Despite multiple studies showing that family history of premature coronary heart disease (CHD) is associated with an increased risk of cardiovascular events, the predictive value of adding family history to established risk scores is often small, and many individuals with family history may not be at increased risk.

This apparent discrepancy has several potential explanations. First, in many epidemiological studies, it is difficult to consistently and accurately account for the presence of a strong family history of premature CHD. For instance, many studies only consider parental history, although there are data to suggest that sibling history of premature CHD may have a stronger association with coronary atherosclerosis. Moreover, most studies do not consider exposure to other risk factors (eg, smoking; diabetes mellitus) among affected family members from prior generations, and only a few studies account for the number of afflicted family members with premature disease. Finally, the age cut point that is used to define premature disease has varied across studies, and almost all studies have used a binary threshold for each sex, which does not allow for any gradation in risk. Put simply, almost all studies have used a binary threshold for each sex, not be at increased risk.

Second, even if we were able to adequately capture detailed information on family history of CHD as well as risk factors that existed in these members (as we often do in the clinical setting), the incremental value of such data beyond risk factors is often small, and many individuals with family history may not be at increased risk.

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In keeping with prior work, the presence of coronary plaque increased with age, male sex, and the presence of traditional risk factors, whereas a higher proportion of noncalcified plaque, as a percent of total plaque, was detected in younger individuals and in women. Interestingly, in a subset of 338 participants who were enrolled in the study because of premature CAD of their sibling, those with a strong sibling history (representing 14% and occurring if ≥50% of the participant’s siblings were affected and ≥1 additional sibling was affected aside from the proband) had a higher prevalence (84% versus 63%, P=0.04) and volume of plaque than those who had a lesser sibling history. These findings support the concept that having multiple affected family members, particularly siblings, confers a higher risk and that obtaining such a history could be used to enrich the rather heterogeneous subgroup of individuals with a family history of premature CAD.

Nevertheless, the study by Kral et al did not report the age at which probands developed disease (all were <60 years old) and did not provide any data on other modifiable risk factors that could have contributed to CAD in the probands. The current study also has no control arm, and thus it is difficult to estimate the burden of excess disease that study participants may have had that could be attributable to their family history rather than to their clinical risk factors. However, notwithstanding these limitations, the study suggests that there is a possible role for screening for CAD in patients with a family history of premature CHD but raises the questions: how, when, and in whom?

How?
CAC scanning offers the ability to noninvasively detect the presence and burden of coronary atherosclerosis and integrates an individual’s exposure to both measured and unmeasured risk factors. Among individuals with no prior CAD, the presence of severe CAC identifies individuals at high risk, even in the absence of risk factors. Conversely, the absence of CAC identifies low-risk individuals with an annual event rate of <0.1%, and consequently the number needed to treat to prevent a CHD event in such individuals would be much higher. Nasir et al found that among 5347 participants in the Multi Ethnic Study of Atherosclerosis, a family history of premature CHD was associated with a higher prevalence and severity of coronary artery calcifications, independent of other risk markers and the Framingham Risk Score, and across all ethnic groups. In this study, and consistent with the data from Kral et al, the presence of plaque (ie, CAC > 0) ranged from 64% in those who had a history of premature CHD in both parents and siblings to 58% if only a sibling was affected and 51% if only a parent was affected. By comparison, plaque was present in 40% of those who had no family history of CHD.

The use of coronary computed tomographic angiography can identify both calcified and noncalcified plaque as well as the presence of stenosis but is more costly than CAC scanning and also requires intravenous contrast. Although this test is not recommended for screening asymptomatic individuals, the study by Kral et al serves as a reminder that calcified plaque represents only a small proportion of the total plaque burden. Therefore, it is possible that a carefully selected subgroup of individuals who are more likely to have predominantly or exclusively noncalcified plaque (eg, younger individuals) may benefit from computed tomographic angiography screening when such information would be expected to have a significant impact on patient management. Nevertheless, neither published data or guidelines currently support such an approach.

When?
Our understanding of the atherosclerotic process suggests that there may be a benefit for treating earlier stages of disease, thus halting the progression of CAD before the development of cardiovascular events. However, we still do not have data whether such interventions will improve outcomes, and detecting earlier stages of disease poses several challenges. For instance, earlier stages of atherosclerosis (eg, before the development of coronary calcifications) are more difficult to detect. For this reason, CAC testing is generally less helpful in individuals <40 years of age. Second, identification of earlier forms of disease could result in identification of lower risk individuals, and ultimately, the costs and potential harm of screening could then outweigh the potential benefit that would be attributable to early detection.

In Whom?
Screening for CAD should only be performed if the data derived from such testing could result in changes to patient management. Such changes include both intensified therapy, or in patients who are found to have no plaque, reassurance with emphasis on lifestyle changes instead of pharmacotherapy. However, high-risk patients (eg, familiar dyslipidemia associated with cardiovascular events, early onset of CHD in multiple family members) could be treated without any testing, as data form screening will be less likely to result in any changes to patient management.

To date, there are no prospective randomized trial data that treating patients with a family history of premature CHD results in improved outcomes (the absence of such data is also lacking for many other risk markers and virtually all risk scores that are used in guidelines). Design of such a trial would be challenging as patients with a strong family history may opt for treatment (especially if they have other risk factors), whereas those who may be at more moderate risk will have a lower event rate. Therefore, the design of such a trial could be enhanced by screening for the presence of coronary atherosclerosis and only randomize individuals with actual disease (ie, CAC score > 0) to treatment versus no treatment. From a trial design perspective, such an approach would reduce the sample size and increase the power to detect a difference between treatment groups. Future studies also need to improve the way premature family history is defined and is used in developing risk score and guidelines. This will require a better understanding of the sensitivity and specificity of various definitions of premature CHD.

For now, what are clinicians and patients to do? First, despite inconsistent data from some epidemiological cohorts, family history, when taken correctly, can provide important information to refine risk assessment for an individual patient. This is particularly important for patients who are not on
current therapy or for whom decisions about intensification of therapy or lifestyle changes are being considered. This is consistent with the 2013 the American College of Cardiology and the American Heart Association guidelines in which a family history of premature atherosclerotic cardiovascular disease is defined if the age of onset is <55 years of age in a first-degree male relative or <65 years of age in a first-degree female relative. The guidelines suggest that such a history may contribute to risk assessment in selected individuals who are not already in the 4 statin benefit groups (ie, clinical atherosclerotic cardiovascular disease, low-density lipoprotein cholesterol >190 mg/dL, diabetes mellitus and age 40 to 75 years, or estimated 10-year atherosclerotic cardiovascular disease risk >7.5%) for whom a decision to initiate statin therapy is otherwise unclear. Family history of premature CHD should be reviewed even beyond the above scenarios indicated by the guidelines, as a strong family history of premature CHD can improve risk assessment (even if not for all individuals), motivate lifestyle changes, and provides an opportunity to educate patients and their family members about their heart disease risk. But even after obtaining a careful family history and considering all risk factors, the aforementioned discussion reminds us that uncertainty may prevail in many scenarios...now what?

When family history of premature CHD exists and the role of statin therapy is uncertain, the use of CAC scoring may provide additional data to aid in patient-centered decision making, especially in patients who are reluctant to be treated and wish to avoid pharmacotherapy. Under such scenarios, CAC screening may be used to better identify individuals who have an increased risk of cardiovascular events from those who have a low risk and are less likely to benefit from treatment.

Disclosures

None.

References


Key Words: Editorials • atherosclerosis • coronary heart disease risk • family history
Screening for Coronary Artery Disease in Patients With Family History…How, When, and in Whom?
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*Circ Cardiovasc Imaging*, 2014;7:417-419
doi: 10.1161/CIRCIMAGING.114.001985

*Circulation: Cardiovascular Imaging* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-9651. Online ISSN: 1942-0080

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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