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Editorial

How much further do we need to decrease LDL cholesterol levels in heterozygous familial hypercholesterolemia?

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Familial hypercholesterolemia (FH) is a genetic disease characterized by hypercholesterolemia, xanthomas and atherosclerotic cardiovascular diseases (ASCVD) [1]. To prevent atherosclerosis, accurate diagnosis and appropriate treatment from a young age are needed [2]. Statins is the standard therapy and ezetimibe or other lipid lowering drugs are added, if necessary. Usually, the effects of drugs are evaluated using a double blind, randomized, controlled study. It takes several years to get results on the assessment of the effects of a lipid lowering drug on ASCVD prevention. It is unethical to allocate a placebo group to FH patients for several years. Therefore, it has been difficult to evaluate the efficacy of lipid lowering drugs on the prevention of ASCVD in FH.

The paper of Perez-Calahorra et al. published in this issue of *Atherosclerosis* describes an observational, retrospective, multicenter, nationwide study in 1958 heterozygous FH patients in Spain [3]. The conclusion of the study from the clinical practice setting were as follows: 1. the proportion of cardiovascular disease (CVD) in FH was identified. 2. The prevalence of CVD decreased after statins were launched, showing a 10-fold lower risk. 3. The longer the exposure to lipid-lowering drugs, the higher the prevention rate of CVD. 4. In patients taking a high intensity statin, CVD risk was low. However, as the number of classical risk factors increase, CVD risk also increases.

In FH, the exposure to high LDL-C levels usually starts from birth and continues, and atherosclerosis progresses from childhood. Carotid intra-media thickness (IMT) in FH children compared with their non-FH siblings shows a significant increase from about 9 years of age, and the difference increases as age progresses [4]. CVD occurs more frequently in males between 30 and 40 years, females between 40 and 50 years, and FH patients have CVD 15–20 years younger than healthy individuals [5]. According to the paper by Nordestgaard et al., if a cumulative LDL-C is increased to the threshold level, the patient may have CVD [6]. The results of the current paper also show that patients registered under the age of 40 have a low morbidity rate of CVD and their incidence increases as the age of treatment intervention rises.

CVD risk factors in FH have been reported to age, male sex, diabetes mellitus, hypertension, high triglyceride levels, low HDL-C levels, high Lp (a) levels, mutations in *LDLR*, mutations in both *LDLR* and *PCSK9*, and so on [7–9]. In this study, the prevalence of CVD increased with the increasing number of classic risk factors under treatment with high intensity statins. In FH, since the amount of LDL-C is close to the threshold value, it is conceivable that the threshold value itself is lowered due to the presence of the risks, resulting in high incidence of CVD in young age. It may be possible to perform risk stratification of FH dependent on scoring the risks by accumulation and analyze the data of FH as described in the current paper.

Many guidelines of FH describe the importance of diagnosis and treatment interventions in childhood [2,10]. The safety and efficacy of statins from childhood have already been shown [10,11]. The accumulation of LDL-C can be lowered by early therapeutic intervention. Needless to say, the most effective prevention of CVD in FH is represented by an early diagnosis and appropriate treatment. Screening in childhood is mainly performed by cascade screening, when patients are diagnosed as FH, their family needs to be screened. On the other hand, in some areas, universal screening is conducted. If this is a chance to change the patients' lifestyle, consult a doctor and start an appropriate therapy, it has a positive effect on their health status. From the view point of cost-effectiveness, cascade screening is useful.

As mentioned, it is difficult for lipid lowering drugs to prove the preventive effect of ASCVD in FH. It was reported ASCVD occurred at an older age after statin treatment was launched [5]. Not only launching statins but also patients' life style such as diet, risk of cigarette smoking, hypertension, etc. were significantly improved. It is reported that the prognosis of FH patients taking statins is almost the same as that of general residents in the Rotterdam Study [12]. In the current paper, the risk of CVD is low in patients taking high intensity statins and the longer the exposure to lipid-lowering drugs, the higher the prevention rate of CVD. It clearly suggests that high intensity statins

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Table 1
Target LDL C levels in heterozygous familial hypercholesterolemia in each guideline.

	ESC/EAS (2016)	AACE/ACE (2017)	JAS (2017)
Primary prevention	< 100 mg/dL Children < 135 mg/dL	< 70 mg/dL	Adults < 100 mg/dL or < 50% of pretreatment level Children < 140 mg/dL
Secondary prevention	< 70 mg/dL	< 55 mg/dL	< 70 mg/dL

ESC: European Society of Cardiology; EAS: European Atherosclerosis Society; JAS: Japan Atherosclerosis Society; AACE: American Association of Clinical Endocrinologists; ACE: American College of Endocrinology.

have a significant effect on CVD prevention.

From the view point of LDL-C accumulation, the target LDL-C levels should be low in FH. The therapeutic target level of LDL-C in FH for primary prevention is less than 100 mg/dL, and for secondary prevention, less than 70 mg/dL in some guidelines (Table 1) [10,13]. In the AACE/ACE guidelines, target levels are lower for primary prevention, 70 mg/dL, and secondary prevention, 55 mg/dL, [14]. Santos et al. reported the concept of severe FH, which is defined according to high untreated LDL-C levels, the presence of subclinical atherosclerosis and clinical ASCVD [15]. In the severe FH patients, the ideal goal of LDL-C was suggested to be less than 70 mg/dL and a realistic goal was to decrease LDL-C levels to less than 50% of the pretreatment level [15]. In patients whose LDL-C levels do not reach the target level using statins and/or ezetimibe, a PCSK9 inhibitor is recommended.

PCSK9 inhibitors, evolocumab and alirocumab, showed 15% reduction in the incidence of ASCVD in randomized controlled studies: FOURIER Study and ODYSSEY Study [16,17]. In the sub-analysis of the FOURIER Study, the lowest LDL-C group showed the lowest incidence of ASCVD. It is considered that the concept of “the lower the better” applies to the extremely low LDL-C value [18]. By using PCSK9 inhibitors, LDL-C levels can be reduced to much lower levels even in FH patients in addition to statins and/or ezetimibe treatment. Since the medical cost of PCSK9 inhibitors is high, the issue of cost-effectiveness is a matter of debate. FH patients with high risks, such as those who have multiple risks as described in the present paper, are thought to be good indicators. It may not be so difficult to reduce LDL-C levels in HeFH patients after launching new drugs, but the issue of whether the target levels of LDL-C in FH patients should be decreased further in guidelines, needs more discussions.

As shown in the present paper, other atherogenic risks need to be taken into account. Residual risks, such as hypertension, diabetes mellitus, obesity, hypertriglyceridemia, need to be strictly controlled. In addition, several drugs have been developed, targeting apolipoprotein (a) and apolipoprotein C3 by using antisense oligonucleotides [19,20]. Their cutting-edge technologies of chemically modified antisense made it possible to target any molecules related to pathogenesis or pathophysiology. In the future, the atherogenic lipoproteins related to residual risks may be controlled using these drugs.

Conflict of interest

Dr. Harada-Shiba reports grants and personal fees from Astellas, grants from Aegerion, grants and personal fees from Astellas Amgen, grants and personal fees from Sanofi, grants from Kaneka Medics, grants and personal fees from MSD, grants from Takeda.

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