Editorial

Optimal Treatment using Statins from Childhood in Heterozygous Familial Hypercholesterolemia

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Familial hypercholesterolemia (FH) is “underdiagnosed and undertreated” and a very common inherited disease. Most FH patients are not appropriately diagnosed and this is a reason why they are not treated intensively¹⁾. Premature coronary artery disease (CAD) remains a menace to the patients with FH even in this era of strong statins. All adult patients with FH should be intensively treated using high-dose statins, but low-density lipoprotein (LDL)-lowering effects of conventional drugs including strong statins are not enough for many FH patients after their cardiovascular events. This is the second reason of “undertreatment”. There is an urgent need to prevent early deaths due to premature coronary artery disease in FH.

Secondary prevention is more difficult than primary prevention. Lowering LDL-C levels to the “normal” range during childhood is more feasible and reliable for reducing the lifetime CAD risk than lowering the levels to <100 or 70 mg/dL in adult FH patients with established atherosclerosis. PCSK9 monoclonal antibodies have recently been developed with remarkable efficacy and considerable safety in clinical studies²⁾, but even with this class of drugs, established atherosclerosis should be irreversible. Early identification is essential to prevent early deaths, and children belonging to FH families should undergo a screening before the age of 10 years³⁾.

It has been hypothesized that atherosclerosis starts in childhood. Clinical studies such as the PDAY study or the Bogalusa Heart Study have demonstrated that dyslipidemia in youth clearly accelerates early ath-

erosclerotic changes in the carotid artery, aorta, and coronary artery^{4, 5)}. Analysis of carotid intima-media thickness (cIMT) has shown that increased cIMT is already evident at the age of 7 years in children with FH⁶⁾. Elevated cholesterol levels early in life accelerate the development of CAD during adulthood, and lowering the levels in children and adolescents must be beneficial in FH.

The cumulative “LDL-C burden” model, in which LDL-C burden = sum of LDL-C levels × years of age, has been recently focused on; the model should be translated as a threshold for CAD⁷⁾, based on the data from the Dutch FH register. The early initiation of low-dose statins could be more beneficial than a late initiation of high-dose statins for FH heterozygotes. For example, low-dose statins initiated at 10 years of age have an advantage over high-dose statins initiated at 18 years of age as per this model (**Fig. 1**).

Which drug should be the first-choice in children with FH? Bile acid-binding resins had been the first choice for children because of their established safety; they exerted their effects only in the intestinal lumen and did not have any systemic effects. In USA, NECEP recommended bile acid-binding resins in 1992⁸⁾. Japanese Guideline has recommended resins so far based on its safety^{9, 10)}. On the other hand, resins have limited effects on LDL-C lowering and limited evidence for CAD prevention compared with statins. The American Heart Association has decided to recommend statins for children with FH in 2006¹¹⁾, and now many guidelines recommend statins for children and adolescents with FH (**Table 1**).

It should be mentioned that many guidelines recommend drug therapy after lifestyle modification approximately at 6–12 months. Sometimes, lipid levels fluctuate widely during puberty. On the other hand, lifestyle interventions are important, but alone are insufficient in FH.

In their article, published in the present issue, Harada-Shiba *et al.* report the efficacy and safety of pitavastatin in Japanese male children with FH¹²⁾.

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Fig. 1. LDL-C burden in non-FH and FH subjects depending on different age groups of starting statin therapy⁷⁾. The cumulative LDL-C burden of a 55 year old non-FH patient is 160 mmol, and it has been reached by an untreated-FH patient by the age of 35 years, by an FH patient treated since age 18 years by the age of 48 years, and by an FH patient treated since age of 10 years by the age of 53 years.

Pitavastatin moderately safely reduced LDL-C levels in these children.

It is noteworthy that no statin had been approved for children in Japan before, and all statins were prescribed for children as off-label use. Although doctors had been able to prescribe statins for children as off-label use, needless to say, official approval is desirable. In the USA and Europe, simvastatin, lovastatin, atorvastatin, pravastatin, fluvastatin, and rosuvastatin have been approved for use in children with FH. In Australia, pravastatin, simvastatin, and fluvastatin have been licensed for children. Now, Livalo® (pitavastatin) has become a sole approved statin for children with FH in Japan with the data of this study. Generic pitavastatin is still off-label for children with FH in Japan officially.

Concerns of adverse effects with statin use in children have been discussed for many years, because children are not miniature adults. One concern of statin use in children is hormonal changes. The guidelines recommend monitoring the physical and sexual development, although repeated short-term have reported showed very small effects in hormonal changes¹³⁾. In addition, the potential effect on the central nervous system has been discussed, and most approved statins are licensed for children >8–10

years of age. Statins are contraindicated for pregnant and nursing women, and all young females with FH are recommended to receive pre-pregnancy counseling. The guidelines recommend the use of oral contraceptives, if indicated. Clinicians also should be aware of the possibility of fetal complication in accidental pregnancy while taking statins, which has been reported to be relatively less¹⁴⁾.

Should boys and girls start treatment at similar ages? The cardiovascular events of female heterozygous FH in the second or third decades are much rare compared with male FH. However, most young females with FH must stop taking statins at least several years in total before planned conception and during pregnancy and nursing. Recent guidelines recommend similar age for starting medications taking into account female disadvantage in LDL-C burden^{3, 15)}. Recent paper reported that CHD mortality rates in young females (aged <55 years) demonstrated no improvements in contrast to dramatic decline in older males or females during three decades¹⁶⁾. Generally, young females have been left behind in CVD prevention, but young female with FH should be one of the highest CVD risk groups even if occurring later in life than in males.

We should be aware of the limitations of the data

Table 1. Summary of the Drug Recommendations in Guidelines for Children and Adolescents with Heterozygous FH^{1, 3, 8, 11, 18-23)}

Area (year)	Guideline committee/ Academic society	Medication considered after adequate diet-therapy in	First-choice drug	Initial LDL-C targets	Ref.
USA (1992)	NCEP Expert Panel on Blood Cholesterol Levels in Children and Adolescents	Age ≥ 10 years and LDL-C ≥ 190 , or > 160 mg/dL with additional CVD risks [*]	Bile acid-binding resins	–	8
USA (2006)	American Heart Association	Age ≥ 10 years in males and after menarche in females, and LDL-C ≥ 130 mg/dL	Statins	LDL-C < 130 mg/dL	11
USA (2007)	American Heart Association	Age ≥ 10 years in males and after menarche in females, and LDL-C ≥ 190 , or > 160 mg/dL with additional CVD risks [*]	Statins	Minimal, LDL-C < 130 mg/dL Ideal, LDL-C < 110 mg/dL	18
USA (2008)	American Academy of Pediatrics	Age ≥ 8 years, and LDL-C > 190 , or > 160 mg/dL with additional CVD risks [*]	Statins	LDL-C < 160 mg/dL (110–130 mg/dL in high-risk group)	19
UK (2008)	National Institute for Health and Clinical Excellence	Usually by the age of 10 years with proven FH	Statins	–	20
Australia (2011)	Australian Atherosclerosis Society	Age ≥ 10 years in males and after menarche in females.	Statins	Intermediate risk: LDL-C < 155 mg/dL High risk: LDL-C < 116 mg/dL	21
USA (2011)	American Academy of Pediatrics	Age ≥ 10 years and LDL-C ≥ 190 or ≥ 160 mg/dL with additional CVD risks [*]	Statins	LDL-C < 130 mg/dL	22
USA (2011)	National Lipid Association Expert Panel on Familial Hypercholesterolemia	Age ≥ 8 years and LDL-C ≥ 190	Statins	50% reduction in LDL-C or LDL-C < 130 mg/dL.	23
Japan (2012)	Japan Atherosclerosis Society	Age $\geq 8-10$ years in males and after menarche in females, and LDL-C ≥ 190 , or ≥ 160 mg/dL with additional CVD risks [*]	Bile acid-binding resins	–	9,10
Europe (2013)	European Atherosclerosis Society	Age $\geq 8-10$ years with proven FH	Statins	LDL-C < 135 mg/dL	1
Global (2014)	International FH Foundation	Age $\geq 8-10$ years with proven FH	Statins	Age of 8 and 10 years: LDL-C < 155 mg/dL Age > 10 years: LDL-C < 135 mg/dL	3

^{*}Family history of premature CAD in first-degree relatives or additional risk factors. Please refer to original articles for details.

available at present. It is difficult to discuss the absolute CAD events during childhood, and studies have shown the benefit of drug interventions are based on surrogate markers such as cIMT¹⁷⁾. However, it is not ethically realistic to conduct a randomized controlled study from childhood until the age when CAD frequently occurs. In addition, it is still uncertain that the concept of LDL-C burden model can be applied

equally to boys and girls. Moreover, long-term safety data on physical and sexual development including fertility is not currently sufficient. Some increase has been noted in the risk of diabetes on using statins in adults, but data is limited in children. Prospective data must be carefully collected from childhood on the long-term safety.

Optimal treatment with statins since childhood

is a feasible and promising strategy to prevent early cardiac deaths in patients with FH. The early initiation of statins can result in almost normalized CAD risk throughout their life. Although there is some unresolved safety concerns, there are no obvious harmful evidence overwhelming expected benefits till date. We should judge the balance between the merits and demerits of the early initiation of statins in young FH.

Conflicts of Interest

Dr. Nohara
 Sanofi – Research Grants
 MSD – Research Grants
 Shionogi – Research Grants
 Kowa – Research Grants
 Astellas – Research Grants
 Aegerion – Research Grants
 Astra-Zeneca – Research Grants

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