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EDITORIAL COMMENT

Risk Stratification in Familial Hypercholesterolemia

Do Severe Phenotypes Have Clinically Worse Outcomes in Asia Population?*

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Familial hypercholesterolemia (FH) is the most common genetic-associated disease which is characterized by elevated low-density lipoprotein cholesterol (LDL-C) concentration and premature coronary artery disease (CAD) with the frequency of heterozygous FH (HeFH) estimated at 1 in roughly 200-500 individuals including the United States, European, and Asian populations (1,2). Although the pathogenesis of FH has similar mechanism in patients attributing to genetic mutation, individuals with FH have clinically presented a significant heterogenous in real-world practice. Theoretically, this variation in clinical phenotype mainly depends on the gene involved and severity of mutation present (3).

As is well known, patients with homozygous FH (HoFH) phenotype are at highest risk for atherosclerotic cardiovascular disease (CVD). However, with more widespread use of molecule diagnosis, data have shown that some subjects carrying the heterozygous mutation of genes associated with FH have cholesterol concentrations that overlap those deemed characteristic of HoFH (usually ≥10-13 mmol/L [400-500 mg/dL]) are termed compound HeFH, who encountered a higher risk of atherosclerotic CVD (4). Besides, FH subjects with high LDL-C levels and multiple risk factors have also presented high-risk for cardiovascular events. Based on these findings, a concept of severe FH has been developed to cover HoFH and compound HeFH patients who have different genetic mutation background but similar clinical phenotype in order to help to make cardiovascular risk stratification more precise and clinical management more aggressive by the International Atherosclerosis Society (IAS).

Following this notion, much attention has been paid for the individuals who had severe FH phenotype around the world, especially in the United States and in European countries. Several previous studies prospectively examined the association of severe FH, according to IAS definition, with coronary events in HeFH individuals. Humphries et al (5) evaluated the cardiovascular outcomes of 2,929 FH patients aged from 20 to 79 years and recruited from 21 U.K. lipid clinics using a data from the U.K. Simon Broome registry and found that CAD mortality was 64% higher in the severe FH than in nonsevere phenotype ones. Besseling et al (6) analyzed a cohort of 14,238 patients with molecularly defined HeFH identified by the national FH screening program in the Netherlands. They determined the age- and sex-specific percentiles of untreated LDL-C and the percentile corresponding to an LDL-C level of 8 mmol/L (309 mg/dL) in men aged from 36 to 40 years, which was selected as the cut-off value for severe HeFH. The results showed that CVD risk was significantly increased in severe HeFH patients compared to nonsevere HeFH ones. In addition, Pérez-Calahorra et al (7) evaluated 1,732 HeFH cases recruited from the dyslipidemia registry from the Spanish Atherosclerosis Society that covered 50 certified lipid units and found that 656 (77.1%) and 441 (50.1%) of men and women, respectively, fulfilled the IAS criteria for severe HeFH. The patients with severe FH had higher CVD risk (odds ratio [OR]: 3.016; 95% confidence interval [CI]: 3.136 to 4.257; $P < 0.001$) under the condition of the presence of LDL-C >400 mg/dL. Nevertheless, whether this criterion could appropriately stratify high-risk FH patients in Asian patients has not been determined.

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In this issue of *JACC: Asia*, with a cohort of 380 Japanese HeFH individuals, Funabashi et al (8) reported that severe FH accounted for 40.3% of them. The severe HeFH patients were characterized by being older; more frequently male; and having a history of hypertension, type 2 diabetes mellitus (T2DM), and smoking, and having a family history of premature CAD. Additionally, the tendon and skin xanthomas and corneal arcus were more frequently observed in patients with severe HeFH. More importantly, the patients with severe HeFH substantially had elevated atherosclerotic risks, and harbored a heightened CVD risk which involved not only coronary arteries but also other systemic arteries. The magnitude of their increased risks still continued following first atherosclerotic event. These findings might add more information regarding the features of severe FH in the Asia population, supporting IAS-proposed approach in Japanese HeFH patients.

In fact, previous studies have suggested that atherosclerotic CVD risk in FH depends not only on exposure to very high plasma LDL-C concentrations, but also on nonlipid factors, including smoking, obesity, hypertension, diabetes, low high-density lipoprotein cholesterol, and history of premature CAD in the first-degree relatives (9). Consistent with those findings and the IAS severe-FH definition, a recent study from Chinese HeFH patients has shown that FH patients with T2DM had a greater number of diseased vessels, more severe coronary lesions with high Gensini, SYNTAX, and Jeopardy score tertiles, and more hard endpoints within a median of 3.75 years follow-up (10), suggesting that nonlipid disorders could also inflict worse impact on CVD risk in patients with HeFH except for LDL-C concentration.

The other genetic and lipid-related factor can also impose a bad effect on patients with HeFH, for example, lipoprotein(a) [Lp(a)]. A number of studies have shown that elevated Lp(a) concentration might genetically and casually be associated with CVD risk in FH patients, which could be applied as a lipid marker for cardiovascular risk stratification (11). Indeed, the patients with FH had a higher Lp(a) concentration compared to those without (11,12). Recently, an age- and sex-matched case control study showed that plasma proprotein convertase subtilisin/kexin type 9 (PCSK9) level was positively associated with Lp(a) concentration in HeFH patients but not in non-HeFH individuals, suggesting a potential interaction of PCSK9 with Lp(a) in HeFH patients (13). More interestingly, another observation showed that baseline, even on-statin treatment Lp(a) levels could predict cardiovascular events in patients with HeFH (14). Data from Japanese HeFH patients observed by Funabashi et al (8) also suggested a clinical significance of Lp(a) in severe HeFH and showed that patients with severe FH had higher Lp(a) levels (22.7 md/dL vs 16.7 mg/dL, $P = 0.03$) and more cardiovascular events (a 9.3-fold greater risk for first composite outcomes compared to those with nonsevere FH in Japanese individuals). Thereby, further studies may be needed to explore the relation of Lp(a) to cardiovascular outcomes in patients with severe FH because previous subanalysis of FOURIE (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk) and ODYSSEY (Once-daily DTG based ART in Young people vS. Standard thErapY) studies reported that a reduction of Lp(a) level under PCSK9 inhibitors was independently associated with a lower risk of major adverse cardiac events even after adjusting LDL-C level (15). Hence, targeting Lp(a) may ultimately become additional potential approach in overcoming residual risks of severe FH.

Although the clinical value of severe FH definition has been demonstrated by several real-world studies, genetic background for those patients has less been understood. Funabashi et al (8) reported that severe FH had more LDL-receptor pathogenic variants, similar PCSK9 pathogenic variants compared with non-severe FH, and data were unavailable regarding apolipoprotein B pathogenic variants between severe FH and non-severe FH, suggesting a need for more intensive genetic exploration for patients with severe FH. In fact, previous studies have indicated that LDL-C concentrations are affected not only by rare, large effect monogenic variants but also by common, small-effect gene variants, resulting in the overlap of LDL-C concentrations between HoFH and HeFH patients (4). A previous study has shown that expanding genetic analysis could improve the definite diagnosis of severe FH except for the screening genes encoding the LDL receptor, apolipoprotein B, and PCSK9 (16).

On all accounts, the concept of severe FH also has several clinical implications for the Asian population. Characterizing molecular background and defining the role of other cardiovascular risk factors in severe FH may be helpful for further cardiovascular risk stratification in patients with severe FH, which facilitates early and more aggressive treatment for these higher-risk patients with FH, even in the Asian population.

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