Peripheral Vascular Disease

**Novel Cardiovascular Risk Factors Do Not Completely Explain the Higher Prevalence of Peripheral Arterial Disease Among African Americans**

The San Diego Population Study

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**Objectives**

This study was designed to determine whether novel cardiovascular disease (CVD) risk factors explain the high prevalence of peripheral arterial disease (PAD) among African Americans.

**Background**

Compared with Caucasians, African Americans have higher prevalence of PAD, an association that is not explained by traditional CVD risk factors. The degree to which novel CVD risk markers may explain the higher prevalence is uncertain.

**Methods**

A nested case-control study within the San Diego Population Study was performed. The study evaluated 104 persons with PAD and 164 age- and gender-matched control subjects who were employees of a large public university and participated in a peripheral artery and venous disease study. Nine novel CVD risk factors (homocysteine, lipoprotein (a), C-reactive protein, fibrinogen, tumor necrosis factor-alpha, von Willebrand factor, prothrombin fragment 1-2, D-dimer, and plasmin antiplasmin) were measured. Multivariable logistic regression evaluated whether these novel factors attenuated the association of African-American race and PAD and whether there was differential ethnic susceptibility to the novel factors.

**Results**

African Americans had 3-fold higher odds of PAD in age- and gender-matched models (odds ratio [OR] 3.1; 95% confidence interval [CI] 1.5 to 6.4; \( p < 0.01 \)), an association that was modestly attenuated by adjustment for traditional (OR 2.4; 95% CI 0.9 to 6.1; \( p = 0.06 \)) and novel CVD risk markers (OR 1.9; 95% CI 0.7 to 4.7; \( p = 0.18 \)). Among the novel factors, the attenuation was primarily due to fibrinogen and lipoprotein (a). No interactions by novel CVD risk markers (both \( p \) values for interaction \( \geq 0.24 \)) were observed.

**Conclusions**

Traditional and novel CVD risk factors only partially explain the higher prevalence of PAD among African Americans. (J Am Coll Cardiol 2008;51:2347–54) © 2008 by the American College of Cardiology Foundation

Prior studies have consistently demonstrated higher prevalence of peripheral arterial disease (PAD) among African Americans compared to Caucasians (1–6). Although African Americans have a higher prevalence of traditional cardiovascular disease (CVD) risk markers such as diabetes and hypertension, the racial difference in PAD prevalence remains independent and is only modestly attenuated by adjustment for these traditional CVD risk markers (1).

Recently, several novel CVD risk markers have been identified (7), and these provide insight into distinct biologic pathways contributing to CVD. Compared with Caucasians, African Americans have been shown to have different concentrations of several of these risk markers in prior research (8,9). Whether or not higher or lower concentrations of these factors may explain the association of African-American race with PAD has not been extensively studied (8,10).

We hypothesized that the higher prevalence of PAD among African Americans would be at least partially accounted for by novel CVD risk markers. Therefore, we identified 9 serum risk markers that had been associated with PAD and that were reported to have different serum concentrations among African Americans compared with Caucasians.

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in prior literature: homocysteine, lipoprotein (a), C-reactive protein, fibrinogen, tumor necrosis factor-alpha, von Willebrand factor, prothrombin fragment 1-2, D-dimer, and plasmin antiplasmin. We measured these markers in the San Diego Population Study—an ethnically diverse study sample with detailed measurements of arterial disease—and we evaluate whether these novel CVD risk markers attenuated the association of African-American race with PAD.

### Laboratory measurements

At the study visit, venous samples were drawn, and homocysteine was measured by a fluorescence polarization immunoassay (IMx Homocysteine Assay, Axis Biochemicals, Oslo, Norway) using the IMx Analyzer (Abbott Diagnostics, Abbott Park, Illinois). The intra- and interassay coefficients of variation (CVs) were <5%. Lipoprotein (a) was measured using an enzyme-linked immunosorbent assay (ELISA) developed at the University of Vermont and described elsewhere (13). The CVs were <8%. High-sensitivity C-reactive protein was measured using a particle-enhanced immunoturbidimetric assay on a BN-II analyzer (Dade-Behring Inc., Deerfield, Illinois) with CVs <4%. Fibrinogen was measured in an automated clot rate assay based upon the Clauss method (14) using the STA-R instrument (Diagnostica Stago, Asnières sur Seine) with CVs <4%. Tumor necrosis factor-alpha assays also employed a Quantikine ELISA assay (R & D Systems, Minneapolis, Minnesota) with an intra-assay CV of 5.9% and interassay CV of 12.6%. The von Willebrand factor was measured with an immunoturbidimetric assay (Liatest vWF, Stago) on the STA-R analyzer (Stago), whereby latex particles agglutinate in the presence of the von Willebrand factor and increase light absorbance in proportion to its concentration. The CVs were <5%. Prothrombin fragment 1-2 was measured using ELISA (Dade-Behring), and the CVs were <12% (15). The D-dimer measurement also used the Stago immunoturbidimetric assay with CVs <5%. Lastly, the plasminogen-antiplasmin measurement was performed using a 2-site ELISA that detects only complex, and not free, plasmin or antiplasmin (16). The CVs were <4%.

### Methods

#### Subjects

Current and retired employees of the University of California, San Diego and their spouses or significant others were invited to participate in a study focused on both peripheral arterial and venous disease. Methods of recruitment and response rates have previously been reported (11). Briefly, random selection was made within strata defined by age, gender, and race/ethnicity. Women and race/ethnic minority groups were oversampled to enhance power for contrasts between groups. The total sample size was 2,414 subjects and all provided written informed consent after a detailed study description. The study was approved by the Committee on Investigations Involving Human Subjects at University of California, San Diego.

The present study was a nested case-control study. All participants underwent a detailed vascular examination that included ankle-brachial index (ABI) measurement (described in the following sections). From this, we identified 104 persons with PAD. We selected 164 participants without PAD as control subjects, who were frequency matched to cases on the basis of age and gender.

#### Demographic and clinical measurements

At the study visit, participants were interviewed by trained study personnel for demographic and medical history information, including age, gender, race/ethnicity, education, occupation, past personal and family medical history, and medication use. History of CVD was defined as past history of myocardial infarction, percutaneous transluminal coronary angioplasty, coronary artery bypass graft surgery, stroke, or transient ischemic attack. Diabetes was defined by medical history. Current and past smoking history was ascertained, and pack-years were calculated. Hypertension was defined as a systolic blood pressure (SBP) ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or use of antihypertensive medications. Hyperlipidemia was defined by a total/high-density lipoprotein cholesterol ratio ≥6.4 in men and ≥5.6 in women (a threshold previously demonstrated to provide optimal risk prediction for CVD events) (12) or use of lipid-lowering medications.

#### PAD measurement

Subjects underwent a detailed vascular examination at the study visit. Briefly, with the subjects lying supine and using a continuous-wave Doppler, SBP was measured in both brachial arteries, and twice in both posterior tibial arteries. When a signal could not be found at the posterior tibial artery, the dorsalis pedis artery was insonated in the same manner. The ABI for each leg was calculated as the average SBP in the posterior tibial (or dorsalis pedis) artery divided by the higher of the 2 arm SBPs. A PAD was defined as an ABI <0.90, an abnormal Doppler waveform (no negative component and broadened), or previous history of revascularization for PAD.

#### Statistical analysis

We evaluated differences in demographic and clinical data among cases and control subjects by the t test for continuous variables (or Mann-Whitney rank sum test for variables with skewed distributions) and chi-square tests (or Fisher exact test equivalent) for categorical variables. Similarly, we evaluated differences in serum concentrations of the 9 novel risk markers across racial groups. After log-transformation of skewed variables, a Pearson correlation matrix determined that none of the 9 novel factors were highly correlated with one another (highest $r = 0.20$), thereby allowing multiple adjustment without significant colinearity.
Maximum likelihood logistic regression analysis evaluated the associations of race and PAD in 4 separate models. Model 1 was age and gender matched. Model 2 adjusted for important demographics (education and occupation) and traditional cardiovascular risk factors identified, in a prior manuscript (1), as correlates of PAD in this cohort (age, gender, race/ethnicity, diabetes, hypertension, hyperlipidemia, prevalent CVD history, and tobacco use). In exploratory analyses, we observed an inverse association of body mass index (BMI) with PAD, consistent with prior studies (1,3,17–21), but observed a direct association of waist/hip ratio (WHR) with PAD. Recent large observational studies (22,23) have demonstrated that WHR is more strongly associated with future CVD events than BMI. Therefore, we elected to adjust for WHR rather than BMI within Model 2. In Model 3, we selected covariates from the 9 novel biomarkers if they were associated with both African-American race and PAD. Because relatively weak associations may contribute substantial confounding effects (24), any variable associated with both African-American race and PAD with a p value ≤0.25 was included in this model, in addition to variables that were included in Model 2. Skewed variables were log-transformed, and results are presented as 1 standard deviation increase in each, to allow comparison of strength of association across novel risk markers. Lastly, to develop a most parsimonious model, Model 4 excluded all covariates where the p value for association with PAD was >0.25 in Model 3. For each novel marker retained in Model 4, multiplicative interaction terms were created (marker × race/ethnicity) and individually added to Model 4. These interaction terms allowed exploration of the possibility of differential ethnic susceptibility to risk markers. The area under the receiver operator curve were calculated for each model and compared to the preceding model by determination of the c-statistic. Models were also evaluated for goodness of fit by the Hosmer-Lemeshow statistic, and graphical methods evaluated the assumptions of linear relationships between continuous predictors and log-odds of PAD. No violations were observed. Lastly, we compared the percent attenuation in the odds of PAD among African Americans compared to Caucasians after adjustment for traditional and novel CVD risk factors observed in our manuscript to those reported previously. Because the baseline odds ratio would be 1.0 if the association was completely attenuated, we subtracted 1.0 from the odds ratio both before and after adjustment, determined their ratio, and subtracted this ratio from 1. Two-tailed p < 0.05 was considered statistically significant. Analyses were performed using STATA version 9.2 (Stata Corp., College Station, Texas).

Results

The 268-person study sample had a mean age of 69 years and was 53% female. Seventy percent were Caucasian, 15% were African American, 9% were Hispanic, and 6% were Asian. African Americans had less frequently attained a college education; were less likely to have an administrative, technical, or professional occupation; and more frequently had diabetes, hypertension, and larger BMI, as demonstrated previously (1). We observed 104 cases of PAD (4.4% of the parent study sample). In persons with PAD, the average ABI was 0.78 in men and 0.82 in women. Seven subjects (7%) were categorized as PAD cases on the basis of history of prior revascularization. Age and gender were balanced across PAD groups, reflecting the matched study design (Table 1). Persons with PAD were more frequently African American and less likely to have graduated from college or to have worked in a technical, administrative, or professional position. In addition, PAD cases had higher prevalence of diabetes, hypertension, hyperlipidemia, prevalent CVD, cumulative pack-years of tobacco use, and had higher WHR. The PAD cases also had significantly higher homocysteine, lipoprotein (a), fibrinogen, von Willebrand factor, D-dimer, and plasmin antiplasmin levels; whereas C-reactive protein, tumor necrosis factor-alpha, and prothrombin fragment 1-2 did not differ significantly across PAD groups.

Table 2 shows the concentrations of the 9 novel CVD risk markers by African-American or Caucasian race. African Americans had higher lipoprotein (a), fibrinogen, von Willebrand factor, and D-dimer concentrations in age- and gender-adjusted models. Median C-reactive protein concentrations were higher and prothrombin fragment 1-2 were lower in African Americans; these associations were of borderline statistical significance (p = 0.12 and 0.13, respectively).

In univariate analysis, African Americans had greater than 3-fold odds of PAD compared with Caucasians (Table 3). Adjustment for traditional CVD risk markers attenuated the association by 33% but African Americans remained at 2.4-fold higher odds of PAD (Model 2 in Table 3). In the next model (Model 3), we included novel risk markers if they were at least weakly associated (p ≤ 0.25) with both African American race and PAD in univariate analysis (lipoprotein (a), C-reactive protein, fibrinogen, von Willebrand factor, and D-dimer). With their inclusion, the odds of PAD among African Americans was attenuated an additional 36%. Thus, traditional and novel CVD risk factors collectively attenuated the association by 57%, but African Americans remained at approximately 2-fold higher odds of PAD compared to Caucasians (Model 3 in Table 3). Last, we developed a parsimonious model that retained only those variables that were at least modestly associated with PAD (p ≤ 0.25) within Model 3. Among the novel CVD risk markers, only lipoprotein (a), C-reactive protein, and fibrinogen were retained by this inclusion criterion. In this model, African Americans remained at nearly 2-fold odds of PAD compared to Caucasians (Model 4 in Table 3). We observed no evidence of effect modification by any of the 3 novel risk factors (all p values for interaction ≥0.24), and
thus no evidence of greater African-American susceptibility to these novel markers.

**Discussion**

Prior studies have consistently demonstrated a 3-fold higher prevalence of PAD among African Americans compared with Caucasians (1,3,4,8). Even though PAD is strongly associated with traditional CVD risk markers (3,25), we previously reported that these factors do not account for the higher prevalence of PAD (1). African Americans have different blood levels of several novel markers; therefore, we hypothesized that these factors may account for the higher prevalence of PAD (1,2). The present study demonstrates that the association of African-American race with PAD was only partially attenuated by the 9 novel markers studied and that lipoprotein (a) and fibrinogen were the 2 factors

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**Table 1** Baseline Characteristics by PAD Status

<table>
<thead>
<tr>
<th>Demographics</th>
<th>PAD (n = 104)</th>
<th>No PAD (n = 164)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs), ± SD</td>
<td>69 ± 10</td>
<td>68 ± 9</td>
<td>0.37</td>
</tr>
<tr>
<td>Female (%)</td>
<td>55 (53)</td>
<td>87 (53)</td>
<td>0.98</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian (%)</td>
<td>69 (66)</td>
<td>120 (73)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>African American (%)</td>
<td>25 (24)</td>
<td>14 (9)</td>
<td></td>
</tr>
<tr>
<td>Hispanic (%)</td>
<td>6 (6)</td>
<td>18 (11)</td>
<td></td>
</tr>
<tr>
<td>Asian American (%)</td>
<td>4 (4)</td>
<td>12 (7)</td>
<td></td>
</tr>
<tr>
<td>College education</td>
<td>38 (37)</td>
<td>97 (59)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Technical, administrative, or professional occupation</td>
<td>59 (57)</td>
<td>119 (78)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Medical history</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>26 (25)</td>
<td>7 (4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>82 (79)</td>
<td>98 (60)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Hyperlipidemia (%)</td>
<td>35 (35)</td>
<td>33 (21)</td>
<td>0.01</td>
</tr>
<tr>
<td>Cardiovascular disease (%)</td>
<td>33 (32)</td>
<td>10 (6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pack-yrs of tobacco*</td>
<td>10 (0, 44)</td>
<td>0 (0, 15)</td>
<td></td>
</tr>
<tr>
<td>Measurements</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ankle-brachial index, ± SD</td>
<td>0.78 ± 0.24</td>
<td>1.10 ± 0.09</td>
<td>—</td>
</tr>
<tr>
<td>Waist/hip ratio, ± SD</td>
<td>0.91 ± 0.09</td>
<td>0.88 ± 0.08</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Novel cardiovascular risk factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Homocysteine (μmol/l), ± SD</td>
<td>12.4 ± 4.9</td>
<td>11.0 ± 3.5</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Lipoprotein (a) (g/l)*</td>
<td>0.2 (0.1, 0.4)</td>
<td>0.1 (0.1, 0.3)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>C-reactive protein (mg/l)*</td>
<td>1.9 (0.9, 4.8)</td>
<td>1.6 (0.8, 3.5)</td>
<td>0.22</td>
</tr>
<tr>
<td>Fibrinogen (mg/dl), ± SD</td>
<td>349 ± 88</td>
<td>332 ± 62</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tumor necrosis factor-alpha (pg/ml), ± SD</td>
<td>2.3 ± 1.2</td>
<td>2.2 ± 1.0</td>
<td>0.55</td>
</tr>
<tr>
<td>von Willebrand factor (%), ± SD</td>
<td>155 ± 58</td>
<td>135 ± 55</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Prothrombin fragment 1-2 (nmol/l)*</td>
<td>2.7 (2.0, 4.1)</td>
<td>2.6 (1.9, 4.1)</td>
<td>0.99</td>
</tr>
<tr>
<td>D-dimer (mg/l)*</td>
<td>0.35 (0.22, 0.65)</td>
<td>0.26 (0.16, 0.47)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Plasmin-antiplasmin (nmol/l), ± SD</td>
<td>8.8 ± 4.8</td>
<td>6.9 ± 3.8</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

*Median (interquartile range) evaluated by the Mann-Whitney rank sum test. PAD = peripheral arterial disease.

**Table 2** Novel Cardiovascular Risk Factor Concentrations by Race

<table>
<thead>
<tr>
<th>Homocysteine (μmol/l), ± SD</th>
<th>African American (n = 39)</th>
<th>Caucasian (n = 189)</th>
<th>p Value</th>
<th>Age and Gender Adjusted p Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipoprotein (a) (g/l)†</td>
<td>0.3 (0.1, 0.7)</td>
<td>0.1 (0.1, 0.3)</td>
<td>&lt;0.001</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>C-reactive protein (mg/l)†</td>
<td>3.1 (1.1, 7.8)</td>
<td>1.6 (0.9, 3.9)</td>
<td>0.07</td>
<td>0.12</td>
</tr>
<tr>
<td>Fibrinogen (mg/dl), ± SD</td>
<td>370 ± 98</td>
<td>345 ± 70</td>
<td>0.15</td>
<td>0.03</td>
</tr>
<tr>
<td>Tumor necrosis factor-alpha (pg/ml), ± SD</td>
<td>2.4 ± 1.4</td>
<td>2.2 ± 1.0</td>
<td>0.53</td>
<td>0.36</td>
</tr>
<tr>
<td>von Willebrand factor (%), ± SD</td>
<td>160 ± 61</td>
<td>143 ± 56</td>
<td>0.13</td>
<td>0.03</td>
</tr>
<tr>
<td>Prothrombin fragment 1-2 (nmol/l)†</td>
<td>2.1 (1.7, 3.1)</td>
<td>2.7 (2.0, 4.2)</td>
<td>0.02</td>
<td>0.13</td>
</tr>
<tr>
<td>D-dimer (mg/l)†</td>
<td>0.40 (0.21, 0.72)</td>
<td>0.28 (0.18, 0.47)</td>
<td>0.05</td>
<td>0.01</td>
</tr>
<tr>
<td>Plasmin-antiplasmin (nmol/l), ± SD</td>
<td>7.9 ± 4.8</td>
<td>7.7 ± 4.2</td>
<td>0.86</td>
<td>0.43</td>
</tr>
</tbody>
</table>

*Median (interquartile range) evaluated by the Mann-Whitney rank sum test. †Evaluated by linear regression. Skewed variables (lipoprotein (a), C-reactive protein, prothrombin fragment 1-2, and D-dimer) were log-transformed.
that accounted for the attenuating effects. Collectively, adjustment for traditional and novel CVD risk markers attenuated the association by 57%. However, despite the attenuation, African Americans remained at nearly 2-fold higher odds of PAD. There was no evidence for differential ethnic susceptibility to the novel risk markers. Therefore, traditional and novel CVD risk markers only partially account for the higher prevalence of PAD among African Americans, and the residual association remains unexplained.

To the best of our knowledge, only 2 prior studies have evaluated the contribution of novel CVD risk markers to the association of African-American race with PAD. In the MESA (Multi-Ethnic Study of Atherosclerosis), Allison et al. (8) evaluated 9 novel CVD risk markers (homocysteine, C-reactive protein, interleukin-6, D-dimer, fibrinogen, plasmin antiplasmin, factor VIII, von Willebrand factor, and Chlamydia pneumoniae titer). Among these, interleukin-6 and fibrinogen were most strongly associated with PAD in multivariable models. The novel factors

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Reference</th>
<th>Reference</th>
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<th>Reference</th>
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<tbody>
<tr>
<td>Race/ethnicity</td>
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</tr>
<tr>
<td>Caucasian</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>3.1 (1.5–6.4)</td>
<td>2.4 (0.9–6.1)</td>
<td>1.9 (0.7–5.1)</td>
<td>1.9 (0.7–4.7)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>0.6 (0.2–1.5)</td>
<td>0.4 (0.1–1.4)</td>
<td>0.5 (0.1–1.8)</td>
<td>0.6 (0.2–2.0)</td>
</tr>
<tr>
<td>Asian American</td>
<td>0.6 (0.2–1.9)</td>
<td>1.4 (0.3–5.6)</td>
<td>1.2 (0.2–6.1)</td>
<td>1.3 (0.2–6.5)</td>
</tr>
</tbody>
</table>

**Medical history**

- Diabetes: 5.9 (1.9–18.5) <0.01 3.7 (1.2–12.0) 3.6 (1.3–10.1) 0.02
- Hypertension: 2.1 (1.0–4.3) 2.1 (0.9–4.3) 1.8 (0.9–3.8) 0.04 0.06 0.10
- Hyperlipidemia: 1.6 (0.7–3.3) 1.4 (0.6–3.2) 0.23 0.37
- Cardiovascular disease: 4.9 (2.0–11.9) 4.2 (1.6–11.0) 5.4 (2.2–12.9) 0.01 <0.01 <0.01
- Pack-yrs tobacco (per 10 yrs): 1.2 (1.1–1.4) 1.2 (1.0–1.4) 1.1 (1.0–1.3) <0.01 0.02 0.04
- Waist/hip ratio: 0.6 (0.0–24.6) 1.2 (0.0–62.7) 0.80 0.93

**Novel cardiovascular risk factors**

- Log-lipoprotein (a): 1.4 (1.0–2.0) 1.4 (1.0–2.0) 0.06 0.06
- Log-C-reactive protein: 0.8 (0.5–1.2) 0.8 (0.5–1.1) 0.25 0.17 <0.01
- Fibrinogen: 1.5 (1.0–2.4) 1.7 (1.1–2.5) 0.04 0.01
- von Willebrand factor: 0.97 (0.7–1.4) 0.97 (0.7–1.4) 0.86 0.35
- Log-D-dimer: 1.2 (0.8–1.7) 0.80, 0.34#

**Model diagnostics**

- Area under ROC curve, c-statistic: 0.59 0.79, <0.001# 0.81, 0.12# 0.80, 0.34#
- Hosmer-Lemeshow p value: 1.00 0.62 0.35 0.36

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*Confidence interval; OR = odds ratio; PAD = peripheral arterial disease; ROC = receiver-operator characteristic.*
provided only a modest attenuation in the odds of PAD among African Americans (odds ratio decreased from 1.7 to 1.5) (8). The investigators suggested that future studies should evaluate lipoprotein (a) (8). Indeed, lipoprotein (a) levels are consistently 2-fold higher among African Americans (26,27), and have been associated with low ABI (28,29), symptomatic PAD (30), PAD severity (31), and progression (32). Moreover, lipoprotein (a) is potentially modifiable (33,34).

Khawaja et al. (10) evaluated lipoprotein (a), fibrinogen, C-reactive protein, and homocysteine in the GENOA (Genetic Epidemiology Network of Arteriopathy) study. After adjustment for traditional CVD risk markers and these 4 novel measures, the investigators also observed a modest attenuation in the odds of PAD among African Americans (odds ratio 3.0 to 2.1). However, African-American race remained strongly associated with PAD (10). Because only these 4 novel measures were available, it was possible that the remaining association was due to other unmeasured risk markers.

The present manuscript confirms the findings in these 2 prior studies and highlights the consistency among them. Although the 3 study samples differ in regards to age, geography, prevalence of CVD and traditional CVD risk markers, each demonstrated that African-American race is strongly associated with PAD. Moreover, the studies are strikingly consistent in the magnitude of attenuation in the point estimates when adjusting for traditional and novel CVD risk markers, collectively resulting in 50% to 60% attenuation across the respective studies (Table 4). In each of these studies, African Americans had roughly 2-fold higher odds of PAD, despite extensive statistical adjustment for both traditional and novel markers. Collectively, the studies provide consistent evidence that traditional and novel CVD risk markers do not completely explain the higher prevalence of PAD among African Americans.

Why might African Americans have a higher prevalence of PAD? The association may reflect social differences or health care access disparities that are known to be important risk factors for future CVD events (35). Study inclusion criteria required that participants (or their significant others) were current and former employees of a large public university, and therefore, all had healthcare coverage. We have previously shown (1) that drug treatment of hyperlipidemia was similar among African Americans and Caucasians in this study cohort and that drug treatment of hypertension was appropriately more common in African Americans. Moreover, the association observed in this study remained, despite adjustment for education and occupation. Nonetheless, it remains plausible that unmeasured sociodemographic variables such as diet, physical activity, income, and social stress may account for these differences. Alternatively, African Americans may have greater genetic susceptibility to PAD (36). Recent advances in microarray technology and genetic epidemiology hold promise for evaluating this important hypothesis, although such studies may be particularly challenging among African Americans due to their higher degree of genetic diversity (37). Lastly, the spectrum of vascular disease is different among African Americans compared with Caucasians. African Americans have lower prevalence of coronary artery calcification (38,39)—a highly sensitive marker for flow-limiting coronary atherosclerotic disease (40)—and yet have higher prevalence of PAD. Whether racial differences exist in mechanisms leading to vascular disease or in genes that modify proteins in the causal pathway should be evaluated in future studies. Because the vascular disease patterns are different in these racial groups, such studies may ultimately provide novel insights about vascular disease biology globally and might also lead to race-specific screening modalities or therapies tailored for maximum benefit within groups (41).

Although the results demonstrated here are in part confirmatory of prior studies, the present study has several advantages. First, it evaluated the largest number of novel risk markers while simultaneously including lipoprotein (a). Because lipoprotein (a) levels differ substantially among African Americans and Caucasians, they are strongly associated with PAD, and are potentially modifiable, they represented a particularly important candidate marker. Indeed, lipoprotein (a) was 1 of only 3 novel risk factors that remained associated with PAD risk in multivariable models in our study. Second, our definition of PAD included subjects with prior revascularization, where other studies limited the definition to ABI measurement in isolation. Because roughly 5% of prevalent PAD cases in the population are persons with prior revascularization who may have normal ABIs (42), their inclusion minimizes misclassification bias. Lastly, the existence of 2 prior studies allowed us to compare the strength of association and attenuating effects of traditional and novel cardiovascular risk factors across studies.

### Table 4

<table>
<thead>
<tr>
<th>Race, PAD, Novel Risk Factors</th>
<th>Allison et al. (8)</th>
<th>Khawaja et al. (10)*</th>
<th>Present Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age- and gender-adjusted</td>
<td>2.3</td>
<td>3.1</td>
<td>3.1</td>
</tr>
<tr>
<td>Traditional cardiovascular risk factor adjusted</td>
<td>1.7 46%</td>
<td>2.9 10%</td>
<td>2.4 33%</td>
</tr>
<tr>
<td>Traditional and novel risk factor adjusted</td>
<td>1.5 62%</td>
<td>2.0 52%</td>
<td>1.9 57%</td>
</tr>
</tbody>
</table>

*Reflects weighted average of gender-specific odds ratios (ORs).
Study limitations. This study included relatively small numbers of Hispanics or Asian Americans. However, the differences in PAD prevalence in these race/ethnic groups compared to African Americans appear less pronounced (8). Although the relatively small sample size of this study allowed us to efficiently evaluate a large number of novel CVD risk markers simultaneously, it limited statistical power resulting in nonstatistically significant associations in adjusted models. The precision of these estimates and the margins of error should be considered when interpreting the results. Fortunately, the point estimates and degree of attenuation is highly consistent with prior studies as demonstrated in Table 4. In addition, although this study included a large number of novel CVD risk markers simultaneously, we cannot exclude confounding on the basis of other unmeasured markers, imperfect ascertainment, or measurement at 1 point in time.

Conclusions

The dramatically higher prevalence of PAD among African Americans is not completely explained by higher prevalence of traditional CVD risk markers, by differences in 9 novel CVD risk markers evaluated in this study, or by increased ethnic susceptibility to these risk markers. This finding is consistent across studies. The etiology for the high prevalence of PAD among African Americans remains unexplained for now. Future studies should evaluate differences in lifestyle factors and genetic determinants as possible etiologies.

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REFERENCES

29. Tseng CH. Lipoprotein(a) is an independent risk factor for peripheral arterial disease in Chinese type 2 diabetic patients in Taiwan. Diabetes Care 2004;27:517–21.
34. Shlipak MG, Simon JA, Vittinghoff E, et al. Estrogen and progestin, lipoprotein(a), and the risk of recurrent coronary heart disease events after menopause. JAMA 2000;283:1845–52.