# Prevalence and Distribution of Sub-Clinical Atherosclerosis by Screening Vascular Ultrasound in Low and Intermediate Risk Adults: The New York Physicians Study

John E. Postley, MD, Alejandro Perez, BS, Nathan D. Wong, PhD, and Julius M. Gardin, MD,
*New York, New York; Irvine, California; Hackensack, New Jersey*

*Background:* Many persons experiencing cardiovascular disease (CVD) events are not at high calculated CVD risk by Framingham risk score. The identification of carotid and femoral plaque has been associated with CVD events. In this study, the prevalence of plaques in adults at low and intermediate risk was examined.

*Methods:* Asymptomatic patients without CVD (n = 715; 43% women) were screened for carotid and femoral plaque using B-mode ultrasound.

*Results:* Significant predictors of plaque were male gender and age and, among women, dyslipidemia. Overall plaque prevalence was 32.8% among women and 40.5% among men aged 50 to 64 years. Among subjects with plaque in this age group, 56% of women and 31% of men had plaque exclusively in the femoral artery and would have been missed if only carotid ultrasound had been performed.

*Conclusion:* Ultrasound screening of the carotid and femoral arteries in a population with low and intermediate Framingham risk scores can identify potentially high risk subjects for whom intensive CVD risk factor modification may be appropriate. (J Am Soc Echocardiogr 2009;22:1145-51.)

*Keywords:* Ultrasound, Carotid, Femoral, Subclinical atherosclerosis

Cardiovascular disease (CVD) is the leading cause of death in the United States and in other developed countries. In the United States, there are 770,000 annual cases of myocardial infarction and acute coronary syndromes, with a 38% fatality rate within the year of occurrence.[1] Traditional risk factors can identify approximately half of these patients but fail to identify the other half and have lacked adequate specificity and sensitivity for identifying subclinical CVD.[2,3]

Noninvasive imaging of the cardiovascular system is able to identify subclinical atherosclerosis, which may help in the diagnosis of CVD before it becomes apparent through a serious event.[4,5] For example, coronary calcium screening can increase the sensitivity of diagnosis in subjects at low or intermediate risk for coronary heart disease (CHD).[6-10] However, this technology is associated with significant costs, radiation exposure, and equipment needs, thus limiting its use as an effective screening modality.

Ultrasound scanning of the peripheral vasculature is a noninvasive, high-resolution technique that is both mobile and free of radiation. A large outcome study (CAFES-CAVE) followed 10,000 low-risk patients for 10 years and demonstrated a close relation between ultrasonic abnormalities of the carotid and femoral arteries and future risk for myocardial infarction and stroke.[11] This study demonstrated that among low-risk subjects with nonstenosing plaques of the femoral or carotid artery, there was a 39% 10-year CVD event rate.

In this study, we examined the use of carotid and peripheral ultrasound screening in asymptomatic patients at low or intermediate risk for CHD by Framingham risk score (FRS).[12] Specifically, we examined gender-related and age-related associations with carotid and femoral plaque with the goal of determining whether this ultrasound examination might be appropriate in expanded populations.

## METHODS

### Study Population

The population consisted of 715 asymptomatic adults aged 23 to 85 years (43% women) within a multispecialty university-based group medical practice, self-referred for screening vascular ultrasound evaluation at their annual preventive physical examinations between July 2007 and April 2009. Lipid-lowering treatment was an exclusion so that subjects' FRS could be accurately calculated. Other study exclusions included previous evidence of CVD as demonstrated by a history

From the Department of Medicine, College of Physicians and Surgeons, Columbia University, New York, New York (J.E.P.); the Heart Disease Prevention Program, University of California, Irvine, Irvine, California (A.P., N.D.W.); New York Physicians LLP, New York, New York (J.E.P.); the Department of Medicine, Touro University College of Medicine, Hackensack, New Jersey (J.M.G.); and Hackensack University Medical Center, Hackensack, New Jersey (J.M.G.).

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Reprint requests: John E. Postley MD, 635 Madison Avenue, New York, NY 10022 (E-mail: *jpostley@aol.com*).

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**Table 1** Demographics of the total population

| | | FRS | | Age (y) | | | Plaque | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Variable | Total | ≤10 | 10-20 | <50 | 50-64 | ≥65 | None | Any | Carotid only | Femoral only |
| n | 715 | 582 | 133 | 244 | 352 | 119 | 461 | 254 | 85 | 102 |
| Body mass index (kg/m$^2$) | 25.6 | 25.1† | 27.2 | 26.5† | 25.2 | 24.6 | 25.7 | 25.2 | 24.7 | 25.7 |
| Waist circumference (in) | 33.1 | 32.7† | 35.1 | 33.7* | 33 | 32.5 | 33.1 | 33.2 | 32.7 | 33.3 |
| Blood pressure (mm Hg) | | | | | | | | | | |
| Systolic | 122.8 | 119.8† | 135.9 | 120.5† | 122.5 | 128.4 | 121.9* | 124.4 | 122.4 | 125.1 |
| Diastolic | 75.4 | 74.3† | 80.3 | 75.5 | 75.4 | 75.2 | 75.4 | 75.4 | 76.1 | 75.4 |
| Lipids (mg/dL) | | | | | | | | | | |
| Total cholesterol | 217.4 | 216.6 | 220.7 | 214 | 219.7 | 217.6 | 215.8 | 220.3 | 223.6 | 216.6 |
| HDL cholesterol | 63.4 | 65.6† | 53.7 | 56.9† | 67.4 | 64.8 | 64.7* | 61.1 | 62.9 | 60.5 |
| LDL cholesterol | 132.1 | 130.5† | 139.3 | 132.6 | 132 | 131.6 | 129.5† | 136.9 | 137.9 | 135.1 |
| Triglycerides | 107.3 | 99.6† | 141.4 | 117.9* | 102.1 | 101.4 | 105.8 | 110.1 | 104 | 108.8 |
| Carotid IMT (mm) | | | | | | | | | | |
| Average | 0.737 | 0.72† | 0.809 | 0.667† | 0.744 | 0.859 | 0.702† | 0.801 | 0.803* | 0.766 |
| Maximum | 0.888 | 0.869† | 0.969 | 0.814† | 0.894 | 1.02 | 0.85† | 0.956 | 0.964* | 0.916 |
| Smoking | | | | | | | | | | |
| Never | 69% (493) | 69.6% (405) | 66.2% (88) | 73% (178) | 67.9% (239) | 63.9% (76) | 73.8% (340)† | 60.2% (153) | 62.4% (53) | 63.7% (65) |
| Previous | 25.9% (185) | 26% (151) | 25.6% (34) | 19.7% (48)† | 27.3% (96) | 34.5% (41) | 21.7% (100)† | 33.5% (85) | 30.6% (26) | 32.4% (33) |
| Current | 5.2% (37) | 4.5% (26) | 8.3% (11) | 7.4% (18) | 4.8% (17) | 1.7% (2) | 4.6% (21) | 6.3% (16) | 7.1% (6) | 3.9% (4) |
| Hypertension medication | 10.4% (74) | 6.9% (40)† | 25.6% (34) | 3.3% (8)† | 12.2% (43) | 19.3% (23) | 10% (46) | 11% (28) | 9.4% (8) | 10.8% (11) |
| Hypertension | 26% (186) | 17.9% (104)† | 61.7% (82) | 18.9% (46)† | 26.1% (92) | 40.3% (48) | 24.3% (112) | 29.1% (74) | 23.5% (20) | 27.5% (28) |
| Diabetes mellitus | 2.1% (15) | 1.4% (8)† | 5.3% (7) | 1.6% (4) | 2.3% (8) | 2.5% (3) | 1.7% (8) | 2.8% (7) | 2.4% (2) | 2.9% (3) |
| Dyslipidemia | 37.8% (270) | 35.7% (208)* | 46.6% (62) | 39.3% (96) | 37.8% (133) | 34.5% (41) | 36.2% (167) | 40.6% (103) | 41.2% (35) | 38.2% (39) |

*$P < .05$.
†$P < .01$ compared across gender, FRS group, age group, plaque status, or carotid plaque only versus femoral plaque only.

of known myocardial infarction, angina pectoris, stroke, transient ischemic attack, or claudication or a calculated FRS >20% for CHD.

## Risk Factor Evaluation

Systolic and diastolic blood pressure were obtained by cuff sphygmomanometry at the time of the ultrasound examination. A fasting lipid profile was performed by a commercial laboratory, either LabCorp (New York, NY) or Quest (New York, NY). Current smoking was defined as smoking > 20 cigarettes during the week preceding examination. Dyslipidemia was defined as one or more of the following: total cholesterol > 240 mg/dL, high-density lipoprotein (HDL) cholesterol < 40 mg/dL, triglycerides > 200 mg/dL, or the use of lipid-lowering medication. Hypertension was defined as blood pressure > 140/90 mmHg or the use of blood pressure–lowering medication. Diabetes mellitus was defined as fasting glucose ≥ 126 mg/dL, glycosylated hemoglobin > 7.0%, or the use of hypoglycemic medication. The FRS was determined by age, gender, smoking history, blood pressure, presence or absence of diabetes mellitus, and total and HDL cholesterol levels. Low risk was defined as <10% CHD risk over 10 years and intermediate risk as 10% to 20% 10-year risk.[12]

## Ultrasound Evaluation

Carotid and femoral ultrasound examinations were carried out using a 7.5-MHz linear-array transducer and a SonoSite MicroMaxx (SonoSite, Inc, Bothell, WA) ultrasound machine by a single technician using the same equipment. The carotid and femoral arteries were interrogated in transverse and longitudinal planes. Carotid artery examina-

**Table 2a** Comparison of demographics by gender

| Variable | Men | Women |
|---|---|---|
| n | 404 | 311 |
| Body mass index (kg/m$^2$) | 26.7† | 24.0 |
| Waist circumference (in) | 35.3† | 30.4 |
| Blood pressure (mm Hg) | | |
| Systolic | 125.1† | 119.8 |
| Diastolic | 76.7† | 73.8 |
| Lipids (mg/dL) | | |
| Total cholesterol | 210.7† | 226.0 |
| HDL cholesterol | 56.6† | 72.3 |
| LDL cholesterol | 130.2 | 134.6 |
| Triglycerides | 116.7† | 95.1 |
| Carotid IMT (mm) | | |
| Average | 0.738 | 0.736 |
| Maximum | 0.891 | 0.883 |
| Smoking | | |
| Never | 71.5% (289) | 65.6% (204) |
| Previous | 22.3% (90)* | 30.6% (95) |
| Current | 6.2% (25) | 3.9% (12) |
| Hypertension medication | 10.4% (42) | 10.3% (32) |
| Hypertension | 29.2% (118)* | 21.9% (68) |
| Diabetes mellitus | 2% (8) | 2.3% (7) |
| Dyslipidemia | 35.4% (143) | 40.8% (127) |

*$P < .05$.
†$P < .01$ compared across gender.

Table 2b Demographics of men

| Variable | Total | FRS ≤10 | FRS 10-20 | Age (y) <50 | Age (y) 50-64 | Age (y) ≥65 | Plaque None | Plaque Any | Plaque Carotid only | Plaque Femoral only |
|---|---|---|---|---|---|---|---|---|---|---|
| n | 404 | 300 | 104 | 172 | 178 | 54 | 256 | 148 | 45 | 56 |
| Body mass index (kg/m$^2$) | 26.7 | 26.5 | 27.3 | 27.4† | 26.4 | 25.6 | 27* | 26.2 | 25.8 | 27.1 |
| Waist circumference (in) | 35.3 | 35.0† | 36 | 35.2 | 35.4 | 35.1 | 35.4 | 35 | 34.9 | 35.2 |
| Blood pressure (mm Hg) | | | | | | | | | | |
| Systolic | 125.1 | 121.3† | 136.2 | 123.7† | 124.5 | 132.1 | 124.2 | 126.7 | 122.3* | 129.4 |
| Diastolic | 76.7 | 75.5† | 80.3 | 77.3 | 76.3 | 76.1 | 76.9 | 76.4 | 76.4 | 77.1 |
| Lipids (mg/dL) | | | | | | | | | | |
| Total cholesterol | 210.7 | 208.9 | 216.1 | 215.9† | 210.6 | 194.9 | 211.6 | 209.2 | 209 | 204.1 |
| HDL cholesterol | 56.6 | 57.8* | 53.2 | 52.5† | 60.5 | 56.5 | 57.9* | 54.3 | 54.6 | 53.4 |
| LDL cholesterol | 130.2 | 128.8 | 134.3 | 136.3† | 127.9 | 118.7 | 129.9 | 130.9 | 129.1 | 127.5 |
| Triglycerides | 116.7 | 107.2† | 144.3 | 129.6* | 109.5 | 99.7 | 116.8 | 116.7 | 110.9 | 115.7 |
| Carotid IMT (mm) | | | | | | | | | | |
| Average | 0.738 | 0.715† | 0.804 | 0.673† | 0.754 | 0.888 | 0.701† | 0.802 | 0.799 | 0.775 |
| Maximum | 0.891 | 0.866† | 0.964 | 0.822† | 0.91 | 1.051 | 0.85† | 0.962 | 0.967 | 0.927 |
| Smoking | | | | | | | | | | |
| Never | 71.5% (289) | 73.7% (221) | 65.4% (68) | 74.4% (128) | 70.8% (126) | 64.8% (35) | 74.6% (191) | 66.2% (98) | 64.4% (29) | 75% (42) |
| Previous | 22.3% (90) | 21% (63) | 26% (27) | 16.9% (29)* | 24.2% (43) | 33.3% (18) | 19.9% (51) | 26.4% (39) | 28.9% (13) | 19.6% (11) |
| Current | 6.2% (25) | 5.3% (16) | 8.7% (9) | 8.7% (15) | 5.1% (9) | 1.9% (1) | 5.5% (14) | 7.4% (11) | 6.7% (3) | 5.4% (3) |
| Hypertension medication | 10.4% (42) | 5.7% (17)† | 24% (25) | 3.5% (6)† | 12.9% (23) | 24.1% (13) | 10.2% (26) | 10.8% (16) | 4.4% (2) | 14.3% (8) |
| Hypertension | 29.2% (118) | 18.3% (55)† | 60.6% (63) | 23.3% (40)† | 29.2% (52) | 48.2% (26) | 27% (69) | 33.1% (49) | 17.8% (8)* | 35.7% (20) |
| Diabetes mellitus | 2% (8) | 1.7% (5) | 3% (3) | 1.7% (3) | 2.3% (4) | 1.9% (1) | 2.3% (6) | 1.4% (2) | 0% | 1.8% (1) |
| Dyslipidemia | 35.4% (143) | 32.3% (97)* | 44.2% (46) | 45.4% (78)† | 29.8% (53) | 22.2% (12) | 37.9% (97) | 31.1 (46) | 26.7% (12) | 28.6% (16) |

*$P < .05$.
†$P < .01$ compared across gender, FRS group, age group, plaque status, or carotid plaque only versus femoral plaque only.

tion included evaluation of the common carotid artery within 2 cm of the origin of the carotid bulb, the carotid bulb itself, and the internal but not the external carotid artery. Both carotid arteries were examined, and 2 measurements were obtained of each common carotid artery for intima-media thickness (IMT), a total of 4 measurements for each subject. Plaque was defined as a focal projection of ≥1.5 mm of the arterial wall into the lumen.[13-16] SonoCalc (SonoSite) software was used for plaque and automated carotid IMT measurement. The reproducibility of carotid IMT measurement has been previously described.[17] The reproducibility of the assessment of plaque presence was 93% when 100 random examinations were reexamined by an experienced vascular physician under blinded conditions.

## Statistical Analysis

The $\chi^2$ test of proportions was used to compare the prevalence of carotid and femoral plaque by age group (< 50, 50-64, and ≥ 65 years), gender, and cardiovascular risk factors. Multiple logistic regression was used to estimate the odds ratios for the presence of carotid and/or femoral plaque according to age group, gender, and risk factors and to examine for factors independently associated with the likelihood of plaque. SAS version 9.1.3 (SAS Institute Inc, Cary, NC) was used to perform all analyses.

## RESULTS

Our study included 715 subjects ranging in age from 23 to 85 years, of whom 311 (43%) were women. Population characteristics are described in Table 1, with analyses by gender described in Tables 2a, 2b, and 2c. Men had higher body mass indexes and systolic and diastolic blood pressures but lower total cholesterol and higher triglyceride levels compared with women ($P < .01$ for all), but there was no gender difference in low-density lipoprotein (LDL) cholesterol (Table 2a). With respect to FRS group, both low-risk men (Table 2b) and low-risk women (Table 2c) compared with intermediate-risk men and women had lower body mass indexes and higher HDL cholesterol levels, waist circumferences, blood pressures, and triglyceride levels ($P < .01$), and low-risk compared with intermediate-risk women had lower LDL cholesterol levels ($P < .01$). In neither men nor women was total cholesterol different by FRS group; in men, the LDL level was not significantly different between low-risk and intermediate-risk FRS groups.

When differentiated by age group, both younger men (Table 2b) and younger women (Table 2c) compared with those who were older had lower systolic blood pressures ($P < .01$), and younger women had lower diastolic blood pressures ($P < .05$) and lower total and LDL cholesterol levels ($P < .01$), while younger men had higher total and LDL cholesterol levels ($P < .01$).

With respect to the presence or absence of any plaque, only among women (Table 2c) was there a significant association with elevated total and LDL cholesterol ($P < .01$). Among women, there was also a significant number of never smokers among those with no plaque compared with those with plaque ($P < .01$). Among men, those with versus without plaque had significantly lower HDL cholesterol levels ($P < .05$; Table 2b).

In attempting to identify characteristics that might differentiate subjects with carotid plaque alone from those with femoral plaque alone,

**Table 2c** Demographics of women

| Variable | Total | FRS | | Age (y) | | | Plaque | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | ≤10 | 10-20 | <50 | 50-64 | ≥65 | None | Any | Carotid only | Femoral only |
| n | 311 | 282 | 29 | 72 | 174 | 65 | 205 | 106 | 40 | 46 |
| Body mass index (kg/m²) | 24 | 23.7† | 27 | 24.4 | 24 | 23.7 | 24.1 | 23.9 | 23.6 | 24 |
| Waist circumference (in) | 30.4 | 30.2* | 32 | 30.1 | 30.5 | 30.3 | 30.2 | 30.8 | 30.3 | 31 |
| Blood pressure (mm Hg) | | | | | | | | | | |
| Systolic | 119.8 | 118.2† | 135.1 | 112.8† | 120.6 | 125.4 | 119.1 | 121.2 | 122.5 | 120 |
| Diastolic | 73.8 | 73.1† | 80.1 | 71.4* | 74.5 | 74.4 | 73.7 | 73.9 | 75.9 | 73.2 |
| Lipids (mg/dL) | | | | | | | | | | |
| Total cholesterol | 226 | 224.9 | 237 | 209.3† | 229 | 236.4 | 221† | 235.6 | 240.1 | 231.8 |
| HDL cholesterol | 72.3 | 74† | 55.4 | 67.5* | 74.5 | 71.8 | 73.1 | 70.7 | 72.3 | 69.2 |
| LDL cholesterol | 134.6 | 132.2† | 157.3 | 123.7† | 136.2 | 142.4 | 129.1† | 145.33 | 147.7 | 144.4 |
| Triglycerides | 95.1 | 91.4† | 130.8 | 89.8 | 94.4 | 102.8 | 92.2 | 100.8 | 96.3 | 100.5 |
| Carotid IMT (mm) | | | | | | | | | | |
| Average | 0.736 | 0.726† | 0.828 | 0.653† | 0.733 | 0.834 | 0.703† | 0.798 | 0.809* | 0.755 |
| Maximum | 0.883 | 0.873† | 0.987 | 0.794† | 0.879 | 0.994 | 0.850† | 0.947 | 0.960 | 0.904 |
| Smoking | | | | | | | | | | |
| Never | 65.6% (204) | 65.3% (184) | 69% (20) | 69.4% (50) | 64.9% (13) | 63.1% (41) | 72.7% (149)† | 51.9% (55) | 60% (24) | 50% (23) |
| Previous | 30.6% (95) | 31.2% (88) | 24.1% (7) | 26.4% (19) | 30.5% (53) | 35.4% (23) | 23.9% (49)† | 43.4% (46) | 32.5% (13) | 47.8% (22) |
| Current | 3.9% (12) | 3.6% (10) | 6.9% (2) | 4.2% (3) | 4.6% (8) | 1.5% (1) | 3.4% (7) | 4.7% (5) | 7.5% (3) | 2.2% (1) |
| Hypertension medication | 10.3% (32) | 8.2% (23)† | 31% (9) | 2.8% (2)* | 11.5% (20) | 15.4% (10) | 9.8% (20) | 11.3% (12) | 15% (6) | 6.5% (3) |
| Hypertension | 21.9% (19) | 17.4% (49)† | 65.5% (19) | 8.3% (6)† | 23% (40) | 33.9% (22) | 21% (43) | 23.6% (25) | 30% (12) | 17.4% (8) |
| Diabetes mellitus | 2.3% (7) | 1.1% (3)† | 13.8% (4) | 1.4% (1) | 2.3% (4) | 3.1% (2) | 1% (2)* | 4.7% (5) | 5% (2) | 4.4% (2) |
| Dyslipidemia | 40.8% (127) | 39.4% (111) | 55.2% (16) | 25% (18)† | 46% (80) | 44.6% 29) | 34.2% (70)† | 53.8% (57) | 57.5% (23) | 50% (23) |

*$P < .05$.
†$P < .01$ compared across gender, FRS group, age group, plaque status, or carotid plaque only versus femoral plaque only.

only in men compared with women was higher systolic blood pressure associated with a predominance of femoral plaque ($P < .01$). When viewed as a total population, there was a significant association of both average and maximum carotid IMT with carotid plaque alone compared with femoral plaque alone ($P < .05$; Table 1). Although there was a trend toward this association in men (Table 2b), only in women (Table 2c) was the average carotid IMT significantly associated with carotid plaque alone ($P < .01$). It is possible that with a greater number of subjects, this association would have been significant for both genders.

The frequency of plaque by age and FRS group is presented by gender in Figures 1A and 1B. There were no women aged <50 years in the intermediate-risk group. There was a significant association of age with the frequency of plaque in low-risk women and both low-risk and intermediate-risk men. Of particular note, there was no difference in plaque frequency in men aged 50 to 64 years between the low-risk and intermediate-risk groups.

Plaque frequency by age, gender, and plaque location is presented in Table 3 and Figures 2A and 2B. The influence of age on plaque frequency is apparent in both men and women. Among those aged 50 to 64 years, 56% of the women and 31% of the men who had plaque had it exclusively in the femoral artery.

The frequency of plaque by age and number of CVD risk factors (dyslipidemia, hypertension, smoking, and diabetes) is presented for each gender in Table 4 and Figures 3A and 3B. Other than elderly women, in whom there was a significant association of risk factors and plaque frequency, there was no significant relationship between risk factor frequency and plaque. Of note, there were very few subjects with diabetes in this study.

## DISCUSSION

This study confirms the lack of specificity of low and intermediate FRS for excluding atherosclerotic disease detectable by ultrasound. Specifically, we have shown that among men aged 50 to 64 years, 39.7% of those at low risk and 42.1% of those at intermediate risk had carotid and/or femoral plaque. Among women aged 50 to 64 years, 30.4% of those at low risk and 56.3% of those at intermediate risk had plaque. The concept that FRS underrepresents the presence of atherosclerotic disease in low-risk populations, especially in women, has been established by others who have examined coronary artery calcification scores,[9] atherosclerotic plaque burden by computed tomographic angiography,[18] and myocardial infarction[19] in relation to FRS. This is the first attempt to demonstrate this principle with the ultrasound assessment of both carotid and femoral arteries in a North American population of healthy low-risk and intermediate-risk persons.

The underlying premise is that femoral and carotid plaque identification indicates an increased risk for subsequent myocardial and cerebrovascular events. The CAFES-CAVE study followed 10,000 Italian men and women at low cardiovascular risk aged 35 to 65 years for 10 years without treatment.[11] These subjects were chosen from a population because they had no evidence of diabetes, hypertension,

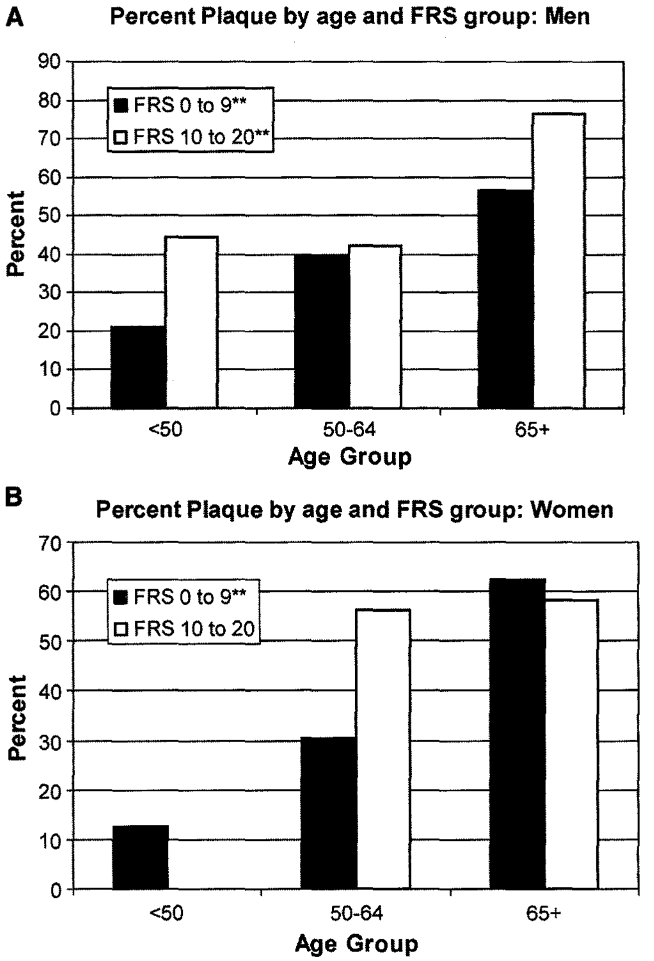


**Figure 1** Frequency of any plaque by age group and FRS in **(A)** men and **(B)** women. $P < .01$ comparing plaque prevalence in men and women aged <50 versus 50 to 64 versus ≥65 years, among those with FRS of 0 to 9, and among those with FRS of 10 to 20.

**Table 3** Frequency of plaque by location and age

| Age group (y) | Plaque | | | |
|---|---|---|---|---|
| Men | Any† | Carotid only | Femoral only† | Both† |
| <50 (n = 172) | 22.1% (38) | 39.4% (15) | 44.7% (17) | 15.7% (6) |
| 50-64 (n = 178) | 40.5% (72) | 33.3% (24) | 30.5% (22) | 36.1% (26) |
| ≥65 (n = 54) | 70.4% (38) | 15.7% (6) | 44.7% (17) | 39.4% (15) |
| Women | Any† | Carotid only* | Femoral only* | Both† |
| <50 (n = 72) | 12.5% (9) | 55.5% (5) | 33.3% (3) | 11.1% (1) |
| 50-64 (n = 174) | 32.8% (57) | 35.0% (20) | 56.1% (32) | 7.0% (4) |
| ≥65 (n = 65) | 61.5% (40) | 37.5% (15) | 27.5% (11) | 35.0% (14) |

*$P < .05$.
†$P < .01$ across age groups.

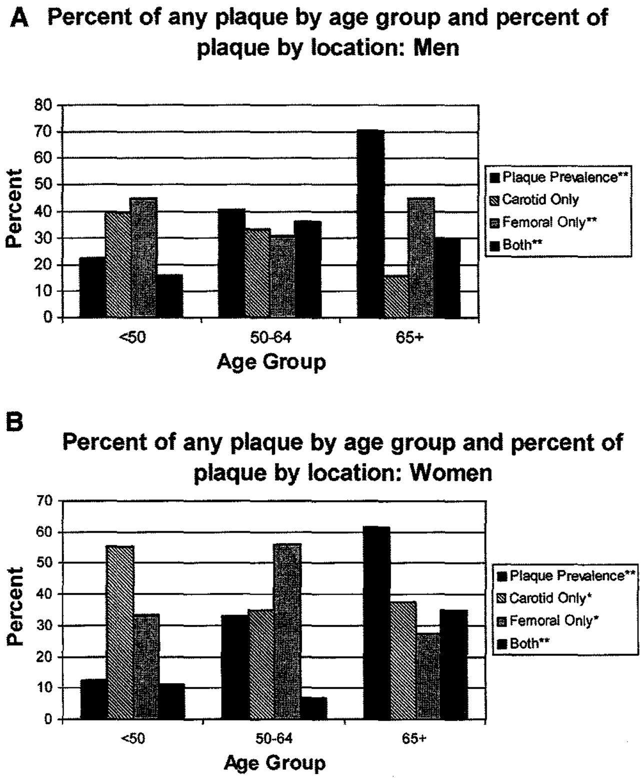


**Figure 2** Frequency of plaque by location by age in **(A)** men and **(B)** women. $P < .01$ comparing plaque prevalence (any, femoral only, and both) in men aged <50 versus 50 to 64 versus ≥65 years. $P < .01$ comparing plaque prevalence (any and both) in women aged <50 versus 50 to 64 versus ≥65 years; $P < .05$ comparing plaque prevalence (carotid only and femoral only) in women aged <50 versus 50 to 64 versus ≥65 years.

or total cholesterol > 200 mg/dL. Because these subjects were felt to be at such low risk, no treatment was initiated when abnormalities were identified. Cardiovascular event risk in this study ranged from 0.1% to 81.1% over 10 years according to class of abnormality (ranging from no ultrasound abnormality to having hemodynamically significant plaque). There was an overall 7.1% 10-year risk among the entire sample, consistent with low risk by American Heart Association standards.[12] Even evidence of hemodynamically nonstenotic plaques conferred a 10-year risk of 39.1%, which was more than 4-fold greater than in those with carotid IMT ≥ 1.0 mm but no plaque (8.7%). Remarkably, screening vascular ultrasound identified the members of this generally low risk population who were at very high risk notwithstanding the absence of other risk factors. The event rates of 39% with early plaque identification and 81% with hemodynamically significant plaque are higher than those reported in populations screened for coronary calcification,[7] suggesting ultrasound plaque evaluation may be an effective technique for predicting CVD events without subjecting patients to radiation.

We chose to stratify our population by age because the ultrasound standard has been validated only with 10-year risks for those subjects aged ≤65 years. Furthermore, because CVD events occur in an age-related progression, we chose to see if age group analysis could specify a higher risk group within the population for whom screening would be helpful. The importance of screening both the carotid and femoral arteries is suggested by the prevalence of plaque exclusive to one or the other in both men and women of all ages (Figures 2A and 2B). In subjects aged 50 to 64 years, failure to interrogate the femoral arteries would have missed 56% of women and 31% of men who were ultimately found to have plaques.

In addition to advancing age and male gender, we have shown that traditional risk factors such as cigarette smoking and dyslipidemia independently increase the likelihood of plaque in a low-risk and intermediate-risk population among women. With respect to men,

**Table 4** Frequency of any plaque by age and cardiovascular risk factors

| Age group | Number of cardiovascular risk factors | | | |
|---|---|---|---|---|
| Men | 0 (n) | 1 (n) | 2 (n) | ≥3 (n) |
| <50 (n = 172) | 22.8% (13) | 18.1% (13) | 30.6% (11) | 14.3% (1) |
| 50-64 (n = 178) | 38.8% (26) | 38.6% (27) | 46.9% (15) | 44.4% (4) |
| ≥65 (n = 54) | 69.2% (9) | 76.0% (19) | 60.0% (9) | 100% (1) |
| Women | | | | |
| <50 (n = 72) | 5.0% (2) | 23.5% (4) | 20.0% (3) | NA |
| 50-64 (n = 174) | 21.3% (10) | 32.9% (24) | 42.0% (21) | 50.0% (2) |
| ≥65 (n = 65)* | 56.3% (9) | 44.4% (12) | 82.4% (14) | 100% (5) |

*NA*, Not available.
*$P < .05$ across cardiovascular risk factor numbers.

there was no association between total or LDL cholesterol and plaque, and younger men had significantly higher total and LDL cholesterol levels than older men, which would be expected, because for older men to have low or intermediate FRS, something would have to compensate for the effect of the greater age in the FRS formula. Nevertheless, there remains a substantial group without identifiable risk factors who have observable plaque on ultrasound screening of the carotid and femoral arteries. This appears to be much more important in men than women. Although the absence of risk factors may be comforting in assessing risk in women aged < 50 years, there is no such comfort zone in men. The percentage of men without risk factors who have plaque is not significantly different than the overall prevalence of plaque in the group of men with risk factors at all ages. Analysis of factors favoring either carotid or femoral plaque reveals only that with respect to the total population, an increased average and maximum carotid IMT is associated with a predominance of carotid plaque. Only among women is an increased average carotid IMT associated with carotid plaque, although there is a trend for this in men as well as associations with maximum carotid IMT in both men and women that do not reach levels of significance. It is possible that with a greater number of subjects, these associations would be significant.

An important insight that can be derived from this study is that in men of any age at low or intermediate risk, evaluation by screening ultrasound of both the carotid and femoral arteries may help identify those with atherosclerosis who could potentially benefit from more intensive risk factor modification. Among women aged <50 years, the absence of risk factors other than family history of premature CVD diminishes the need for performing screening ultrasound examinations in those at low risk. However, the prevalence of plaque in subjects aged 50 to 64 years among women increases greatly the utility of ultrasound evaluation; the high prevalence of plaque exclusive to either the femoral or the carotid artery in this group suggests the clinical utility of screening both vascular beds. Such screening may address the potentially significant long-term risk for CVD events in women that is frequently underestimated by the FRS and other global risk algorithms.

Several limitations of this study should be noted. First, this was a cross-sectional study of a clinic-based sample that comprised many "worried well," who may not represent the general population. In addition, CVD event outcomes were not available. However, the very high incidence of CVD events among those subjects with any plaque, 39% minimum over a 10-year period, in the CAFES-CAVE study[11] makes an ethical outcome trial difficult to envision. In addition, the sample was almost entirely Caucasian and moderately affluent, so our findings may not be applicable to other segments of the population or the population as a whole. However, the ethnicity of our sample is consistent with the population studied in the CAFES-CAVE study. Abe et al[20] studied the demographics of a randomly selected northern Manhattan cohort and found substantial racial and ethnic differences among groups with low FRS risk: whites had a 21% incidence of carotid plaque, whereas only 10% of Hispanics had carotid plaque. There were no corresponding outcomes data, so the relationship of these findings to subsequent events is not known.

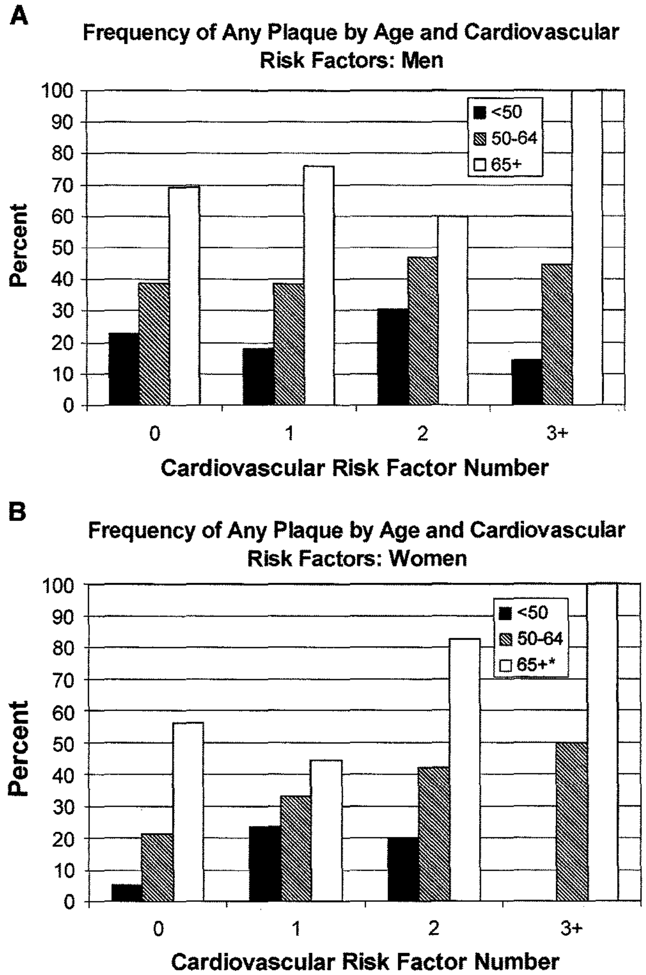


**Figure 3** Frequency of any plaque by age and number of cardiovascular risk factors in **(A)** men and **(B)** women. Nonsignificant for trend across number of risk factors for men aged <50 versus 50 to 64 versus ≥ 65 years. $P < .05$ for trend across number of risk factors for women aged ≥ 65 years only.

The potential for refining CVD risk stratification by ultrasound examination has been suggested by several expert consensus panels.[5,21,22] Simon et al[23] reviewed the comparative performance of various tests of subclinical atherosclerosis in published outcome studies, although they neglected to include CAFES-CAVE among them. They reported 10-year CHD risk of 25% among men with carotid plaque alone[24] and rates of 20% to 28% in men and women with coronary calcium scores > 300[25] to 400.[26] We have shown that ultrasound screening of the peripheral vasculature for atherosclerotic plaque in either the carotid or the femoral arteries can identify a potentially high risk group of patients among those with low or intermediate FRS for CHD. With half of persons experiencing first coronary events not identified by FRS assessment,[2,3] a simple noninvasive and inexpensive method of evaluating atherosclerotic burden, such as ultrasound, may be clinically useful in helping identify those who may potentially benefit from earlier, more aggressive risk factor and clinical intervention. Importantly, however, the cost-effectiveness and long-term efficacy of such an approach on clinical outcomes has yet to be demonstrated.

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## REFERENCES

1. American Heart Association. 2008 heart and stroke statistical update. Available at: http://www.americanheart.org. Accessed October 13, 2008.
2. Kannel WB, D'Agostino RB, Sullivan L, Wilson PW. Concept and usefulness of cardiovascular risk profiles. Am Heart J 2004;148:16-26.
3. Brindle P, Emberson J, Lampe F, Walker M, Whincup P, Fahey T, Ebrahim S. Predictive accuracy of the Framingham coronary risk score in British men: prospective cohort study. BMJ 2003;327:1267-72.
4. Wilson PWF, Smith SC, Blumenthal RS, Burke GL, Wong ND. Task Force #4—how do we select patients for atherosclerosis imaging? J Am Coll Cardiol 2003;41:1898-906.
5. Greenland P, Abrams J, Aurigemma GP, Bond MG, Clark LT, Criqui MH, et al. Prevention Conference V. Beyond secondary prevention: identifying the high-risk patient for primary prevention: tests for silent and inducible ischemia: Writing Group III. Circulation 2000;101:E16-22.
6. Raggi P, Callister TQ, Cooil B, He ZX, Lippolis NJ, Russo DJ, et al. Identification of patients at increased risk of first unheralded acute myocardial infarction by electron-beam computed tomography. Circulation 2000; 101:850-5.
7. Kondos GT, Hoff JA, Sevrukov A, Daviglus ML, Garside DB, Devries SS, et al. Electron-beam tomography coronary artery calcium and cardiac events: a 37-month follow-up of 5635 initially asymptomatic low- to intermediate-risk adults. Circulation 2003;107:2571-6.
8. Desai MY, Nasir K, Braunstein JB, Rumberger JA, Post WS, Budoff MJ, et al. Underlying risk factors incrementally add to the standard risk estimate in detecting subclinical atherosclerosis in low- and intermediate-risk middle-aged asymptomatic individuals. Am Heart J 2004;148: 871-7.
9. Michos ED, Nasir K, Braunstein JB, Rumberger JA, Budoff MJ, Post WS, et al. Framingham risk equation underestimates subclinical atherosclerosis risk in asymptomatic women. Atherosclerosis 2006;184:201-6.
10. Lakoski SG, Greenland P, Wong ND, Schreiner PJ, Herrington DM, Kronmal RA, et al. Coronary artery calcium scores and risk for cardiovascular events in women classified as "low risk" based on Framingham risk score: the Multi-Ethnic Study of Atherosclerosis (MESA). Arch Intern Med 2007;167:2437-42.
11. Belcaro G, Nicolaides AN, Ramaswami G, Cesarone MR, De Sanctis M, Incandela L, et al. Carotid and femoral ultrasound morphology screening and cardiovascular events in low risk subjects: a 10-year follow-up study (the CAFES-CAVE study). Atherosclerosis 2001;156:379-87.
12. National Cholesterol Education Program (NCEP) Expert Panel on Detection. Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation 2002;106:3143-421.
13. Polak JF, Shemanski L, O'Leary DH, Lefkowitz D, Price TR, Savage PJ, et al. Hypoechoic plaque at US of the carotid artery: an independent risk factor for incident stroke in adults aged 65 years or older. Cardiovascular Health Study [published correction appears in Radiology 1998;209:288-9]. Radiology 1998;208:649-54.
14. Hunt KJ, Duggirala R, Göring HH, Williams JT, Almasy L, Blangero J, et al. Genetic basis of variation in carotid artery plaque in the San Antonio Family Heart Study. Stroke 2002;33:2775-80.
15. Kitamura A, Iso H, Imano H, Ohira T, Okada T, Sato S, et al. Carotid intima-media thickness and plaque characteristics as a risk factor for stroke in Japanese elderly men. Stroke 2004;35:2788-94.
16. Jørgensen L, Jenssen T, Joakimsen O, Heuch I, Ingebretsen OC, Jacobsen BK. Glycated hemoglobin level is strongly related to the prevalence of carotid artery plaques with high echogenicity in nondiabetic individuals: the Tromsø study. Circulation 2004;110:466-70.
17. Korcarz CE, Hirsch AT, Bruce C, DeCara JM, Mohler ER, Pogue B, et al. Carotid intima-media thickness testing by non-sonographer clinicians: the Office Practice Assessment of Carotid Atherosclerosis Study. J Am Soc Echocardiogr 2008;21:117-22.
18. Johnson KM, Dowe DA, Brink JA. Traditional clinical risk assessment tools do not accurately predict coronary atherosclerotic plaque burden: a CT angiography study. Am J Radiol 2009;192:235-43.
19. Akosah KO, Schaper A, Cogbill C, Schoenfeld P. Preventing myocardial infarction in the young adult in the first place: how do the National Cholesterol Education Panel III guidelines perform? J Am Coll Cardiol 2003; 41:1475-9.
20. Abe Y, Rundek T, Sciacca RR, Jin Z, Sacco RL, Homma S, et al. Ultrasound assessment of subclinical cardiovascular disease in a community-based multiethnic population and comparison to the Framingham score. Am J Cardiol 2006;98:1374-8.
21. Roman MJ, Naqvi TZ, Gardin JM, Gerhard-Herman M, Jaff M, Mohler E. Clinical application of non invasive vascular ultrasound in cardiovascular risk stratification: a report from the American Society of Echocardiography; Society of Vascular Medicine and Biology. J Am Soc Echocardiogr 2006;19:943-54.
22. Redberg RF, Vogel RA, Criqui MH, Herrington DM, Lima JA, Roman MJ. 34th Bethesda Conference: Task Force #3—what is the spectrum of current and emerging techniques for the noninvasive measurement of atherosclerosis? J Am Coll Cardiol 2003;41:1886-98.
23. Simon A, Chironi G, Levenson J. Comparative performance of subclinical atherosclerosis tests in predicting coronary heart disease in asymptomatic individuals. Eur Heart J 2007;28:2967-71.
24. Salonen T, Salonen R. Ultrasonically assessed carotid morphology and the risk of coronary heart disease. Arterioscler Thromb 1991;11:1245-9.
25. Greenland P, Labree L, Azen SP, Doherty TM, Detrano RC. Coronary artery calcium score combined with Framingham score for risk prediction in asymptomatic individuals. JAMA 2004;291:210-5.
26. Arad Y, Goodman KJ, Roth M, Newstein D, Guerci AD. Coronary calcification, coronary disease risk factors, C-reactive protein, and atherosclerotic cardiovascular disease events: the St. Francis Heart Study. J Am Coll Cardiol 2005;46:158-65.