Superficial Femoral Artery Plaque, the Ankle-Brachial Index, and Leg Symptoms in Peripheral Arterial Disease

The Walking and Leg Circulation Study (WALCS) III

Mary M. McDermott, MD; Kiang Liu, PhD; James Carr, MD; Michael H. Criqui, MD, MPH; Lu Tian, ScD; Debiao Li, PhD; Luigi Ferrucci, MD, PhD; Jack M. Guralnik, MD, PhD; Christopher M. Kramer, MD; Chun Yuan, PhD; Melina Kibbe, MD; William H. Pearce, MD; Jarett Berry, MD; Walter McCarthy, MD; Yihua Liao, MS; Dongxiang Xu, PhD; Jennifer Orozco, MMS, PA-C; Timothy J. Carroll, PhD

Background—The clinical significance of magnetic resonance–imaged plaque characteristics in the superficial femoral artery (SFA) is not well established. We studied associations of the ankle-brachial index (ABI) and leg symptoms with MRI-measured plaque area and percent lumen area in the SFA in participants with and without lower-extremity peripheral arterial disease (PAD).

Methods and Results—Four hundred twenty-seven participants (393 with PAD) underwent plaque imaging of the first 30 mm of the SFA. Twelve 2.5-mm cross-sectional images of the SFA were obtained. Outcomes were normalized plaque area, adjusted for artery size (0 to 1 scale, 1 = greatest plaque), and lumen area, expressed as a percent of the total artery area. Adjusting for age, sex, race, smoking, statins, cholesterol, and other covariates, lower ABI values were associated with greater normalized mean plaque area (ABI <0.50:0.79; ABI 0.50 to 0.69:0.73; ABI 0.70 to 0.89:0.65; ABI 0.90 to 0.99:0.62; ABI 1.00 to 1.09:0.48; ABI 1.10 to 1.30:0.47 (P trend <0.001)) and smaller mean percent lumen area (P trend <0.001). Compared with PAD participants with intermittent claudication, asymptomatic PAD participants had lower normalized mean plaque area (0.72 versus 0.65, P=0.005) and larger mean percent lumen area (0.30 versus 0.36, P=0.01), adjusting for the ABI and other confounders.

Conclusions—Lower ABI values are associated with greater MRI-measured plaque burden and smaller lumen area in the first 30 mm of the SFA. Compared with PAD participants with claudication, asymptomatic PAD participants have smaller plaque area and larger lumen area in the SFA.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00520312.

(Circ Cardiovasc Imaging. 2011;4:246-252.)

Key Words: atherosclerosis ▪ MRI ▪ peripheral vascular disease ▪ plaque

Direct atherosclerotic plaque visualization has improved our understanding of the development and progression of atherosclerosis.1,2 However, little is known about clinical correlates of lower-extremity atherosclerotic plaque characteristics in patients with lower-extremity peripheral arterial disease (PAD).

Clinical Perspective on p 252

High-resolution MRI has emerged as the most promising modality for direct atherosclerotic plaque imaging.3 In the present study, we used MRI to directly image consecutive cross-sectional slices of the superficial femoral artery (SFA). We assessed associations of the ankle-brachial index (ABI), an established clinical tool for assessing presence and severity of PAD, with MRI-measured plaque area and lumen area in the SFA among participants with and those without PAD. We hypothesized that lower ABI values would be associated with greater plaque area and smaller percent lumen area in directly imaged cross sections of the proximal SFA. We also...
studied associations of the ABI with plaque area and percent lumen area in the SFA in the subset of participants with PAD. We determined whether plaque area and percent lumen area differed between PAD participants with distinct types of leg symptoms. Finally, we studied associations of the ABI with plaque measures in PAD participants with and without diabetes mellitus to determine whether associations of lower ABI values with plaque area and percent lumen area were similar in PAD participants with versus without diabetes mellitus.

Methods

Subjects

Participants with PAD were identified from among consecutive PAD patients in the noninvasive vascular laboratories at Northwestern Memorial Hospital, Jesse Brown Veterans Administration (VA), Rush Medical Center, and Mt Sinai Hospital in Chicago. Additionally, lists of consecutive patients with a diagnosis of PAD in the vascular surgery, cardiology, endocrinology, general medicine, and geriatric practices at Northwestern Medical Faculty Foundation and in the vascular surgery practice at the Jesse Brown VA were contacted and invited to participate. Participants without PAD were identified from among consecutive patients ages 65 years and older in Northwestern’s general internal medicine practice who had no history of smoking, diabetes mellitus, or established cardiovascular disease, including PAD. The protocol was Institutional Review Board–approved by Northwestern University Feinberg School of Medicine and all participating sites. Participants gave informed consent. Enrollment occurred between October 26, 2007, and December 22, 2009.

Inclusion Criteria

For participants with PAD, the inclusion criterion was an ABI <1.00. This inclusion criterion was selected because truly normal ABI values are 1.10 to 1.30 or 1.10 to 1.40,6 and because including participants with ABI <1.00 ensured a broad range of severity of lower-extremity atherosclerosis. For participants without PAD, the inclusion criterion was ABI 1.00 to 1.30.7

Exclusion Criteria

Potential participants with dementia and those with a Mini-Mental Status Examination score <23 were excluded because of concerns about their cognitive function. Nursing home residents, wheelchair-bound patients, and patients with foot or leg amputations were excluded because of their severely impaired functioning. Non–English-speaking patients were excluded because investigators were not fluent in non-English languages. Patients with recent major surgery were excluded. Patients with contraindications to MRI testing were excluded. We excluded potential participants requiring oxygen therapy, those who stopped during a 6-minute walk test because of shortness of breath, and those with severe knee osteoarthritis, measured by reported pain in or around the knee joint combined with a radiograph-measured osteoarthritis K/L score of 4.8 PAD patients with bilateral SFA stents were excluded because the stents interfered with plaque imaging. Other lower-extremity vascularizations were not exclusion criteria.

ABI Measurement

After participants rested supine for five minutes, a hand-held Doppler probe (Nicolet Vascular Pocket Dop II, Golden, CO) was used to measure systolic pressures in this order: right brachial, dorsalis pedis, and posterior tibial arteries and left dorsalis pedis, posterior tibial, and brachial arteries. Pressures were repeated in reverse order. The ABI was calculated in each leg by dividing average pressures in each leg by the average of the 4 brachial pressures.10 Average brachial pressures in the arm with highest pressure were used when one brachial pressure was higher than the opposite brachial pressure in both measurement sets, and the two brachial pressures differed by ≥10 mm Hg in at least one measurement set, since in such cases subclavian stenosis was possible.11 For the dorsalis pedis and posterior tibial vessels, zero values and values of incompressible arteries were excluded. Lowest leg ABI was used in analyses.

Leg Symptoms

We used the San Diego claudication questionnaire to classify participants into 1 of 5 leg symptom categories, based on prior studies:13 (1) intermittent claudication (exercise was not begin at rest, causes the participant to stop walking, and resolves within ten minutes of rest); (2) atypical exertional leg pain/carry on (exertional leg symptoms that do not begin at rest and do not stop the individual from walking); (3) atypical exertional leg pain/stop (exertional leg symptoms that do not begin at rest, stop the individual from walking, and do not involve the calves or resolve within 10 minutes of rest); (4) leg pain on exertion and rest (exertional leg pain that sometimes begins at rest); and (5) asymptomatic (no exertional leg symptoms).13

Magnetic Resonance Imaging

We imaged the SFA because it is the most common site of lower-extremity atherosclerosis14 and because it supplies calf muscle, which is typically symptomatic in PAD. The leg with the lowest ABI was imaged. However, if the leg with the lowest ABI had an SFA stent, the opposite leg was imaged. The MRI was performed using a 1.5-T (Siemens) platform with 4-element, phased-array surface coils. The proximal SFA was imaged because it is more amenable to high-quality images than the more deeply located distal SFA. Data were collected using a standard turbo spin-echo acquisition proton density weighted images (TR/TE = 2160 ms/8 ms; bandwidth, 230 Hz/pixel; turbo factor, 15). The field of view was 120 × 120 mm² and images were acquired in matrix 192, yielding an in-plane spatial resolution of 0.625 × 0.625 mm². Three signal averages were acquired. Regional signal saturation bands were played out superiorly and inferiorly to suppress signal from inflowing blood, ensuring dark-blood contrast. Chemically selective lipid saturation pulses eliminated signal from peri-adventitial fat. Twelve sequential 2.5-mm cross-sectional images were obtained, beginning at the bifurcation of the common femoral artery into the SFA and moving distally without gap using 2-dimensional bright blood time-of-flight and proton-density weighted images. Bright-blood 2D time of flight images (TR/TE = 31.0 ms/7.2 ms) were registered to the proton density images and acquired using an identical field of view, slice thickness, and imaging matrix. This method has excellent test retest reliability.15

Two physicians used CASCADE software (Seattle, WA) to trace the outer boundary of lumen of each cross-sectional image, to quantify plaque and lumen area. Measurement of plaque composition was not available in the version of CASCADE used for this study. The lumen was identified in time-of-flight images and was copied onto the proton density–weighted image, where the artery outer wall boundary was traced. Images for each participant were assigned to one primary physician reviewer. Tracings were assessed by the second physician reviewer to ensure accuracy. An example image is shown in Figure 1.

To adjust for the fact that a given plaque area will have a different effect on different-sized arteries, plaque measurements were normalized for artery size.56 Mean and maximum plaque area were normalized by dividing the average and maximum plaque area, respectively, by the median of the outer wall area. Mean and minimum percent lumen area were normalized by dividing the mean and minimum lumen area, respectively, by the outer wall area for each arterial slice.

Poor image quality was identified by the physician reviewers, who were blinded to all other participant characteristics. When poor image quality was identified, every attempt was made to have the participant return to the medical center for repeat imaging. In some cases, poor image quality was related to artifact from artificial joints, large body size, or inability of the participant to remain still during imaging. In some of these cases, even repeat imaging did not result
in a readable image. Each poor quality image was reviewed at least twice by the physician reviewers to confirm that the data were not usable.

Approximately 6% of participants returned on a second day for test retest reliability assessment of the MRI plaque measurement. The coefficient of variation percent values for these test retest reliability assessments were 5.8 for mean plaque area, 8.9 for maximum plaque area, 7.9 for mean percent lumen area, and 12.9 for minimum percent lumen area.

Comorbidities
Medical record review, participant questionnaires, and a primary care physician questionnaire were used to identify and confirm comorbidities using established methods. Hypertension was defined as participant report of physician-diagnosed high blood pressure or physician report of hypertension on the primary care physician questionnaire. Diabetes mellitus was defined as (1) use of a diabetes medication or (2) participant report of diabetes mellitus that was confirmed by the primary care questionnaire or medical record review.

Low-Density Lipoprotein Levels and High-Density Lipoprotein Levels
Low-density lipoprotein cholesterol (LDL-C) was determined by a homogenous direct method from Roche Diagnostics (Indianapolis, IN). High-density lipoprotein cholesterol (HDLC) was measured using a direct enzymatic colorimetric assay.

Other Measures
Height and weight were measured at the study visit. Body mass index (BMI) was calculated as weight kg/(height [m])². Seated systolic blood pressure was measured with an Omron automatic blood pressure machine after a 5-minute rest period, using an established protocol. Cigarette smoking history was measured with self-report. Participants brought their medication bottles or a medication list to their study visit. Medication names were recorded. The study principal investigator (M.M.M.) identified which participants were taking statin medications, blinded to all other participant characteristics.

Statistical Analyses
Based on previous study, the following ABI categories were defined in an a priori fashion: ABI <0.50; ABI 0.50 to 0.69; ABI 0.70 to 0.89; ABI 0.90 to 0.99; ABI 1.00 to 1.09; and ABI 1.10 to 1.30. Differences in continuous and dichotomous variables were compared across the ABI categories using analyses of variance and χ² tests, respectively. Mean plaque area, maximum plaque area, mean percent lumen area and minimum percent lumen area were compared across each ABI category and across each leg symptom category, adjusting for age, race, sex, smoking, BMI, statins, diabetes, hypertension, systolic blood pressure, LDL-C, and HDL-C. Analyses of leg symptoms additionally adjusted for the ABI. BMI, systolic blood pressure, LDL-C, and HDL-C were included as continuous variables because these characteristics were measured at the study visit. In each set of analyses, pairwise comparisons were performed between the highest ABI category and the remaining ABI categories. Analyses were repeated in the subset of participants with PAD. Among PAD participants, pairwise comparisons were performed between those with intermittent claudication and each remaining leg symptom category. Analyses of ABI and plaque measures were repeated among PAD participants with and without diabetes mellitus, respectively. A test for interaction was performed to determine whether associations of ABI with plaque measures differed between PAD participants with versus without diabetes mellitus.

Analyses were performed using SAS Statistical Software version 9.2 (SAS Inc, Cary, NC).

Results
We mailed recruitment letters to 3391 consecutive patients identified from recruitment sources with an established diagnosis of PAD. Of these, 1161 did not respond, 504 met 1 or more exclusion criteria, 954 were not interested, and 304 could not be scheduled or did not show for their study visit, leaving 468 participants with PAD. An additional 5 PAD participants were identified from among participants identified from the internal medicine practice who were screened with the ABI (total=473 PAD participants). We mailed recruitment letters to 558 consecutively identified patients ages 65 years and older in the internal medicine practice.
without history of diabetes, smoking, or established atherosclerosis. Of these, 283 did not respond to the recruitment letter, 62 met 1 or more exclusion criteria, 125 were not interested in participating, 41 could not be scheduled or did not show for their visit, and 5 had a low ABI consistent with PAD, leaving 42 participants without PAD. Of the 515 participants with and without PAD, 16 had poor-quality MRIs and 72 were missing covariate data used in our analyses, leaving 427 participants for the current analyses.

Table 1 shows characteristics of the cohort. Compared with participants with ABI 1.00 to 1.30, those with ABI <1.00 included higher proportions of men and participants with intermittent claudication and lower proportions of participants who were asymptomatic (Table 1).

Table 2 shows associations of baseline ABI values with participant characteristics. Lower ABI values were associated with higher prevalence of males, hypertension, and statin use (Table 2). Furthermore, participants with ABI values of <0.50, 0.50 to 0.69, 0.70 to 0.89, and 0.90 to 0.99, respectively, had significantly greater mean and maximum plaque area and smaller mean and minimum percent lumen area, compared with the reference group of participants with ABI values of 1.10 to 1.30 (Table 3).

In the subset of participants with ABI <1.00, lower ABI values remained associated with greater mean and maximum plaque area and smaller mean and minimum percent lumen area.

Table 2. Associations of Participant Characteristics With ABI Values

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>ABI &lt;0.50 (n=77)</th>
<th>ABI 0.50 to 0.69 (n=143)</th>
<th>ABI 0.70 to 0.89 (n=131)</th>
<th>ABI 0.90 to 0.99 (n=42)</th>
<th>ABI 1.00 to 1.09 (n=14)</th>
<th>ABI 1.10 to 1.30 (n=20)</th>
<th>P Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>70.7 (9.0)</td>
<td>70.8 (9.8)</td>
<td>67.7 (10.9)</td>
<td>67.9 (9.5)</td>
<td>74.14 (6.4)</td>
<td>70.6 (6.9)</td>
<td>0.390</td>
</tr>
<tr>
<td>ABI</td>
<td>0.41 (0.08)</td>
<td>0.61 (0.06)</td>
<td>0.79 (0.06)</td>
<td>0.94 (0.03)</td>
<td>1.05 (0.03)</td>
<td>1.16 (0.04)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male sex, %</td>
<td>67.5</td>
<td>77.6</td>
<td>66.4</td>
<td>52.4</td>
<td>28.6</td>
<td>35.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>African-American, %</td>
<td>33.8</td>
<td>30.8</td>
<td>26.0</td>
<td>31.0</td>
<td>21.4</td>
<td>15.0</td>
<td>0.090</td>
</tr>
<tr>
<td>Current smoker, %</td>
<td>23.4</td>
<td>21.7</td>
<td>23.7</td>
<td>28.6</td>
<td>0.00</td>
<td>0.00</td>
<td>NA</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>49.4</td>
<td>42.0</td>
<td>30.5</td>
<td>42.9</td>
<td>0.00</td>
<td>0.00</td>
<td>NA</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>97.4</td>
<td>90.9</td>
<td>86.3</td>
<td>88.1</td>
<td>78.6</td>
<td>65.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>51.2 (16.7)</td>
<td>48.5 (17.2)</td>
<td>50.4 (16.5)</td>
<td>49.5 (14.3)</td>
<td>67.1 (18.9)</td>
<td>67.1 (21.0)</td>
<td>0.001</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dL</td>
<td>93.9 (30.1)</td>
<td>83.7 (32.7)</td>
<td>94.9 (29.6)</td>
<td>103.1 (37.9)</td>
<td>110.1 (34.3)</td>
<td>123.2 (37.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Statin use, %</td>
<td>80.5</td>
<td>76.2</td>
<td>73.3</td>
<td>73.8</td>
<td>64.3</td>
<td>10.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prior lower-extremity revascularization, %</td>
<td>49.4</td>
<td>39.2</td>
<td>41.2</td>
<td>47.6</td>
<td>0.00</td>
<td>0.00</td>
<td>NA</td>
</tr>
<tr>
<td>Intermittent claudication, %</td>
<td>37.7</td>
<td>24.5</td>
<td>18.3</td>
<td>19.1</td>
<td>0.00</td>
<td>0.00</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Asymptomatic, %</td>
<td>9.1</td>
<td>19.6</td>
<td>22.9</td>
<td>28.6</td>
<td>71.4</td>
<td>65.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Leg pain/carry on, %</td>
<td>15.6</td>
<td>8.4</td>
<td>9.2</td>
<td>11.9</td>
<td>0.00</td>
<td>0.00</td>
<td>5.0</td>
</tr>
<tr>
<td>Atypical exertional leg pain, %</td>
<td>14.3</td>
<td>19.6</td>
<td>23.7</td>
<td>14.3</td>
<td>14.3</td>
<td>10.0</td>
<td>0.787</td>
</tr>
<tr>
<td>Pain on exertion and rest, %</td>
<td>23.4</td>
<td>28.0</td>
<td>26.0</td>
<td>26.2</td>
<td>14.3</td>
<td>20.0</td>
<td>0.571</td>
</tr>
<tr>
<td>Normalized mean plaque area:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 to 1 scale, 1=most plaque</td>
<td>0.79 (0.19)</td>
<td>0.72 (0.17)</td>
<td>0.65 (0.14)</td>
<td>0.61 (0.14)</td>
<td>0.51 (0.04)</td>
<td>0.48 (0.05)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Normalized maximum plaque area:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 to 1 scale, 1=most plaque</td>
<td>1.1 (0.55)</td>
<td>0.94 (0.30)</td>
<td>0.84 (0.26)</td>
<td>0.81 (0.30)</td>
<td>0.64 (0.09)</td>
<td>0.59 (0.07)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean % lumen area</td>
<td>0.24 (0.14)</td>
<td>0.30 (0.14)</td>
<td>0.36 (0.13)</td>
<td>0.42 (0.07)</td>
<td>0.50 (0.05)</td>
<td>0.52 (0.05)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Minimum percent lumen area</td>
<td>0.16 (0.13)</td>
<td>0.22 (0.13)</td>
<td>0.28 (0.13)</td>
<td>0.33 (0.10)</td>
<td>0.42 (0.06)</td>
<td>0.46 (0.06)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

N/A indicates not applicable.

Data shown are means and standard deviations.

Figure 2. Unadjusted mean plaque area across ABI categories (n=427). Mean plaque area has been normalized for artery size by dividing average wall area by the median outer wall area normalized for artery size.
Table 3. Adjusted Associations of the ABI With Plaque Characteristics in the Proximal Superficial Femoral Artery

<table>
<thead>
<tr>
<th>Plaque Characteristics</th>
<th>ABI &lt;0.50 (n=77)</th>
<th>ABI 0.50 to 0.69 (n=143)</th>
<th>ABI 0.70 to 0.99 (n=131)</th>
<th>ABI 0.90 to 0.99 (n=42)</th>
<th>ABI 1.00 to 1.09 (n=14)</th>
<th>ABI 1.10 to 1.30 (n=20)</th>
<th>P Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants with and without PAD (ABI &lt;1.30) (n=427)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean vessel plaque area</td>
<td>0.79 (0.02)*</td>
<td>0.73 (0.01)*</td>
<td>0.65 (0.01)*</td>
<td>0.62 (0.02)*</td>
<td>0.48 (0.04)</td>
<td>0.47 (0.04)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Maximal vessel plaque area</td>
<td>1.09 (0.04)*</td>
<td>0.95 (0.03)*</td>
<td>0.84 (0.03)†</td>
<td>0.81 (0.05)†</td>
<td>0.59 (0.09)</td>
<td>0.56 (0.08)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean % lumen area</td>
<td>0.25 (0.01)*</td>
<td>0.30 (0.01)*</td>
<td>0.36 (0.01)†</td>
<td>0.42 (0.02)†</td>
<td>0.51 (0.03)</td>
<td>0.53 (0.03)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Minimum % Lumen area</td>
<td>0.16 (0.01)*</td>
<td>0.21 (0.01)*</td>
<td>0.28 (0.01)*</td>
<td>0.32 (0.02)*</td>
<td>0.43 (0.03)</td>
<td>0.46 (0.03)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Participants with PAD (ABI &lt;1.00) (n=393)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean vessel plaque area</td>
<td>0.79 (0.02)*</td>
<td>0.73 (0.01)*</td>
<td>0.65 (0.01)</td>
<td>0.61 (0.03)</td>
<td>N/A</td>
<td>N/A</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Maximal vessel plaque area</td>
<td>1.08 (0.04)*</td>
<td>0.95 (0.03)§</td>
<td>0.83 (0.03)</td>
<td>0.81 (0.05)</td>
<td>N/A</td>
<td>N/A</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean % lumen area</td>
<td>0.25 (0.02)*</td>
<td>0.30 (0.01)†</td>
<td>0.36 (0.01)</td>
<td>0.42 (0.02)</td>
<td>N/A</td>
<td>N/A</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Minimum relative % lumen area</td>
<td>0.16 (0.01)*</td>
<td>0.22 (0.01)*</td>
<td>0.28 (0.01)</td>
<td>0.32 (0.02)</td>
<td>N/A</td>
<td>N/A</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

N/A indicates not applicable.

Data are adjusted for age, sex, race, hypertension, systolic blood pressure, diabetes mellitus, HDL cholesterol, LDL cholesterol, BMI, smoking, and statin use. Pairwise comparisons were performed between the highest ABI category and each lower ABI category: *P<0.001; †P<0.002; ‡P=0.01; §P=0.02; and |P=0.03.

Plaque area is normalized for total artery size (range, 0 to 1, 1=greatest plaque). Percent lumen area represents lumen area divided by total arterial wall area.

Discussion

Among 427 men and women with an ABI <1.30, lower ABI values were associated independently and significantly with greater mean and maximum normalized plaque area and smaller mean and minimum percent lumen area in the proximal superficial femoral artery, compared with higher ABI values. Findings were independent of potential confounders including age, sex, race, BMI, atherosclerotic disease risk factors, and statin use. These associations were maintained even when analyses were restricted to PAD participants only. PAD participants who were asymptomatic had smaller mean and maximum plaque area and greater mean and minimum percent lumen area as compared with PAD participants with intermittent claudication. PAD participants with atypical leg pain/carry on had smaller normalized maximum plaque area than PAD participants with intermittent claudication. Our results suggest that plaque measures visualized in a short segment of the proximal superficial femoral artery may be surrogate measures for total lower-extremity plaque burden as measured by the ABI.

A previous study of 87 PAD participants who underwent MRI of the superficial femoral artery demonstrated a correlation between the ABI and plaque area in the superficial femoral artery of −0.26. However, this correlation was not adjusted for confounders. In addition, this prior study did not assess associations of leg symptoms with MRI-measured atherosclerotic plaque.

The ABI, a ratio of Doppler-recorded systolic blood pressures in the lower and upper extremities, is an important prognostic indicator in people with and without PAD.
Lower ABI values are associated with greater functional impairment, increased cardiovascular event rates, increased all-cause mortality, and greater functional decline among men and women with and without PAD.21–24 Further study is needed to determine whether greater plaque area and smaller lumen area in the proximal superficial femoral artery, measured by MRI, are associated with increased cardiovascular event rates and greater functional decline in patients with PAD.

In certain settings, measuring atherosclerotic plaque directly with MRI has potential advantages over the ABI. For example, the ABI can be influenced by medial arterial calcinosis. Stiff lower-extremity arteries can increase the ABI measurement independent of presence or progression of lower-extremity atherosclerosis, resulting in insensitivity of the ABI to progression of lower-extremity atherosclerosis over time. Consistent with this phenomenon, previous study shows that the ABI does not readily change over time, even as functional performance deteriorates among individuals with PAD.25 In addition, the ABI may be influenced by collateral vessel flow. Thus, direct measurement of atherosclerotic plaque in the superficial femoral artery may better assess progression or regression of plaque than changes in the ABI over time. Further study is needed to determine whether MRI is more sensitive to progression of atherosclerotic plaque than changes in the ABI.

Our MRI techniques did not allow us to separate the arterial wall from atherosclerotic plaque when quantifying total plaque area or percent lumen area. Because of individual variation in artery size, our measures of plaque area and percent lumen area were normalized to total artery size. Our results show that in men and women with ABI values of 1.00 to 1.30, mean lumen area comprised 50% of total artery size. However, our images do not allow us to quantify atherosclerotic plaque separately from wall area.

Previous work from our group demonstrated that some asymptomatic patients with PAD have greater functional impairment and faster functional decline than PAD participants with intermittent claudication.26–27 However, results presented here indicate that asymptomatic PAD participants have less atherosclerotic plaque in the proximal SFA than PAD participants with intermittent claudication. Asymptomatic PAD participants may consist of a heterogeneous group of individuals, including individuals with mild PAD and those with more severe disease who have limited their walking speed or slowed their activity to avoid leg symptoms.26–27 Differences in study inclusion and exclusion criteria for the current cohort compared with our prior studies may have contributed to our finding that asymptomatic PAD participants had less atherosclerosis than those with intermittent claudication. Further study is needed to better characterize and define causes of asymptomatic PAD.

This study has limitations. First, data are cross-sectional. Further study is necessary to establish associations of changes in the ABI with changes in lower-extremity atherosclerotic disease burden. Second, MRI data were obtained on a relatively small segment of the proximal superficial femoral artery. Associations of the ABI with directly-measured plaque in other lower-extremity arteries are unknown. Third, data on plaque composition, such as lipid-rich necrotic core, were not available. Fourth, the relatively small number of participants without PAD may limit the representativeness of our findings regarding non-PAD participants.

In conclusion, MRI-measured plaque area and percent lumen area in the proximal superficial femoral artery are highly correlated with the ABI among men and women with PAD. PAD participants who were asymptomatic had smaller plaque area and greater percent lumen area compared with PAD participants with intermittent claudication. Prospective data are necessary to better identify the prognostic value and clinical significance of directly visualized plaque in the superficial femoral artery.

### Sources of Funding

This study was supported by the National Heart, Lung, and Blood Institute (R01-HL083064), the Intramural Research Program of the National Institute on Aging, and the Jesse Brown VA Medical Center.

### Disclosures

Dr Yuan receives research support from VP Diagnostics and from Philips Healthcare. Dr Kramer receives research support from Siemens Healthcare. Dr Xu is a technical consultant for VP Diagnostics and owner of Imaging Biomarker Solutions.

### References


### Table 4. Adjusted Associations of Leg Symptoms With Plaque Area and Lumen Area in Superficial Femoral Artery in Participants With Peripheral Arterial Disease

<table>
<thead>
<tr>
<th>Plaque Characteristics</th>
<th>Asymptomatic (n=77)</th>
<th>Atypical Exertional Leg Pain/Carry on (n=41)</th>
<th>Atypical Exertional Leg Pain and Rest (n=76)</th>
<th>Leg Pain on Exertion and Rest (n=103)</th>
<th>Intermittent Claudication (n=96)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normalized mean plaque area</td>
<td>0.65 (0.02)*</td>
<td>0.68 (0.02)</td>
<td>0.71 (0.02)</td>
<td>0.71 (0.02)</td>
<td>0.72 (0.02)</td>
<td>0.058</td>
</tr>
<tr>
<td>Normalized maximal plaque area</td>
<td>0.85 (0.04)†</td>
<td>0.84 (0.06)‡</td>
<td>0.94 (0.04)</td>
<td>0.95 (0.04)</td>
<td>0.97 (0.04)</td>
<td>0.121</td>
</tr>
<tr>
<td>Mean % lumen area</td>
<td>0.36 (0.02)§</td>
<td>0.33 (0.02)</td>
<td>0.33 (0.01)</td>
<td>0.32 (0.01)</td>
<td>0.30 (0.01)</td>
<td>0.134</td>
</tr>
<tr>
<td>Minimum % lumen area</td>
<td>0.27 (0.02)¶</td>
<td>0.26 (0.02)</td>
<td>0.23 (0.01)</td>
<td>0.23 (0.01)</td>
<td>0.22 (0.01)</td>
<td>0.091</td>
</tr>
</tbody>
</table>

Data are adjusted for age, sex, race, hypertension, systolic blood pressure, HDL cholesterol, LDL cholesterol, BMI, smoking, ABI, and statin use. The P value shown in the final column represents a test for homogeneity across all leg symptom categories. Pairwise comparisons were performed between participants with intermittent claudication (reference group) and each remaining leg symptom category: *P*=0.005; †P=0.03; ‡P=0.045; and §P=0.01.

**CLINICAL PERSPECTIVE**

Among 427 participants with and without lower-extremity peripheral arterial disease (PAD), we found that lower ankle-brachial index values were associated with greater atherosclerotic plaque and smaller lumen area in the proximal segment of the superficial femoral artery (SFA). Associations remained in the subset of participants with PAD and were independent of age, sex, race, and atherosclerotic disease risk factors. PAD participants who had no exertional leg symptoms (that is, were asymptomatic) had less atherosclerotic plaque and a larger lumen area in the proximal region of the SFA. These findings suggest that SFA plaque and lumen area in the initial segment of the SFA may be surrogates for atherosclerotic disease burden in the lower extremities as measured by the ankle-brachial index.
Superficial Femoral Artery Plaque, the Ankle-Brachial Index, and Leg Symptoms in Peripheral Arterial Disease: The Walking and Leg Circulation Study (WALCS) III
Mary M. McDermott, Kiang Liu, James Carr, Michael H. Criqui, Lu Tian, Debiao Li, Luigi Ferrucci, Jack M. Guralnik, Christopher M. Kramer, Chun Yuan, Melina Kibbe, William H. Pearce, Jarett Berry, Walter McCarthy, Yihua Liao, Dongxiang Xu, Jennifer Orozco and Timothy J. Carroll

Circ Cardiovasc Imaging. 2011;4:246-252; originally published online March 24, 2011; doi: 10.1161/CIRCIMAGING.110.962183
Circulation: Cardiovascular Imaging is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2011 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-9651. Online ISSN: 1942-0080

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circimaging.ahajournals.org/content/4/3/246

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation: Cardiovascular Imaging can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation: Cardiovascular Imaging is online at:
http://circimaging.ahajournals.org//subscriptions/