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,¹ 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.²,³ 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, is a 50-year-old nonsmoking active woman at the same level of risk if she has a father who was a smoker and had a myocardial infarction at age 57 than if she has a history of myocardial infarction of multiple first-degree family members, including a mother who had her first myocardial infarction in her 40s?

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. In a prospective study of parents and offspring from the Framingham Heart Study, participants who were hospitalized for acute myocardial infarction, unstable angina with coronary revascularization, or angina with stenosis ≥50% in ≥1 coronary artery had a family history of early-onset coronary artery disease (CAD) that did or did not develop incident cardiovascular disease can be tentatively identified individuals with increased risk who have atherosclerosis. 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, is a 50-year-old nonsmoking active woman at the same level of risk if she has a father who was a smoker and had a myocardial infarction at age 57 than if she has a history of myocardial infarction of multiple first-degree family members, including a mother who had her first myocardial infarction in her 40s?

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. In a prospective study of parents and offspring from the Framingham Heart Study, participants who had ≥1 parent with premature cardiovascular disease had an age-adjusted odds ratio of 2.0 for men and 1.7 for women for having cardiovascular disease over 8 years of follow-up. However, the incorporation of parental history of premature cardiovascular disease into a multivariable model that included traditional cardiovascular risk factors and lipid levels only increased the C-statistic from 0.82 to 0.83.⁴ This minimal improvement in discriminating between individuals who did or did not develop incident cardiovascular disease can be explained by the high C-statistic of the baseline model (0.82); it would be challenging for any marker to add value to such a robust model.

A third possible explanation is that family history, as we currently define it in most studies and collect it clinically, is not a sensitive enough marker of increased risk for the multifactorial process that accounts for CHD. The development and progression of CHD is a complex process that depends on both genetic and environmental factors. Although family history allows us to identify some possible heritable traits associated with this disease, even in cases where genome sequencing is performed, genes associated with this disorder have variable penetrance and do not consistently improve the prediction of future events beyond clinical risk factors.⁵,⁶ Therefore, although family history may provide us with information on the phenotype that resulted from interactions of genes and exposure to measured and unmeasured risk factors in an individual’s family member(s), such information cannot be used to consistently discriminate high-risk from low-risk individuals.

In this issue of *Circulation: Cardiovascular Imaging*, Kral et al⁷ report the distribution of calcified and noncalcified coronary plaque in a cohort of 805 asymptomatic individuals with a family history of early-onset coronary artery disease (CAD) who underwent screening coronary computed tomographic angiography and coronary artery calcium (CAC) scanning. The study recruited the siblings, offspring, and offspring of the siblings of individuals <60 years of age (ie, the probands) who were hospitalized for acute myocardial infarction, unstable angina with coronary revascularization, or angina with stenosis ≥50% in ≥1 coronary artery. All participants had to be 30 to 75 years of age and have no prior history of CAD. The majority of the subjects were low risk by the Framingham Risk Score.

Notably, 55% of the study participants did not have any evidence of calcified or noncalcified plaque, 45% had plaque, and 5% had exclusively noncalcified plaque (ie, plaque despite a CAC score of zero). These findings are consistent with the fact that family history of premature CAD does not consistently identify individuals with increased risk who have atherosclerosis, particularly when considering the extremely low cardiovascular event rates associated with normal coronary computed tomographic angiography or CAC scan⁸.
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\(^7\) 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.\(^{10}\) Among individuals with no prior CAD, the presence of severe CAC identifies individuals at high risk, even in the absence of risk factors.\(^{11}\) Conversely, the absence of CAC identifies low-risk individuals with an annual event rate of <0.1%,\(^6\) and consequently the number needed to treat to prevent a CHD event in such individuals would be much higher.\(^{12}\) Nasir et al\(^2\) 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,\(^7\) 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\(^7\) 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 intensification of 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
Screening for Coronary Artery Disease in Patients With FamHx

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None.

References

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