Noncalcified Coronary Plaque Volumes in Healthy People With a Family History of Early Onset Coronary Artery Disease

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**Background**—Although age and sex distributions of calcified coronary plaque have been well described in the general population, noncalcified plaque (NCP) distributions remain unknown. This is important because NCP is a putative precursor for clinical coronary artery disease and could serve as a sentinel for aggressive primary prevention, especially in high-risk populations. We examined the distributions of NCP and calcified coronary plaque in healthy 30- to 74-year-old individuals from families with early onset coronary artery disease.

**Methods and Results**—Participants in the GeneSTAR family study (N=805), mean age 51.1±10.8 years, 56% women, were screened for coronary artery disease risk factors and coronary plaque using dual-source computed tomographic angiography. Plaque volumes (mm³) were quantified using a validated automated method. The prevalence of coronary plaque was 57.8% in men and 35.8% in women (P<0.0001). NCP volume increased with age (P<0.001) and was higher in men than women (P<0.001). Although NCP, as a percentage of total plaque, was inversely related to age (P<0.01), NCP accounted for most of the total plaque volume at all ages, especially in men and women <55 years (>70% and >80%, respectively). Higher Framingham risk was associated with the number of affected vessels (P<0.01), but 44% of men and 20.8% of women considered intermediate risk had left main and 3-vessel disease involvement.

**Conclusions**—The majority of coronary plaque was noncalcified, particularly in younger individuals. These findings support the importance of assessing family history and suggest that early primary prevention interventions may be warranted at younger ages in families with early onset coronary artery disease. (Circ Cardiovasc Imaging. 2014;7:446-453.)

**Key Words:** asymptomatic diseases ■ atherosclerosis ■ multidetector computed tomography

ECG-gated noncontrast computed tomography (CT) is routinely used to quantify calcified coronary plaque (CCP) to assess coronary artery disease (CAD) risk in high-risk healthy populations. CCP is associated with CAD risk factors, particularly men and older age, and is generally less useful in younger people.1,2 Coronary plaque calcification is a late manifestation of atherosclerosis.3 Earlier stages of atherogenesis are represented by noncalcified or mixed composition plaques containing extracellular lipid and fibrous tissue4,5 and are particularly prone to plaque rupture, thrombosis, and acute CAD events.6,7 Thus, CCP on noncontrast CT imaging is used as a marker for subclinical CAD and as a proxy for the extent of atherosclerosis. However, because this method cannot detect noncalcified plaque (NCP),6,8 it does not necessarily reflect the true extent of coronary artery plaque.6 The extent of subclinical NCP, a putative precursor for CAD events, may have important implications for primary prevention, especially in younger people from high-risk populations.

Familial-clustered CAD accounts for ≈60% of all CAD before 65 years of age.11–13 A positive family history of early onset CAD in a parent or sibling is associated with a markedly increased risk of CAD events.11,11 Apparently healthy adults from these families have a high prevalence of inducible ischemia by myocardial perfusion imaging,15 but the extent of total coronary plaque and NCP remains unknown. To date only coronary calcium scores have been studied, with higher levels found in persons from families with early onset CAD.16,17 Because plaque vulnerability is so closely linked to incident CAD events and NCP is more likely to represent vulnerable plaque, we designed this study to examine the true extent of total coronary plaque, inclusive of NCP, using multidetector computed tomographic angiography (CTA) in healthy asymptomatic members of early onset CAD families.

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Methods

Sample and Recruitment
Participants (n=805) were randomly selected and then recruited (92% of those invited participated) from the larger ongoing Genetic Study of Atherosclerosis Risk (GeneSTAR), a prospective study of 4000 individuals designed to characterize genetic and biological factors associated with cardiovascular disease phenotypes in 883 families with early onset coronary heart disease. Probands <60 years of age with documented acute myocardial infarction, unstable angina with coronary revascularization, or acute angina with angiographic evidence of a flow-limiting stenosis of >50% diameter in ≥1 coronary artery were identified during hospitalization and excluded. Apparently healthy siblings and the offspring of the probands and siblings were eligible if they were 30 to 75 years of age and had no known personal history of CAD. Siblings and offspring were excluded if they had systemic autoimmune disease, known allergy to iodinated contrast media, or chronic kidney disease. The study was approved by the Johns Hopkins Medicine Institutional Review Board, and all participants gave informed consent.

Participant Screening
Participants underwent a comprehensive risk factor screening after a 12-hour overnight fast. Medical history, pedigree and family history information, and current medication use were elicited. A physical examination was performed by a study physician. Height was determined using a fixed stadiometer, and weight was measured on a balance scale with the subject wearing light clothing and no shoes. Body mass index was calculated as kg/m². Current cigarette smoking behavior was assessed by self-report and verified by expired carbon monoxide (CO) levels of <8 ppm. Blood pressure was measured according to the American Heart Association guidelines 3 times during the course of the day. Hypertension was defined as an average blood pressure ≥140 mm Hg systolic, or ≥90 mm Hg diastolic, and use of an antihypertensive drug. Blood was obtained, and total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglyceride levels were measured using the U.S. Centers for Disease Control standardized methods. Low-density lipoprotein (LDL) cholesterol was estimated using the Friedewald formula for persons with triglyceride levels up to 400 mg/dL. Direct measurement of LDL cholesterol using ultracentrifugation was used for persons with triglyceride levels ≥4.22 mmol/L (400 mg/dL; n=5). Glucose concentration was measured using the glucose oxidase method. Type 2 diabetes mellitus was defined as a physician diagnosed history, a fasting glucose level ≥126 mg/dL (≥7.0 mmol/L), and use of prescribed hypoglycemic medications. We calculated the 10-year Framingham Risk Score (FRS) to categorize siblings as low risk (<10%), intermediate risk (10% to 20%), or high risk (>20%) for total CAD events based on their risk factor levels.

Assessment of Subclinical Coronary Plaque
All participants underwent coronary CTA using a newest generation dual-source multidetector scanner (SOMATOM Definition Flash, Siemens Medical Solutions, Forchheim, Germany). Because of the high temporal resolution and excellent image quality of the scanner, β-blockade was not necessary for reducing the heart rate. A noncontrast scan was first performed to determine the coronary artery calcium volume as well as the traditional Agatston score. Subsequently, coronary CTA was performed to examine the presence, location, composition, and severity of any coronary plaque; ≥80 mL of isosmolar contrast agent (320 mg iodine/mL) was injected at 6 mL/s. Prospective ECG-gating was used in patients with low, steady heart rates (<65 bpm) and low heart rate variability. For patients with variable heart rates or heart rates >65 bpm, retrospective gating with dose modulation was used. Tube potential was selected on a per patient basis by the performing technologist assessment of patient size; 100 kV was used for patients who were not overweight or obese; otherwise 120 kV was used. We reconstructed 0.75-mm thick axial slices at 0.4-mm intervals with a B26 kernel; 10 reconstructions were made at 10% increments in the R-R interval. All scans were evaluated with the computed tomographic radiologist blinded to the participants’ risk factor profiles. The coronary arterial tree was segmented according to the standard American Heart Association classification, and the segments were investigated for plaque and luminal narrowing. Any focal stenoses >50% in severity were identified with the use of quantitative software (COR Analyzer System, Radial Medical Imaging, Haifa, Israel) and verified by the expert reader.

Quantitative Plaque Volumes
The volume of CCP was measured on a workstation (Leonardo Multimodality Workstation, Syngo, Siemens Medical Solutions, Malvern, PA) using noncontrast images. Regions of interest were placed over each of the coronary arteries, and a threshold of ≥130 HU was used for determining per vessel volumes of CCP (mm³) using standard validated methods. Vessel CCP volumes were summed for a total CCP volume. A total Agatston score was also determined using standard methods.

For each affected coronary segment, noncalcified plaque volumes (mm³) were quantified using AUTOPLAQ (Cedars-Sinai Medical Center, Los Angeles, CA) as previously described. This automated method of NCP measurement has high interobserver correlation (r=0.97) and has been previously validated against intravascular ultrasound. For the present study, we also found high reproducibility for measured NCP volumes (intraobserver r=0.99, mean percentage error 3.6%) based on 2 blinded reads performed 6 to 12 months apart on a random sample (N=30). To quantify each affected segment, CTA images were examined in multiplanar format, and proximal and distal limits of the plaque were manually marked. Control points defining the lumen centerline were placed. Subsequent NCP plaque quantification was then fully automated using adaptive algorithms that are scan specific per individual. Segmental NCP volumes were summed for a total NCP volume per vessel, including the left main (LM), left anterior descending (LAD), left circumflex (LCX), and right coronary arteries (RCA). The vessel-specific volumes were summed for a total NCP volume. Total coronary plaque (TCP) was calculated as the sum of CCP+TCP. The percentage of total plaque consisting of CCP and TCP was calculated by dividing by TCP for each. For stenoses >50% in severity, plaques were classified as noncalcified (no calcium), calcified (>50% volume calcified plaque) or mixed (≤50% volume calcified plaque), based on the quantified volumetric measurements.

Statistical Analyses
Standard descriptive analyses were used to examine distributions of sociodemographic and CAD risk factor variables. The Kolmogorov–Smirnov statistic was used to test for normality of continuous variables. The median and interquartile range of NCP and CCP volumes, as well as the relative amount of NCP and CCP to total plaque volume, were examined by age and sex in subjects with coronary plaque. Total coronary plaque was transformed as log [TCP + 0.5(minimum)], given the non-normal distribution and presence of zero plaque in many individuals. Standard multivariable regression analyses were performed predicting plaque outcomes using the Generalized Estimating Equations (GEE) to account for nonindependence within families. The Cochran Armitage Trend test was used to examine trends across Framingham Risk categories for the prevalence of plaque, including by vessel location, and stenoses >50%. Given the variability of strength of family history within families, we used pedigree information in separate analyses in a subset of full siblings of affected probands to determine the incremental effect of strength of sibling history on subclinical coronary plaque burden. TCP volumes in participants with a greater number of siblings affected with clinically manifest CAD (strong family history, defined as ≥50% of siblings in the family) were compared with those with a lesser sibling history (only the proband or <50% of siblings affected in the family). A multivariable GEE regression model
controlled for age, sex, race, current smoking, hypertension, diabetes mellitus, LDL cholesterol, statin medication use, and within family correlations. Logistic regression predicting any stenoses >50% was performed with the same dependent variables and inclusion of the transformed CCP, NCP, or TCP volumes, and the area under the curve (AUC) calculated.

Results

Population Demographics and Presence of Coronary Plaque

The study population consisted of 805 apparently healthy individuals identified from 388 families with the onset of CAD <60 years of age (1 index case per family, 2.1±1.5 participants per index case). Study participants were siblings (n=424) of the index patient or adult offspring of the index patient or the siblings (n=381). The sample was 56.1% female and 39.2% black. All were healthy and without any chest pain or angina-equivalent symptoms. Overall, 45.5% of the total population had subclinical coronary plaque, including 5.5% with exclusively NCP without any CCP. Population demographics and CAD risk factors by the presence or absence of any coronary plaque are shown in Table 1. Coronary plaque was significantly associated with older age, men, white race, hypertension, diabetes mellitus, lower HDL cholesterol, and higher triglyceride levels. There was no difference in mean LDL cholesterol levels, but subjects with plaque were more likely to be taking a statin medication, suggesting that subjects with plaque had a priori higher LDL cholesterol levels that triggered initiation of statin therapy. Subjects with plaque had a significantly higher 10-year mean Framingham Risk Score than those without plaque, but overall most subjects were in the low Framingham risk group.

| Table 1. Population Demographics and Coronary Artery Disease Risk Factors by the Absence or Presence of Coronary Plaque (N=805)* |
|-----------------|-----------------|-----------------|
| **Variable**    | **Plaque Absent** | **Plaque Present** |
| **Age, y**      | 46.4±9.7         | 56.9±9.0        | <0.0001 |
| **Female sex, %** | 64.2             | 35.8            | <0.0001 |
| **Black, %**    | 41.5             | 34.4            | 0.04    |
| **Hypertension, %** | 30.6             | 57.9            | <0.0001 |
| **Diabetes mellitus, %** | 8.0              | 15.9            | 0.0005 |
| **Current smoking, %** | 18.3             | 20.5            | 0.43    |
| **LDL cholesterol, mmol/l (mg/dL)** | 2.92±0.92 (113.7±35.4) | 2.92±0.98 (112.8±38.0) | 0.73 |
| **HDL cholesterol, mmol/l (mg/dL)** | 1.51±0.46 (58.2±17.5) | 1.42±0.43 (55.0±16.6) | 0.009 |
| **Triglycerides, mmol/l (mg/dL)** | 1.12±0.62 (105.9±54.7) | 1.41±0.91 (125.1±80.4) | 0.0001 |
| **BMI, kg/m²** | 30.0±6.5         | 30.6±5.5        | 0.19    |
| **Statin medications, %** | 14.8             | 39.3            | <0.0001 |
| **Calculated 10-year Framingham Risk** | 4.6±3.8          | 9.6±7.2         | <0.0001 |

BMI indicates body mass index; HDL, high-density lipoprotein; and LDL, low-density lipoprotein.

*Continuous variables presented as mean±1 SD.

Prevalence of Coronary Plaque

Figure 1 shows the prevalence of coronary plaque for men and women by age. The prevalence of coronary plaque increased with age in both men and women (P<0.0001 for both). The prevalence of coronary plaque was significantly higher in men at all age ranges until after age 65 years, when both sexes had a prevalence >80% (P<0.0001 and P=0.08, respectively). Even in the youngest age group (30 to 45 years of age), nearly one quarter of men had plaque, increasing to ≤60% in those 45 to 54 years of age. Using calcium scoring alone, 39.8% of all participants were identified as having plaque, whereas the addition of NCP information from the CTA identified 45.2% of the population as having plaque. The additive value of CTA varied by age, sex, and race. Of the 364 persons with plaque on CTA, 87.9% had plaque on coronary artery calcium screening, yielding an incremental identification of plaque by CTA of 12.1% overall.

Age and Sex Distribution of Noncalcified and Calcified Plaque Volumes

Of those subjects with coronary plaque, females were twice as likely to have NCP exclusively compared with males (16.8% versus 8.3%, P=0.01). The volumes of NCP and CCP by age and sex in subjects with plaque are shown in Table 2. NCP volume was strongly associated with older age and male sex, P<0.0001 for both. CCP volume was also associated with older age and men, <0.0001 and P=0.0002, respectively. The total Agatston score is shown for comparison with calculated CCP volumes. Agatston scores were highly correlated with CCP volumes (r=0.98), with similar distributions by age and sex.

Figure 2 shows the composition of total plaque volume by age and sex in subjects with plaque. NCP accounted for more than half of TCP in both sexes at all ages and represented >75% of TCP in men and 80% in women ≤55 years of age. NCP, as a percentage of TCP, was significantly and inversely related to increasing age in both men and women (P<0.01). Adjusting for age, the percentage of TCP that was noncalcified tended to be higher in women (P=0.06).

Multivariable regression analysis controlling for age, sex, race, statin medication use, and intrafamilial correlation was performed for the transformed volumes of TCP. Covariates in the model included LDL cholesterol level, body mass index,
and the presence of hypertension, diabetes mellitus, and current smoking behavior. All modifiable risk factors were independently associated with TCP, including the presence of hypertension ($P=0.005$), diabetes mellitus ($P=0.05$), and current smoking behavior ($P=0.0004$), as well as higher LDL cholesterol levels ($P=0.02$). Higher body mass index showed a near significant association ($P=0.08$).

Using the family design of this study to examine the significance of family history to TCP, we examined TCP volumes in a subset of 338 full siblings of affected probands ($n=49$) compared with those with a lesser sibling history ($n=289$). In this subset, subjects were 58.9±7.4 years of age (range 36–74), 55% female, and 36% black. Subjects with a strong sibling history ($n=49$) were 3.0 times (95% confidence intervals, 1.3–6.6) more likely to have any coronary plaque and had markedly greater volumes of all forms of plaque than those with a lesser sibling history ($n=289$; Table 3). A strong sibling history remained a significant independent predictor of TCP volume when adjusted for all other variables in multivariate GEE regression analysis.
with coronary plaque and 15% of subjects without coronary plaque were taking statin medications, we performed the same analyses in 254 males (n=124 with plaque) and 342 females (n=98 with plaque) who were not taking statin medications and found similar sex-specific distributions of FRS categories and the same significant trends for the prevalence of plaque phenotypes across FRS categories. Although this was a cross-sectional study and the incremental value of CTA over coronary calcium alone for clinical outcomes is yet to be determined in this population, noncalcified plaque volume was significantly associated with the presence of at least 1 stenosis >50% (P<0.0001), independent of all traditional risk factors. Total plaque volume improved the AUC from 0.87 to 0.90 compared with the Agatston Score alone (P=0.04).

**Discussion**

In this first study of the age and sex distributions of noncalcified coronary plaque in healthy men and women from families with early onset CAD, we found a strikingly high prevalence of coronary plaque, even in participants <45 years of age. Importantly, noncalcified plaque was more prevalent than calcified plaque, particularly in those <55 years of age, in whom 75% to 80% of plaque was noncalcified. It is noteworthy that coronary calcium may markedly underestimate the total plaque burden in this population. In addition, we found a high prevalence of triple vessel and left main artery plaque. This is particularly striking considering that the majority of participants had a low or intermediate FRS. Finally, we were able to demonstrate that strength of sibling history was an independent predictor of the presence and extent of total coronary plaque. These findings suggest that conditioning aggressive primary prevention on traditional coronary calcium scoring algorithms or on the FRS, which does not include family history, may obviate appropriate risk reduction interventions in high-risk individuals, such as young men and women with a family history of early onset CAD.

Although a positive family history of CAD has been independently associated with higher coronary calcium scores,16,17 there is a paucity of data regarding the prevalence of NCP in asymptomatic populations, with a few studies reporting on older, higher risk individuals referred to CTA for clinical suspicion of CAD31,32 or in Asian populations.33 We did not

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<th>Table 3. Distribution of Coronary Plaque by Strength of Sibling History (N=338)</th>
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<td>Strong Sib History</td>
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<tr>
<td>(n=49)</td>
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<tr>
<td><strong>Median [IQR]</strong></td>
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<tr>
<td>Any plaque, %</td>
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<tr>
<td>Total plaque, mm³</td>
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IQR indicates interquartile range.  
* A multivariate Generalized Estimating Equations regression model controlled for age, sex, race, current smoking, hypertension, diabetes mellitus, low-density lipoprotein cholesterol, statin medication use, and within family correlations.

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<th>Table 4. Sex-Specific Plaque Prevalence and Characteristics by Framingham Risk Group (n=805)</th>
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<tr>
<td>Framingham Risk</td>
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<tr>
<td>N=254</td>
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<tr>
<td>Any plaque</td>
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<tr>
<td>No. affected vessels</td>
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<td>At least 1 stenosis &gt;50%</td>
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<td>NCP</td>
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<td>CCP</td>
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<td>Mixed</td>
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CCP indicates calcified plaque; LAD, left anterior descending; LCX, left circumflex; LM, left main; NCP, noncalcified plaque; and RCA, right coronary artery.
have a control population for a direct comparison of NCP, but the degree of age-, sex-, and race-specific coronary calcification using the Agatston Score was notably higher than that observed in the Multi-Ethnic Study of Atherosclerosis. Importantly, given the excess risk of incident CAD already demonstrated in the GeneSTAR family population and their concomitant higher rates of silent myocardial ischemia on stress myocardial perfusion imaging, it is most likely that the prevalence and amount of noncalcified and total coronary plaque are also greater than would be seen in the general population. Moreover, strength of sibling history of early onset CAD was independently associated with TCP volumes, highlighting the fact that family history is an important determinant of our findings. The classification by sibling history into lesser versus greater family risk was in part based on previous studies showing that ≥2 affected first-degree relatives conveys the highest risk. Further studies using continuous comprehensive family history scores are needed to support heritability of NCP.

Multiple studies have shown that the presence of CCP in asymptomatic individuals from the general population is associated with incident CAD events. However, calcium scores reflect the stage of plaque progression and maturity and do not necessarily reflect the true atherosclerotic burden of the degree and location of coronary stenoses, especially in younger individuals. Vulnerable coronary plaques have been thought to be predominantly noncalcified and nonstenotic, and the presence of such noncalcified plaques on CTA is correlated with acute coronary syndromes. The observed high prevalence of NCP in our study in subjects at young ages could reflect a more aggressive process of early onset vascular aging; this may at least in part explain the higher CAD event rates observed at younger ages in populations with a strong family history of early onset CAD.

CTA tends to overestimate calcified plaque and underestimate noncalcified plaque when compared with intravascular ultrasound. Most studies report the burden of coronary calcium using the Agatston scoring system, which is calculated by multiplying the lesion area by a weighted attenuation coefficient, derived to better reflect overall plaque burden and disease severity. We used the calcium volume score representing actual CCP volumes (mm³) for comparison with NCP (mm³). This method has improved reproducibility with significantly less interscan variability than the Agatston scoring method, especially with lower levels of CCP. However, calculated CCP volumes tend to overestimate true CCP volumes at higher plaque densities, and thus our results likely underestimate the relative extent of NCP to total plaque.

Our findings highlight the importance of family history in the development of aggressive coronary artery disease at young ages. However, current primary prevention guidelines still do not provide specific recommendations for individuals with a family history of early onset CAD. Although most subjects in the current study were low or intermediate risk using the FRS, traditional modifiable risk factors were significantly associated with higher total coronary plaque volumes independent of age and sex, suggesting a role for earlier aggressive risk factor modification in apparently healthy persons from high-risk families. However, longitudinal studies are needed to further elucidate the significance of NCP volumes and characteristics in vulnerable asymptomatic populations. Thus, we would not recommend expensive screening for NCP using CTA at this time. However, CTA is a promising modality to improve on CCP screening, especially now that low-radiation dose CTA allows for screening of both NCP and CCP at near equivalent radiation doses as coronary artery calcium screening alone.

**Conclusion**

Apparently healthy men and women from families with early onset CAD have a high prevalence of subclinical CAD, composed primarily of noncalcified plaque. These findings highlight the importance of screening for family history and the implementation of primary preventive interventions at younger ages in both men and women with a family history of early onset CAD.

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**Disclosures**
None.

**References**


CLINICAL PERSPECTIVE

Familial-clustered early onset coronary artery disease (CAD) accounts for a large percentage of all CAD occurring at a young age (<60 years). A family history of early CAD carries ≥50% excess risk of incident CAD, independent of known risk factors. Thus, understanding the nature and extent of the disease in its preclinical state provides an opportunity to design optimal primary prevention strategies for people with a family history of early onset CAD. Although previous studies have only examined coronary calcium scores in high-risk families, in this study, we used computed tomographic angiography to directly quantify early noncalcified plaque, calcified plaque, and total plaque volumes, offering additional information over and above Agatston scoring. We found a high prevalence of noncalcified and total plaque overall, including triple vessel disease, and plaque in the left main coronary artery, even in young individuals considered low or intermediate risk using traditional risk factors and the Framingham Risk Score. Importantly, noncalcified plaque accounted for 75% of all plaque. Thus, considerably more plaque is present than would be identified by traditional coronary artery calcium screening. Additionally, the strength of a family history was independently associated with the presence and extent of coronary plaque on computed tomographic angiography. Although we would not advocate mass screening using computed tomographic angiography in families, these data provide a strong impetus to assess family history, measure risk factors, and optimize early prevention strategies in all healthy family members of people with early onset CAD.
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