furthermore, lifestyle habit guidance should be continued after starting drug treatment.

#### 4.4.1.1 Dietary Therapy

Excluding obese children, the daily energy intake should be the normal amount for the age group and physique<sup>59)</sup>. Food quantity and exercise level should be evaluated, and adjusted according to increases in height and weight.

The nutritional balance in children is the same as for adults with dyslipidemia<sup>33)</sup>, recommending that fat should account for 20-25% of energy and carbohydrate 50-60%. Saturated fatty acids should account for  $<7\%$  of energy and patients should reduce the intake of trans-fatty acids, reduce the intake of cholesterol limited to 200 mg/day.

Initiating strict dietary therapies in children has

**Table 3.** Pediatric FH diagnostic criteria

1. Hyper-LDL cholesterolemia: LDL-C level of $\geq 140$ mg/dL when untreated (If total cholesterol level is $\geq 220$ mg/dL, measure the LDL-C level)
2. Family history of FH or premature CAD (blood relative closer than the two parents)
<ul style="list-style-type: none"> <li>• Excluding secondary hyperlipidemia, if two items are satisfied, FH is diagnosed.</li> <li>• During the growth phase, there are fluctuations in LDL-C; therefore, careful observation is required.</li> <li>• In pediatric cases, there are few clinical symptoms such as xanthomatosis; therefore, it is important to investigate the family history for FH. Use the family survey results of those beyond the parents as a reference if necessary.</li> <li>• Early CAD is defined as CAD with an onset at <math>&lt;55</math> years of age for males and <math>&lt;65</math> years of age in females, respectively</li> <li>• If xanthoma is present, LDL-C is suspected to be extremely high (homozygote).</li> </ul>

been found to be difficult. In recent years, the westernization of the Japanese diet style has resulted in a tendency toward an increased fat intake so efforts should be made to avoid overconsumption of fat and carbohydrates.

Thus, guidance should focus on Japanese food, with a good balance of vegetables, soybean products, fish and fruit, and pickiness should not be allowed. Care should be taken to avoid consuming too much salt.

#### 4.4.1.2 Anti-Obesity Measures

Even in FH, it is important to maintain a proper weight. Obesity, particularly that with excessive accumulation of visceral fat, can easily lead to abnormal secretion of adipocytokines<sup>(60)</sup>, resulting in complications. In assessing children for obesity, “percentage of overweight (POW)”, which is calculated in relation to standard weights by gender, age and height is used. For school age children, proper weights are within  $\pm 20\%$  of the standard and for infants  $\pm 15\%$ <sup>(61)</sup>. For school-children, a waist circumference (navel level) of  $\geq 80$  cm is considered to strongly suggest excessive accumulation of visceral fat<sup>(60, 61)</sup>.

In obesity, because the energy intake is above the required level, returning to normal intake is necessary. Intake of vegetables should be increased and care should be taken with regard to beverages and seasonings (condiments). Height increases in children make it easy to improve the obesity degree. However, they should be encouraged to keep active at the same time. For advanced obesity, it is necessary to restrict energy intake.

#### 4.4.1.3 Exercise Therapy

For patients with HoFH and serious HeFH, exercise guidance should be provided after assessment for aortic valve stenosis and supraaortic stenosis by echocardiography and screening or secondary testing for CAD have been carried out. While the effect of exercise therapy in lowering LDL-C is limited, it is

effective for preventing obesity or improving the obesity degree and improving insulin sensitivity. The focus of guidance should be on obese children and those with no exercise habit in particular.

Generally, adults should perform slightly challenging aerobic exercise for at least 30 min per day, preferably every day. Children should also perform roughly the same type of exercise for the same duration. The type of exercise is not important, but it should be done outdoors as much as possible. It is important that the exercise is enjoyed and continued. Attention should also be paid to stopping children from watching TV and playing computer games for long periods of time. If individual children have problems with heart function, a separate exercise program should be specified.

#### 4.4.1.4 Smoking Education

Emphasize the point that patients should never smoke during their lifetime and obtain the cooperation of family and those around the patient in preventing passive smoking.

#### 4.4.2 Drug Therapy

Hyper-LDL-cholesterolemia from childhood is an independent risk factor for atherosclerosis and it has been reported that IMT thickening is observed in many pediatric HeFH<sup>(62)</sup>. In recent years, many overseas guidelines have mentioned the importance of treatment from childhood for the purpose of preventing future cardiovascular events<sup>(63-65)</sup>. In pediatric HeFH, if the LDL-C level is persistently  $\geq 180$  mg/dL despite lifestyle improvement, such as through dietary or exercise therapies, drug therapy should be considered for both boy and girl patients from the age of 10. Since drugs have to be taken long-term in drug therapy for pediatric HeFH, its necessity should be adequately explained to the guardian and as well as the patient (if possible), and gain their understanding before initiating treatment. Children aged  $<10$  years with sustained LDL-C levels of  $\geq 200$  mg/dL should be taken to a

specialist.

Drug therapy should be selected in consideration of the magnitude of the LDL-C level, age, and family history. Statins are the first-line drugs but they should be initiated at the minimal dose. In Japan, pitavastatin<sup>66)</sup> has been indicated for children of  $\geq 10$  years since June 2015. Regarding statins indicated for use in children in other countries, simvastatin, atorvastatin, pravastatin, fluvastatin and rosuvastatin are approved for children in the US and Europe. While the indicated age in many cases is from the age of 10 years, the use of pravastatin has been approved from the age of 8 years in the US, that of rosuvastatin from the age of 6 in Europe and that of atorvastatin from the age of 6 years in Australia.

If the minimum dose of statin does not decrease LDL-C levels sufficiently, the following should be considered: ① increasing the dose, ② changing to a more potent statin and increasing the dose or ③ combining statin with another type of lipid lowering drug. Concomitant medications for which efficacy has been reported in children are ezetimibe and resins (negative ion exchange resins: cholestyramine and colestimide). Although ezetimibe is approved for use in children from the age of 10 years in the US and Europe, it is not covered by health insurance in Japan. Resins were previously recognized as first-line drugs in both the US and Japan. However, they are not approved in Europe for children due to numerous adverse events, such as abdominal pain, abdominal distension and constipation, and there had been little evidence for an atherosclerosis prevention effect. Furthermore, as resins inhibit the absorption of folic acid and fat-soluble vitamins, regular monitoring and occasional supplementation may be necessary.

#### 4.4.3 LDL-C Management Target Levels and Post-Treatment Follow-Up

The management target level for LDL-C in pediatric FH is less than 140 mg/dL. When there is a family history of premature CAD, or in the case that diabetes is also present, intensification of drug treatment may be necessary to achieve LDL-C levels below 140 mg/dL. While it is difficult to achieve the target in serious cases, efforts should be made to get as close as possible through combination drug therapy. Guidance regarding lifestyle habits including that on diet should be continued after starting drug therapy.

The safety and tolerability of statins in children are considered to be similar to those in adults. Statins should be initiated at the lowest dose and up-titrated according to LDL-C lowering response and tolerability. AST, ALT and other indicators of liver function as well as CK, serum lipids and symptoms such as mus-

cle pain should be evaluated before starting treatment, and the first evaluation after initiating statin should be performed within a month. Comparing levels with those before initiating drugs, monitor patients for adverse events such as liver dysfunction, myopathy, and rarely rhabdomyolysis.

Depending on the statuses of LDL-C lowering, adverse events and other factors, if required, examine the patient and carry out tests the following month as well. If there are no adverse events and LDL-C is stable, afterwards, follow up 3–4 times a year. It is also necessary to monitor growth as well as physical and sexual development. Fasting blood sugar and HbA1c levels should be monitored<sup>67)</sup>.

### 5. Female FH Patients Capable of Becoming Pregnant

While improvement of lifestyle habits is fundamental to therapy, it is usually necessary to lower LDL-C through drug therapy<sup>68)</sup>. In the case of female patients at an age where they are capable of becoming pregnant, a specialist in dyslipidemia treatment from puberty onwards should be consulted. Taking account of the degree of risk for individual patients, the specialist should consider when to commence drug therapy, the type of drug and other aspects.

In pregnancy, as there is the risk of fetal malformation and other problems with lipid-lowering drugs other than bile acid adsorbing resins, care has to be taken. According to the National Institute for Health and Clinical Excellence, if a patient is determined to be pregnant during drug therapy, medication should be immediately withdrawn. If a patient desires to become pregnant during drug therapy, administration should be discontinued 3 months before conception is planned, during pregnancy and lactation.

To ensure concern-free pregnancies and births in HoFH patients desiring to conceive, CAD as well as aortic valve stenosis and supravalvular aortic stenosis should be screened for and appropriate treatment conducted as necessary<sup>69)</sup>.

It is particularly important for HoFH patients to plan their pregnancy and the arteriosclerosis status should be assessed through screening prior to conception by means of echocardiography, electrocardiography, exercise electrocardiograms or carotid ultrasonography. Lipid lowering drugs other than bile acid adsorbing resins should be ceased 3 months prior to the planned date of conception. LDL-C and TG levels are known to rise further during pregnancy in FH patients and increases of around 30% in LDL-C and around 100% in TG have been observed from the 24th week of pregnancy onwards<sup>70)</sup>.

The following have been observed during pregnancy in FH. Blood coagulation and platelet function were enhanced, which increased blood viscosity tests<sup>71)</sup>, and in HoFH, uteroplacental blood flow was decreased as compared with normal pregnancy but blood flow improved with LDL apheresis therapy<sup>72)</sup>. In the final phase of pregnancy, particularly around the time of birth, as there is great stress on the cardiovascular system, it is advisable for the patient to undergo LDL apheresis. LDL apheresis may be safely performed during pregnancy and problem-free births afterwards have been reported<sup>49, 73, 74)</sup>. During breast feeding too, it is advisable to withdraw lipid-lowering drugs other than bile acid adsorbing resins and continue to perform LDL apheresis periodically to keep LDL-C under control.

### COI

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## Classification of Evidence Levels in Relation to Treatment and Diagnosis

- 1 + High-quality RCT\* and their MA/SR
- 1 Other RCT\* and their MA/SR
- 2 Prospective cohort studies, their MA/SR, and (pre-determined) RCT sub-analysis
- 3 Non-randomized comparative studies, before–after comparative studies, and retrospective cohort studies. Case–control studies, their MA/SR, and RCT post hoc sub-analysis
- 4 Cross-sectional studies and case series

## RCT: Randomized Controlled Trial, MA: Meta-Analysis. SR: Systematic Review

\*A high-quality RCT is defined as a study that (1) involves a large number of subjects (high statistical power), (2) is double-blinded and independently assessed, (3) has a high follow-up rate (low drop-out rate) and few of protocol deviations, (4) includes a clear method for random allocation, etc.

## Recommendation Levels

A Strong recommendation

B Weak recommendation

Recommendations made according to consensus are indicated by the word “consensus.”

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