JACC: CARDIOVASCULAR IMAGING
VOL. 10, NO. 10, 2017

ISSN 1936-878X/$36.00
PUBLISHED BY ELSEVIER
http://dx.doi.org/10.1016/j.jcmg.2016.11.014

EDITORIAL COMMENT

What's a Malignant Family History?

You'll Know It When You See It*

Amit Khera, MD, MSc, Parag Joshi, MD, MHS

Several decades of investigation have engrained the now well-established relationship between family history and predilection to coronary heart disease (CHD). In a seminal study by Marenberg et al. (1) investigating more than 20,000 Swedish twins, the increment in risk accompanying a sibling history of CHD was more than 2-fold greater in monozygotic twins than in dizygotic twins, establishing the genetic underpinnings of family history. However, an equally important observation was the relevance of sibling age at the time of first CHD event. The relative risk of CHD death in surviving identical siblings markedly increased when the affected twin's event occurred at a younger age, with an 8-fold risk when a male sibling was younger than 55 years, but only a 2-fold risk if the sibling was older than 75 years. Thus, it seems that genetic influences may predominate at younger ages, but environmental influences and other risk factors may dilute these genetic effects with aging.

Although genetics certainly play a role in the risk afforded by family history of CHD, the exact biological processes underpinning this association remain unclear. In some families, the heritable factor may be one dominant gene, such as the case with heterozygous familial hypercholesterolemia, which affects roughly 1 in 500 individuals and is characterized by markedly elevated low-density lipoprotein cholesterol levels and the onset of CHD roughly 10 years earlier (2). However, in most, a singular implicated gene is not found, and family history can also represent shared lifestyle factors. Nevertheless, a family history of CHD remains a powerful predictor of future CHD events. In the MESA (Multi Ethnic Study of Atherosclerosis) study, family history of myocardial infarction improved markers of discrimination and risk reclassification for the prediction of CHD and was second only to coronary artery calcium (CAC) among novel markers in such metrics (3).

The impetus to evaluate the association between family history of CHD and subclinical atherosclerosis are 2-fold: to evaluate the merits of screening for atherosclerosis in patients with family history and to determine the implications of family history for atherosclerotic disease and risk. Population-based studies have demonstrated an increased prevalence of CAC in individuals with a family history (4-6). In addition, rather than CAC subsuming all of the CHD risk information that accompanies a family history, it was recently demonstrated that family history of CHD is an independent and additive predictor of CHD risk beyond CAC scoring (7). This suggests that CAC may only tell part of the subclinical atherosclerosis story, focusing solely on calcified plaque, rather than on emerging measurements of plaque composition or other vessel characteristics that confer vulnerability for CHD events (8).

Coronary computed tomography angiography (CTA) has provided an enhanced window into the implications of family history. In the CONFIRM (COronary CT Angiography EvaluatioN For Clinical Outcomes: An InteRnational Multicenter Registry) registry, younger patients with a self-reported family history of CHD had a higher prevalence of obstructive coronary artery disease (CAD) and nonobstructive CAD than patients without a family history (9). Interestingly, this difference was driven by a greater prevalence of noncalcified or partially calcified plaque rather than solely calcified plaque, highlighting the potential for missed atherosclerotic disease in younger patients with family history using CAC scanning alone. The GeneSTAR (Genetic Studies of Atherosclerosis Risk) family study performed CTAs for 805 apparently healthy family members of individuals with documented premature CHD (<60 years of age). In this asymptomatic cohort, 45% of

*Editorials published in *JACC: Cardiovascular Imaging* reflect the views of the authors and do not necessarily represent the views of *JACC: Cardiovascular Imaging* or the American College of Cardiology.

From the Department of Internal Medicine, Division of Cardiology, University of Texas Southwestern Medical Center, Dallas, Texas. Both authors have reported that they have no relationships relevant to the contents of this paper to disclose.

subjects had some form of coronary plaque, despite the fact that most were under the age of 55, and there was a preponderance of noncalcified plaque (10). Although that study highlighted the higher burden of subclinical atherosclerosis in coronary CTA in relatives of those with a premature family history of CHD, it did not include a control group and did not investigate emerging markers of plaque composition and vessel remodeling.

SEE PAGE 1128

In this issue of *iJACC*, Christiansen et al. (11) similarly enrolled 88 apparently healthy relatives of individuals with premature CHD for coronary CTA assessment. However, the probands with CHD were identified by having percutaneous coronary intervention or bypass graft surgery before the age of 40, suggesting a particularly malignant course of atherogenesis. In addition, the study also included a control group of registry participants without family history who underwent clinically indicated coronary CTA, but this group consisted of symptomatic patients. A major enhancement in this study was going beyond quantification of calcified and noncalcified plaque but also investigating additional high-risk parameters of plaque composition and vessel characteristics. More recently, it has been demonstrated that these characteristics can be assessed noninvasively with coronary CTA, with 2 particular parameters, low-density noncalcified plaque (LD-NCP) and positive remodeling, which is highly predictive of subsequent acute coronary syndrome, beyond assessment of plaque stenosis (8).

The authors demonstrated that asymptomatic relatives of those with family history had a greater prevalence for any plaque (70%) and obstructive plaque (15%) than symptomatic controls (51% and 10%, respectively), despite the fact that, other than dyslipidemia, the risk factor levels were comparable between the 2 groups. There was also a predilection for more proximal segment CAD, higher Agatston score, and greater calcified and noncalcified plaque volume in those with a family history. Importantly, the adjusted risk of having plaques with positive remodeling or LD-NCP were more than 4-fold greater in those with a family history than without.

Several observations should be noted when deciphering the implications of this carefully performed study. First, the control group included symptomatic participants who commonly had greater atherosclerosis burden and, thus, actually biasing the findings in this study toward the null. Perhaps most importantly, the inclusion criteria included an extreme phenotype for the proband, coronary revascularization before 40 years of age, which is well beyond the standard threshold age used in both clinical practice and most major studies of family history of CHD. As demonstrated in the study by Marenberg et al. (1) more than 20 years ago, the risk increment to family members of those affected by CHD is almost exponential with younger age of CHD onset. In fact, CHD at such young ages raises concerns for familial hypercholesterolemia as the heritable factor, which is known to accompany increased atherosclerosis burden (12). Although the authors mention excluding those with a diagnosis of familial hypercholesterolemia, the diagnostic criteria were not provided. Furthermore, approximately one-third of those with a family history had multiple family members with premature CHD (<40 years of age or between 40 and 55 years of age in males and 40 and 65 years of age in females). Previous studies have demonstrated significantly more CAC in those with multiple family members with premature CHD than in those with just 1 family member (13). By reference, the CONFIRM registry reported significantly lower prevalence of any plaque (40%) and obstructive plaque (11%) in their cohort defined by conventional family history of CHD definitions (9), and the GeneSTAR cohort also reported lower plaque prevalence of 57% and 24% in men and women, respectively, 45 to 54 years of age (comparable to the age of this cohort) (10). In summary, what we are seeing in this study are the repercussions of a particularly malignant family history of CHD.

With these caveats, what are the clinical implications of the study by Christiansen et al. (11) for the assessment and management of CHD risk in patients with family history of CHD? First, the findings reinforce the importance of ascertaining a careful and complete family history of CHD at every clinical encounter to enhance risk and preventive discussions. The clinical relevance of a family history of CHD is frequently underappreciated, particularly in women (14). Also, rather than a binary construct, there are gradations of family history, with especially malignant family histories involving multiple affected first degree relatives or those at unusually young ages. In select individuals, screening for subclinical atherosclerosis, typically with coronary calcium scanning if it will impact treatment decisions, may be considered as the results may provide additive and incremental information for CHD risk (3,7). In fact, family history itself can be a deciding factor when treatment decisions about statins are unclear (15). Whether the addition of coronary CTA information, including markers of vulnerable plaque such as LD-NCP or positive remodeling, adds incremental prognostic value for CHD risk assessment in those with a family history of CHD is unanswered in this study.

JACC: CARDIOVASCULAR IMAGING, VOL. 10, NO. 10, 2017
OCTOBER 2017:1136–8

As such, broad screening for coronary atherosclerotic plaque or vulnerable plaque using coronary CTA in those with a family history cannot be advocated at this time. However, this study certainly adds to the picture of what lies beneath a malignant family history of CHD.

ADDRESS FOR CORRESPONDENCE: Dr. Amit Khera, Division of Cardiology, University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, HA9.133, Dallas, Texas 75390. E-mail: amit.khera@utsouthwestern.edu.

REFERENCES

1. Marenberg ME, Risch N, Berkman LF, Floderus B, de Faire U. Genetic susceptibility to death from coronary heart disease in a study of twins. N Engl J Med 1994;330:1041–6.

2. Nanchen D, Gencer B, Muller O, et al. Prognosis of patients with familial hypercholesterolemia after acute coronary syndromes. Circulation 2016; 134:698–709.

3. Yeboah J, McClelland RL, Polonsky TS, et al. Comparison of novel risk markers for improvement in cardiovascular risk assessment in intermediate-risk individuals. JAMA 2012;308:788–95.

4. Nasir K, Budoff MJ, Wong ND, et al. Family history of premature coronary heart disease and coronary artery calcification: Multi-Ethnic Study of Atherosclerosis (MESA). Circulation 2007;116: 619–26.

5. Parikh NI, Hwang SJ, Larson MG, et al. Parental occurrence of premature cardiovascular disease predicts increased coronary artery and abdominal aortic calcification in the Framingham offspring and third generation cohorts. Circulation 2007; 116:1473–81.

6. Philips B, de Lemos JA, Patel MJ, McGuire DK, Khera A. Relation of family history of myocardial infarction and the presence of coronary arterial calcium in various age and risk factor groups. Am J Cardiol 2007;99:825–9.

7. Paixao AR, Berry JD, Neeland IJ, et al. Coronary artery calcification and family history of myocardial infarction in the Dallas heart study. J Am Coll Cardiol Img 2014;7:679–86.

8. Motoyama S, Ito H, Sarai M, et al. Plaque characterization by coronary computed tomography angiography and the likelihood of acute coronary events in mid-term follow-up. J Am Coll Cardiol 2015;66:337–46.

9. Otaki Y, Gransar H, Berman DS, et al. Impact of family history of coronary artery disease in young individuals (from the CONFIRM registry). Am J Cardiol 2013;111:1081–6.

10. Kral BG, Becker LC, Vaidya D, et al. Noncalcified coronary plaque volumes in healthy people with a family history of early onset coronary artery disease. Circ Cardiovasc Imaging 2014; 7:446–53.

11. Christiansen MK, Jensen JM, Nørgaard BL, et al. Coronary plaque burden and adverse plaque characteristics are increased in healthy relatives of patients with early onset coronary artery disease. J Am Coll Cardiol Img 2017;10: 1128–35.

12. Miname MH, Ribeiro MS 2nd, Parga Filho J, et al. Evaluation of subclinical atherosclerosis by computed tomography coronary angiography and its association with risk factors in familial hypercholesterolemia. Atherosclerosis 2010;213: 486–91.

13. Nasir K, Michos ED, Rumberger JA, et al. Coronary artery calcification and family history of premature coronary heart disease: sibling history is more strongly associated than parental history. Circulation 2004;110:2150–6.

14. Patel MJ, de Lemos JA, Philips B, et al. Implications of family history of myocardial infarction in young women. Am Heart J 2007;154:454–60.

15. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014;63 (25 Pt B):2889–934.

KEY WORDS atherosclerosis, atherosclerotic, coronary artery disease, genetic predisposition to disease, multidetector computed tomography, plaque