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EDITORIAL COMMENT

Seeing Is Believing

Atherosclerotic Burden Predicts Very Long-Term CVD Risk in Patients With HeFH*

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Heterozygous familial hypercholesterolemia (HeFH) is an autosomal dominant disorder affecting approximately 1 in 313 individuals characterized by very elevated low-density lipoprotein-cholesterol (LDL-C) levels leading to premature atherosclerotic cardiovascular disease (ASCVD).[1] The diagnosis of family history (FH) may be made by clinical criteria or via genetic testing with the most common pathogenic mutations occurring in the low-density lipoprotein receptor, apolipoprotein B, proprotein convertase subtilisin/kexin type 9, and low-density lipoprotein receptor adaptor protein 1 genes.

Despite its high worldwide prevalence, affecting up to 30 million people globally, only 10% are currently diagnosed, and >80% do not attain recommended LDL-C goals. However, the high risk of ASCVD can be significantly decreased with the use of statin therapy. Thus, early diagnosis and proper treatment are essential for this group.[2]

The ideal age at which a patient with HeFH should undergo imaging to identify subclinical atherosclerosis remains uncertain due to the heterogeneity of risk, which is due to factors such as the cumulative LDL-C exposure and presence of other ASCVD risk factors. However, postmortem studies have demonstrated that even among persons without FH, the atherosclerotic process begins early in life. In a study of 105 US soldiers killed in Vietnam with a mean age of 22 years, 45% had atherosclerosis and 5% had severe coronary atherosclerosis.[3] Therefore, a better understanding of the natural history of atherosclerosis, its detection on imaging, and associated long-term risk for ASCVD among patients with HeFH is vital for individualized ASCVD risk stratification and determining appropriate LDL-C targets.

However, precise estimation of ASCVD risk among patients with HeFH remains challenging. Risk scores based on traditional ASCVD risk factors such as the pooled cohort equation and the European Systematic Coronary Risk Evaluation (SCORE) were not developed for use in patients with FH and underestimate the ASCVD risk in these patients.[4] A number of other ASCVD risk calculators have been developed for patients with HeFH including Montreal-FH-SCORE, SAFEHEART-RE, and FH-Risk-Score.[5] However, these risk scores have a number of limitations including recommendation for use only among middle-aged persons, prediction of short-term ASCVD risk, and an absence of assessment for cumulative LDL-C exposure.

Both coronary computed tomography angiography (CTA) and carotid ultrasonography are noninvasive imaging modalities to measure an individual's atherosclerotic burden in different vascular beds. Carotid plaque is a stronger predictor of ASCVD than increased carotid intima-media thickness, but both are less strongly associated with ASCVD than measurements of coronary atherosclerosis.[6,7] However, carotid ultrasonography can add complementary information, as even among patients with coronary artery calcium, the presence and extent of carotid plaque detected on ultrasonography have been

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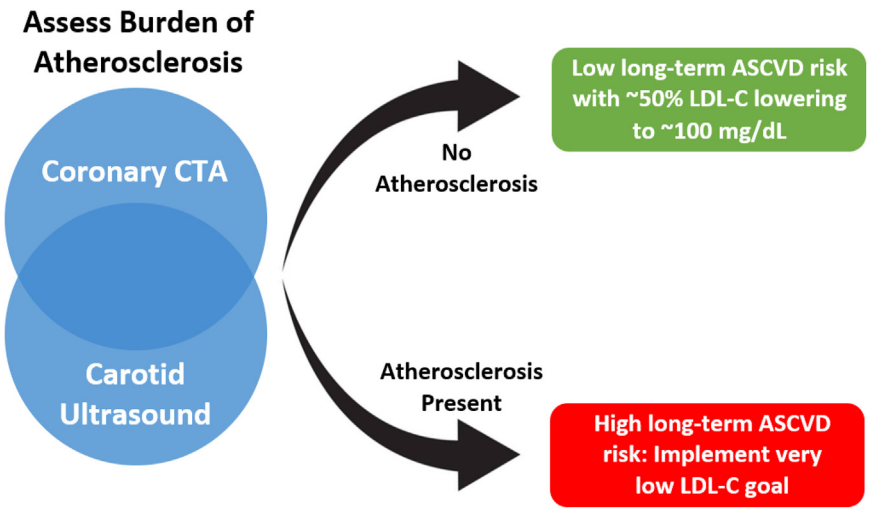
FIGURE 1 Suggested Algorithm for Evaluating Atherosclerotic Cardiovascular Disease Risk and LDL-C Treatment Goal Among Patients With Newly Diagnosed Heterozygous Familial Hypercholesterolemia



ASCVD = atherosclerotic cardiovascular disease; CTA = computed tomography angiography; LDL-C = low-density lipoprotein-cholesterol.

associated with cardiovascular disease risk and incident coronary artery calcium.[8]

In this issue of *JACC: Advances* Tada et al[9] examined 622 patients with newly diagnosed HeFH who had carotid ultrasonography and coronary CTA performed within 1 year of the diagnosis of HeFH. All patients were admitted to Kanazawa University Hospital in Japan between the years 2000 and 2020, where carotid ultrasound is routinely performed for patients with HeFH. Subsequent clinically indicated coronary CTA was also performed, most often due to the presence of carotid plaque. The mean age of patients was 52 years, with approximately equal numbers of men and women and a mean pretreatment LDL-C of 229 mg/dL. Patients were followed over a median of 13.2 years, and a total of 132 patients had major adverse cardiovascular events (MACEs).

The presence of any coronary plaque or carotid plaque was associated with a high absolute rate of MACE, 24.1 and 20.5 per 1,000 person-years, respectively. Furthermore, after adjustment for traditional risk factors, both coronary plaque score (HR: 3.33; 95% CI: 1.88-4.78) and carotid plaque score (HR: 2.24; 95% CI: 1.28-3.20) were significantly associated with an increased with of MACE (**Figure 1**).

This study demonstrated that individuals with HeFH who had an absence of carotid plaque (1.0 per 1,000 person-years) or coronary plaque (0.7 per 1,000 person-years) had a low absolute rate of MACE. Among the 41% of patients with both a carotid and coronary plaque score less than the median, there was also an extremely low long-term rate of MACE over a 20-year follow-up, as seen in the Kaplan-Meier survival analysis. Conversely, patients with above the median carotid and coronary plaque scores at the time of diagnosis had an approximately 75% cumulative incidence of MACE over a 20-year follow-up. These findings highlight the importance of early diagnosis for HeFH and that when LDL-C lowering therapies are started before the development of plaque; excellent long-term ASCVD outcomes are achievable.

Perhaps the most notable finding from this study is the very long follow-up duration with a median of 13.2 years and extending beyond 20 years for some patients is a major strength of this study. To the best of our knowledge, this is the longest follow-up time for cardiovascular disease event outcomes among a HeFH cohort with coronary CTA data.[10,11] The study also benefited from the use of genetic testing, which identified 425 individuals (68.3%) with a pathogenic mutation. Additionally, LDL-C control at follow-up was good, with a mean 47% reduction in LDL-C (baseline 229 mg/dL vs follow-up 108 mg/dL).

One limitation of this study is the lack of universal use of coronary CTA. While carotid ultrasound was performed for all patients with FH, coronary CTA was performed predominantly in

those with evidence of carotid plaque or chest pain. Thus, it is likely that some patients with coronary atherosclerosis but no carotid plaque may have been missed. Additionally, while there was a similar proportion of women and men in this study, further long-term follow-up studies are needed to confirm the generalizability of these findings from a single hospital cohort.

We congratulate the authors of this important study, which provides significant insight into the burden of atherosclerosis and the importance of early atherosclerosis imaging for ASCVD risk stratification among middle-aged patients with newly diagnosed HeFH. Perhaps most importantly, this study demonstrated that even among patients with genotype-confirmed HeFH, there is significant heterogeneity in ASCVD risk and an excellent long-term prognosis for persons without subclinical atherosclerosis who achieve an ~50% reduction in LDL-C to a value of ~100 mg/dL. Accordingly, these results provide strong support for quantifying an individual's atherosclerotic burden early after the diagnosis of HeFH among all persons with HeFH who have not had a clinical ASCVD event. This information provides invaluable prognostic data for individualized ASCVD risk stratification, which can be used to personalize the allocation and intensity of preventive therapies.

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