Compliance with expert population-based dietary guidelines and lower odds of carotid atherosclerosis in women: the Framingham Nutrition Studies1–3

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ABSTRACT

Background: Carotid stenosis, an indicator of subclinical atherosclerosis, predicts future coronary artery disease (CAD) and stroke and provides a noninvasive method to identify candidates for primary prevention. The relation between diet and stenosis is relatively unexplored, particularly in women.

Objective: We evaluated in women the association between nutrient intakes that were consistent with expert population-based dietary guidelines and carotid stenosis.

Design: We used prospective logistic regression analyses to evaluate relations between baseline nutrient intake and the presence of carotid stenosis at 4-y follow-up in 1123 women from the Framingham Offspring-Spouse study, after control for multiple CAD risk factors. We also developed multivariate models that were stratified by compliance with expert population-based dietary guidelines and smoking status.

Results: Baseline nutrient and risk factor profiles differed by women’s compliance and smoking status. Dietary noncompliance and smoking were each associated with odds for stenosis that were 2.5-fold those of dietary compliance and nonsmoking. Odds were highest for dietary noncompliance in combination with smoking (odds ratio: 3.49; 95% CI: 1.67, 7.27).

Conclusions: Nutrient intake consistent with current expert population-based dietary guidelines and smoking abstinence are associated with lower odds of carotid atherosclerosis in women. Unique dietary and risk factor profiles of at-risk women suggest areas for targeted primary CAD prevention.

KEY WORDS Carotid stenosis, total and saturated fat, dietary cholesterol, smoking, preventive nutrition, coronary artery disease, CAD

INTRODUCTION

Coronary artery disease (CAD) remains the leading cause of morbidity and mortality in adult Americans; it accounts for nearly 500 000 deaths annually and contributes to the $300 billion in health care costs and lost individual productivity that is associated with cardiovascular disease (CVD) (1, 2). The primary prevention of CAD, particularly among men and women who have multiple CVD risk factors, is a national public health priority (3–7).

Healthy People 2010 focuses on preventing CAD in addition to other chronic diseases (eg, stroke, obesity, diabetes, and cancer) and on promoting health by encouraging good nutrition and physical activity and the avoidance of smoking (4). The current US Department of Agriculture (USDA) Dietary Guidelines for Americans 2000 (5) and the AHA [American Heart Association] Dietary Guidelines (6), which include lifestyle-related recommendations for CAD prevention, emphasize the population benefits of achieving and maintaining an overall healthy eating pattern, appropriate body weight, desirable lipid and blood pressure measurements, daily physical activity, and the avoidance of smoking. Specific population-based nutrient guidelines to lower CAD risk factor profiles recommend the following daily intakes: ≤30% of total energy as fat, <10% of energy as saturated fat, and <300 mg cholesterol (5, 6). Although these guidelines are similarly applicable to men and women, an even greater potential may exist for primary prevention in women because of the 10–15-y delay in the onset of CAD in women compared with men (7).

Over the past decade, increases in physician and public awareness of the benefits of reducing cholesterol concentrations, improvements in American dietary lipid and cholesterol intakes, and lower population serum cholesterol concentrations have contributed to declining rates of CAD. Nonetheless, recent reports (5, 7) emphasize that future success in reducing the national...
burden of heart disease will depend on identifying effective prevention strategies, particularly those that focus on the following: primary prevention of CAD in the population, feasible targets for behavioral lifestyle modifications, and effective methods to promote long-term behavior change. Experts and clinicians also seek continuing evidence that the existing population-based lifestyle-related guidelines for CAD prevention promote CAD risk reduction (5, 7), including lowering the risk of preclinical CAD. Such research is particularly important in light of the dramatic rise in the proportion of American adults who are overweight and obese and the low rates of leisure-time physical activity noted in the US population (8, 9). In this study, we evaluated in women the relation between compliance with the USDA and AHA dietary guidelines and carotid artery stenosis, an indicator of subclinical atherosclerosis. Carotid stenosis predicts future fatal and nonfatal CAD and stroke (10–17) and offers a noninvasive method of identifying candidates for primary CAD-prevention activities (18, 19).

SUBJECTS AND METHODS

Subjects

The Framingham Study began in 1948 as a longitudinal, population-based study of CVD among residents of Framingham, MA (20; also RB D’Agostino, WB Kannel, unpublished observations, 1988–1989). In 1971, a second-generation cohort was recruited when some 5124 Framingham Study offspring and their spouses were invited to participate in the Framingham Offspring-Spouse (FOS) study (21).

Members of the FOS cohort are examined in the Framingham Study clinic, on average, every 4 y. They participate in a standardized protocol that involves a complete physical examination, laboratory tests, noninvasive diagnostic testing, and updating of medical histories and other pertinent information. At certain examinations, detailed dietary data are collected. The dietary and risk factor data reported here were collected among FOS women at Exam 5, between 1992 and 1996. Some 2007 women, aged 26–84 y, participated in this examination (76% of the original FOS cohort women). Women who were diagnosed with CVD at or before Exam 5 were excluded from these analyses (6.7%; n = 135).

All participants provided written informed consent. This study was approved by the institutional review board at Boston University Medical Center.

Nutrient intake and dietary compliance

Nutrient intake was estimated from 3-d dietary records collected with the use of a validated two-adhering to their usual eating practices. Subjects were trained to record their intake over 2 weekdays and 1 weekend day, while adhering to their usual eating practices. Subjects were invited to participate in the Framingham Offspring-Spouse (FOS) study (21).

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Subjects who were considered compliant had a 3-d dietary mean nutrient intake that met the population-based dietary guidelines for CAD risk reduction as set forth in the AHA Dietary Guidelines and that was consistent with the USDA’s Dietary Guidelines for Americans, including a total of ≤30% of energy as fat (kcal), <10% of energy as saturated fat (kcal), and <300 mg dietary cholesterol (4–6). Noncompliant subjects consumed diets that failed to meet ≥1 of these guidelines. We compared these dietary guidelines with the medical nutrition therapy recommendations (7), to assess the potential benefits associated with population-based recommendations in relation to an early indicator of atherosclerotic heart disease.

Assessment of carotid atherosclerosis

Among 1283 women who provided complete dietary records and who were free of CVD at baseline, the presence of carotid atherosclerosis was assessed at follow-up at Exam 6 (1996–1999). Carotid ultrasound scanning studies were obtained for 1137 subjects (89% of the total cohort). Missing measurements were exclusively due to logistic constraints at the clinic (eg, unavailability of the ultrasound scanning device or the sonographer during the scheduled visit). Reliability studies were ongoing during data acquisition.

Ultrasound imaging studies were conducted with a high-resolution linear-array 5.0 MHz transducer and color Doppler ultrasound scanning device (Toshiba SSH-140; Toshiba Medical Systems, Tustin, CA). Imaging was performed with the subject’s head rotated 45 degrees away from the side being studied, according to a standard protocol. Two gray-scale images were taken at the level of the common carotid artery bulb, and 2 additional images were obtained in the proximal 2 cm of the internal carotid artery. One image of the respective image pairs was acquired with the probe held at 45 degrees from horizontal. For the second image, the sonographer was instructed to position the transducer to best identify any focal lesions. All images were gated to the R-wave of an electrocardiogram, and both sides of the neck were imaged. Images were directly transferred into a computer workstation through a frame-grabber board.

Color Doppler imaging and pulsed Doppler waveforms were used to evaluate blood flow velocities in the proximal internal carotid arteries. Angle-corrected Doppler velocity waveforms were acquired in the proximal internal carotid artery at the site of highest velocity as identified on a color Doppler image. Peak systolic velocities were measured from these tracings. A certified reader reviewed the acquired digital images and made a subjective estimate of the degree of internal carotid artery narrowing, which was graded as 0%, 1–24%, or 25–49% when Doppler-derived peak systolic velocities in the internal carotid artery were <150 cm/s. Internal carotid artery disease was characterized by the maximum stenosis observed on the right or left side and was categorized as 0% (no lesions), 1–24%, 25–49% (focal lesions causing <50% diameter stenosis), or ≥50% (lesions causing ≥50% diameter stenosis). Absence of blood flow corresponded to a total occlusion.

CVD risk factor measurements

CVD risk factors are routinely measured at all Framingham Study examinations (25). All lipid analyses were performed at the Framingham Study laboratory, which participates in the Standardization Program of the Centers for Disease Control and
Prevention and the National Heart, Lung, and Blood Institute Lipid Research Clinics. Venous blood was drawn from all subjects after a 12–24-h fast. Total and HDL-cholesterol concentrations were measured by automated enzymatic methods (26, 27). The cholesterol content of LDL cholesterol was estimated by the method of Friedewald et al (28). Triacylglycerol concentrations were measured enzymatically (26). Blood pressure was determined by duplicate measurements of the subject’s left arm made with the use of a mercury sphygmomanometer while the subject was in a sitting position. Body mass index (BMI; in kg/m²) was calculated from height and weight values measured in the clinic. Diabetes was defined as a history of use of insulin or an oral hypoglycemic agent or a fasting blood glucose concentration of ≥7.8 mmol/L (≥140 mg/dL).

Physical activity was measured with the use of a standardized questionnaire to determine estimates of activity in a usual day, based on a 24-h history. A physical activity index was calculated from the number of hours spent doing specific activities that were categorized (ie, sedentary, slight, moderate, or heavy) and weighted according to the oxygen consumption required to perform them (29). Physical activity index scores ranged from 24 (total bed rest) to 120. Because physical activity was not measured at FOS Exams 3, Exam 2 values were substituted in these analyses, according to the analytic approach routinely used in the Framingham study. Menopausal status and cigarette smoking was self-reported. Pack-years of cigarette smoking were defined as the number of packs of cigarettes smoked per day multiplied by the total number of years a person smoked. This variable takes into account the duration of smoking as well as the amount of cigarette consumption.

Statistical analysis

Our primary objective was to determine whether compliance with the current population-based dietary guidelines for CAD risk reduction (as defined earlier) was related to the presence of carotid atherosclerosis at follow-up. The endpoint of interest was carotid artery stenosis, defined by focal lesions of ≥25% in either the right or left internal carotid artery, in accordance with our previously used threshold (30–32). Previous research suggested potential interaction between diet and smoking (32, 33); thus, we decided to test for such an interaction. Because the null hypothesis (ie, no interaction) could not be rejected (P = 0.10), we decided to stratify by compliance and smoking status and created 4 subgroups: compliant nonsmokers, noncompliant nonsmokers, compliant smokers, and noncompliant smokers.

For descriptive purposes, age-adjusted mean baseline Exam 5 CVD risk factors and nutrient intake profiles were computed for the 4 subgroups. Analysis of covariance was used for calculating the least-squares means of continuous variables by using PROC GLM in SAS (34). For categorical variables, age-adjusted proportions were computed by using the age-adjusted logistic regression (PROC LOGISTIC) (34). If the interaction between smoking and compliance was significant, we compared the 4 subgroups by using Bonferroni’s correction for multiple testing (34). In multivariate analyses, we examined the relation between dietary compliance and carotid atherosclerosis at follow-up with dietary compliance and smoking subgroups by using compliant nonsmokers as the reference group. Odds ratios (ORs) were calculated by using logistic regression in which CVD risk factors were considered separately in age- and energy-adjusted models. Models considered a range of CVD risk factors, including age, systolic and diastolic blood pressures, total cholesterol, LDL-cholesterol, the ratio of total to HDL-cholesterol, plasma triacylglycerols, BMI, physical activity level, menopausal status, and conditions that included obesity, diabetes, and hypertension. In addition, education level (high school or below compared with more than high school) was considered as a proxy indicator of socioeconomic status. The final multivariate model reported here is limited to those variables that were identified as important predictors or potential confounders of the relation of interest. The sample used in the analyses consisted of women with no missing values for carotid stenosis, dietary compliance, smoking, and the covariates retained in the final multivariate model (n = 1123). Analyses were carried out by use of SAS software (version 8.2; SAS Institute Inc, Cary, NC).

RESULTS

Among 1123 women studied, 360 (32%, both smokers and nonsmokers) had baseline age-adjusted mean daily nutrient intakes that complied with all 3 criteria of the USDA and AHA dietary guidelines for CAD risk reduction (5, 6): a total of ≤30% of energy as fat, <10% of energy as saturated fat, and <300 mg dietary cholesterol (Table 1). Some 68% of FOS women (n = 763) had nutrient profiles that failed to meet ≥1 of these current population dietary recommendations (noncompliant smokers and nonsmokers). Compliant and noncompliant subjects (both smokers and nonsmokers) also had markedly different intakes of a wider range of nutrients and CVD risk factors. Specifically, the diets of noncompliant women were higher in total energy, dietary lipids, cholesterol, and sodium; less concentrated in carbohydrate and fiber; and less nutrient-dense overall than were the diets of women who were compliant. Smokers (both compliant and noncompliant) had higher alcohol intakes than did nonsmokers. Noncompliant smokers had the lowest intakes of folate. The baseline CVD characteristics of FOS women are presented in Table 2. Noncompliant women were younger and had lower total:HDl cholesterol than did compliant women. Compared with compliant smokers, noncompliant smokers had higher levels of cigarette exposure at baseline. The means of systolic and diastolic blood pressure; BMI; total, HDL, and LDL cholesterol; physical activity; and the rates of diabetes did not differ significantly between compliant and noncompliant subjects.

The multivariate models, stratified by the combination of dietary compliance and smoking exposure, are presented in Table 3. Compliant women who never smoked were the reference group. Compared with nonsmoking subjects who complied with the current dietary guidelines, noncompliant women who never smoked had 2.5-fold higher odds of carotid stenosis. The odds of carotid stenosis in women with compliant diets at baseline but who smoked was similar to the odds in noncompliant women who smoked. Noncompliant women who also smoked at baseline had odds of carotid atherosclerosis at 4 y of follow-up 3.5 times those in the reference group.

DISCUSSION

This is the first cohort study in women to examine the relation between compliance with population-based dietary guidelines for CAD prevention and the incidence of carotid stenosis, a subclinical marker of systemic atherosclerosis (10, 11, 35, 36)
that predicts future CAD and cerebrovascular events (10, 12-17, 37, 38). More than two-thirds of the women in the FOS Study had nutrient intakes that failed to meet the current population-based nutritional guidelines (from USDA and AHA) at baseline in 1992–1996. Dietary noncompliance and cigarette smoking each more than doubled the odds for stenosis seen with dietary compliance. Noncompliant women who smoked experienced a tripling of the odds of carotid stenosis.

These findings are consistent with emerging evidence on lifestyle behaviors in relation to carotid stenosis, CAD risk, and other health outcomes in adult populations. We have reported on the associations between the 5 distinct dietary patterns of FOS Study women and the presence of carotid stenosis at 12 y of follow-up (32). After multivariate adjustment for age, systolic blood pressure, BMI, total:HDL cholesterol, and pack-years of smoking, women whose dietary patterns were characterized as “empty calorie” (ie, more concentrated in high-fat, high-sugar foods and lower in fruit and vegetables and micronutrient-rich foods) were compared with women with more healthy diets (ie, higher intakes of vegetables, fruit, and low-fat foods), and it was found that the former group had a significantly higher risk of carotid stenosis at 12-y follow-up [relative risk (RR): 2.28; 95% CI: 1.12, 4.62]. In a follow-up study, stratified by smoking status, women in the heart-healthy cluster who had never smoked had a significantly lower risk of carotid stenosis (OR: 0.17; 95% CI: 0.07, 0.36) than did women in the less heart-healthy group at 12-y follow-up (39).

McCullough et al (40) used the 10-item Healthy Eating Index (HEI) (41) to assess the relation between compliance with the USDA’s Dietary Guidelines for Americans (42) and the Food Guide Pyramid (43) and various chronic disease endpoints. Women in the highest quintile of HEI score (which indicated a more desirable eating pattern) had 14% lower CVD risk over 12 y (43) and various chronic disease endpoints. Women in the highest quintile of HEI score (which indicated a more desirable eating pattern) had 14% lower CVD risk over 12 y (43) and various chronic disease endpoints. Women in the highest quintile of HEI score (which indicated a more desirable eating pattern) had 14% lower CVD risk over 12 y (43) and various chronic disease endpoints. Women in the highest quintile of HEI score (which indicated a more desirable eating pattern) had 14% lower CVD risk over 12 y (43) and various chronic disease endpoints. Women in the highest quintile of HEI score (which indicated a more desirable eating pattern) had 14% lower CVD risk over 12 y (43) and various chronic disease endpoints. Women in the highest quintile of HEI score (which indicated a more desirable eating pattern) had 14% lower CVD risk over 12 y (43) and various chronic disease endpoints.
were noncompliant had 3-d mean intakes that failed to meet the guidelines for (AHA) for coronary artery disease (CAD) risk reduction for all 3 of the following nutrients: total fat and cholesterol.

Subject cardiovascular disease (CVD) risk factor characteristics by dietary compliance and smoking status at baseline (1992–1996)

<table>
<thead>
<tr>
<th>CVD risk factor characteristics</th>
<th>Compliant nonsmokers</th>
<th>Compliant smokers</th>
<th>Noncompliant nonsmokers</th>
<th>Noncompliant smokers</th>
<th>p4</th>
<th>p5</th>
<th>p6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>56.8 ± 9.1</td>
<td>56.2 ± 9.1</td>
<td>56.1 ± 10.6</td>
<td>54.0 ± 9.2</td>
<td>0.0071</td>
<td>0.011</td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>124.9 ± 1.4</td>
<td>125.5 ± 1.2</td>
<td>123.5 ± 1.0</td>
<td>123.0 ± 0.8</td>
<td>0.90</td>
<td>0.060</td>
<td></td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>73.0 ± 0.78</td>
<td>72.4 ± 0.68</td>
<td>72.4 ± 0.55</td>
<td>72.2 ± 0.46</td>
<td>0.54</td>
<td>0.56</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.4 ± 0.42</td>
<td>25.7 ± 0.37</td>
<td>26.6 ± 0.29</td>
<td>26.7 ± 0.25</td>
<td>0.47</td>
<td>0.056</td>
<td></td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>207.9 ± 2.7</td>
<td>209.8 ± 2.4</td>
<td>203.3 ± 1.9</td>
<td>208.5 ± 1.6</td>
<td>0.043</td>
<td>0.21</td>
<td></td>
</tr>
<tr>
<td>HDL cholesterol (mg/dL)</td>
<td>55.3 ± 1.2</td>
<td>56.0 ± 1.0</td>
<td>57.3 ± 0.85</td>
<td>57.3 ± 0.70</td>
<td>0.81</td>
<td>0.090</td>
<td></td>
</tr>
<tr>
<td>Total/HDL cholesterol</td>
<td>4.0 ± 0.10</td>
<td>4.1 ± 0.09</td>
<td>3.7 ± 0.07</td>
<td>3.9 ± 0.06</td>
<td>0.099</td>
<td>0.0088</td>
<td></td>
</tr>
<tr>
<td>LDL cholesterol (mg/dL)</td>
<td>125.4 ± 2.5</td>
<td>125.7 ± 2.2</td>
<td>122.5 ± 1.8</td>
<td>125.0 ± 1.5</td>
<td>0.36</td>
<td>0.44</td>
<td></td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>0.05 ± 0.02</td>
<td>0.05 ± 0.01</td>
<td>0.04 ± 0.01</td>
<td>0.04 ± 0.01</td>
<td>0.99</td>
<td>0.35</td>
<td></td>
</tr>
<tr>
<td>Cigarette exposure (pack-years)</td>
<td>0.06</td>
<td>14.6 ± 1.16</td>
<td>0.06</td>
<td>21.1 ± 0.78</td>
<td>0.0025</td>
<td>0.005</td>
<td></td>
</tr>
<tr>
<td>Physical activity index</td>
<td>33.7 ± 0.40</td>
<td>33.8 ± 0.35</td>
<td>33.7 ± 0.28</td>
<td>33.6 ± 0.23</td>
<td>0.82</td>
<td>0.73</td>
<td></td>
</tr>
</tbody>
</table>

The sample includes 1123 women free of CVD at baseline with complete data on covariates. Analysis of covariance was used to obtain the age-adjusted means for continuous variables and to identify significant differences. Logistic regression was used to obtain the age-adjusted proportions and to identify subgroups that differ significantly. Means in a row with different superscript letters are significantly different, *P* < 0.05 (Bonferroni’s corrected *t* tests).

The smoking × noncompliance interaction was not significant.

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The smoking × noncompliance interaction was not significant.

Odds ratios (ORs) for stenosis in women stratified by dietary compliance and smoking status (1996–1999)

<table>
<thead>
<tr>
<th>Coefficient estimate</th>
<th>P²</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compliant nonsmokers (n = 157)</td>
<td>Reference group</td>
<td>1.00</td>
</tr>
<tr>
<td>Noncompliant nonsmokers (n = 311)</td>
<td>0.9298</td>
<td>0.0171</td>
</tr>
<tr>
<td>Compliant smokers (n = 203)</td>
<td>0.9276</td>
<td>0.0214</td>
</tr>
<tr>
<td>Noncompliant smokers (n = 452)</td>
<td>1.2491</td>
<td>0.0009</td>
</tr>
</tbody>
</table>

The sample includes 1123 women free of cardiovascular disease at baseline with complete data on covariates. Dietary compliance is defined as 3-d mean intake that meets the population-based dietary guidelines from the US Department of Agriculture and the American Heart Association for coronary artery disease risk reduction for all 3 of the following nutrients: total fat ≤30% of energy (kcal), saturated fat <10% of energy (kcal), and cholesterol <300 mg. Women who were noncompliant had 3-d mean intakes that failed to meet the guidelines for ≥1 of the 3 nutrients of interest.

A formal test for the effect of the smoking status × dietary compliance interaction on stenosis was conducted and yielded *P* = 0.10.

Multivariate logistic regression model adjusted for age, energy intake, systolic blood pressure, total:HDL cholesterol, BMI, and diabetes.
combination of poor eating behavior and smoking appears to be associated with the highest risk of carotid atherosclerosis. Combined lifestyle risks are increasingly recognized (32, 44) but have yet to be formally integrated on a widespread basis into targeted, combined risk-reduction interventions. The high rates of smoking among women with unfavorable dietary patterns also should be recognized and targeted as a potential barrier to changes in nutrition behavior.

The assessment of carotid stenosis by high-resolution B-mode ultrasonography is accurate in diagnosing subclinical CVD (18, 19, 35, 45) and provides a noninvasive method of identifying potential candidates for primary prevention activities. It may also offer an approach for evaluating interventions that are aimed at delaying the development of atherosclerosis (10, 45).

Our observations were established in a cohort of women, most of whom are white residents of a western Boston suburban community. Although this population may somewhat limit the generalizability of our findings, we note that the Framingham Study models for CVD risk have been repeated and confirmed in domestic and international populations (46–49). Our data encourage further research on the relations in women among dietary patterns, subclinical CVD, and other health outcomes.

BEM provided overall direction to this research, including the identification of research questions and hypotheses, review of data analyses, and the development of all aspects of the manuscript, which included the description of the conceptual framework and context of the research, the presentation of results, and the interpretation and discussion of the findings. PAQ was involved in all aspects of this research and manuscript preparation, particularly the presentation of research methods, the results, and their interpretation and the discussion of findings within the context of epidemiologic literature. B-HN and MJP performed all the statistical analyses related to this research and prepared the analytic methods section of this manuscript. JFP was responsible for providing clinical expertise on the use of the carotid stenosis data sets in these analyses, for the presentation of the clinical methods and findings, and for the discussion and interpretation of the stenosis results in this manuscript. RWK was responsible for the review and the development of all aspects of the manuscript in preparation for publication. JMO, as the development of all aspects of the manuscript, which included the description of the conceptual framework and context of the research, the presentation of results, and the interpretation and discussion of the findings. PAQ was responsible for providing clinical expertise on the use of the carotid stenosis data sets in these analyses, for the presentation of the clinical methods and findings, and for the discussion and interpretation of the stenosis results in this manuscript. JFP was responsible for providing clinical expertise on the use of the carotid stenosis data sets in these analyses, for the presentation of the clinical methods and findings, and for the discussion and interpretation of the stenosis results in this manuscript. RWK was responsible for the review and the development of all aspects of the manuscript in preparation for publication. JMO, as the principal investigator of one of the funded research projects that supported this work, provided significant consultation and advice to the research team during the preparation of research for publication. RBD, as senior biostatistician and head of the Statistical Consulting Unit at the Framingham Study, provided oversight on all aspects of the statistical analyses, the analytic components of this manuscript, and the interpretation of the data. None of the authors had a personal or financial conflict of interest.

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