Clinical Investigation and Reports

Ankle-Arm Index as a Marker of Atherosclerosis in the Cardiovascular Health Study

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Background. **Peripheral arterial disease measured noninvasively by the ankle-arm index (AAI) is common in older adults, largely asymptomatic, and associated with clinically manifest cardiovascular disease (CVD). The criteria for an abnormal AAI have varied in previous studies. To determine whether there is an inverse dose-response relation between the AAI and clinical CVD, subclinical disease, and risk factors, we examined the relation of the AAI to cardiovascular risk factors, other noninvasive measures of subclinical atherosclerosis using carotid ultrasound, echocardiography and electrocardiography, and clinical CVD.**

Methods and Results. **The AAI was measured in 5084 participants ≥65 years old at the baseline examination of the Cardiovascular Health Study. All subjects had detailed assessment of prevalent CVD, measures of cardiovascular risk factors, and noninvasive measures of disease. Participants were stratified by baseline clinical CVD status and AAI (<0.8, ≥0.8 to <0.9, ≥0.9 to <1.0, ≥1.0 to <1.5). Analyses tested for a dose-response relation of the AAI with clinical CVD, risk factors, and subclinical disease. The cumulative frequency of a low AAI was 7.4% of participants <0.8, 12.4% <0.9, and 23.6% <1.0. Participants with an AAI <0.8 were more than twice as likely as those with an AAI of 1.0 to 1.5 to have a history of myocardial infarction, angina, congestive heart failure, stroke, or transient ischemic attack (all $P<.01$). In participants free of clinical CVD at baseline, the AAI was inversely related to history of hypertension, history of diabetes, and smoking, as well as systolic blood pressure, serum creatinine, fasting glucose, fasting insulin, measures of pulmonary function, and fibrinogen level (all $P<.01$). Risk factor associations with the AAI were similar in men and women free of CVD except for serum total and low-density lipoprotein cholesterol, which were inversely associated with AAI level only in women. Risk factors associated with an AAI of <1.0 in multivariate analysis included smoking (odds ratio [OR], 2.55), history of diabetes (OR, 3.84), increasing age (OR, 1.54), and nonwhite race (OR, 2.36). In the 3372 participants free of clinical CVD, other noninvasive measures of subclinical CVD, including carotid stenosis by duplex scanning, segmental wall motion abnormalities by echocardiogram, and major ECG abnormalities were inversely related to the AAI (all $P<.01$).**

Conclusions. **There was an inverse dose-response relation of the AAI with CVD risk factors and subclinical and clinical CVD among older adults. The lower the AAI, the greater the increase in CVD risk; however, even those with modest, asymptomatic reductions in the AAI (0.8 to 1.0) appear to be at increased risk of CVD. (*Circulation.* 1993;88:837-845.)**

KEY WORDS • peripheral vasculature • epidemiology • aging • tests

Older adults are known to be at high risk for atherosclerotic peripheral arterial disease (PAD) of the legs, yet few data are available regarding large numbers of adults ≥65 years of age. In previous population studies, PAD has been associated with older age, male sex, smoking, diabetes, hypertension, and hypercholesterolemia.[1-12] The presence and severity of atherosclerosis in the lower extremities is also highly correlated to disease in other vascular beds.[13,14] There is a particularly strong association between disease in the carotid arteries and the lower extremities.[15] The presence of PAD, whether measured by a history of intermittent claudication[2,16] or noninvasive testing using the ankle-arm index (AAI),[17,18] has also been shown to predict cardiovascular and overall mortality.

These studies suggest that the AAI, a noninvasive measurement of PAD, is a marker for generalized atherosclerotic disease. However, previous studies have used different cutoff points to define an "abnormal" AAI.[5,12] Angiographic studies show that adults without PAD have AAIs >1.0. Whether there is a graded inverse relation between the AAI and measures of

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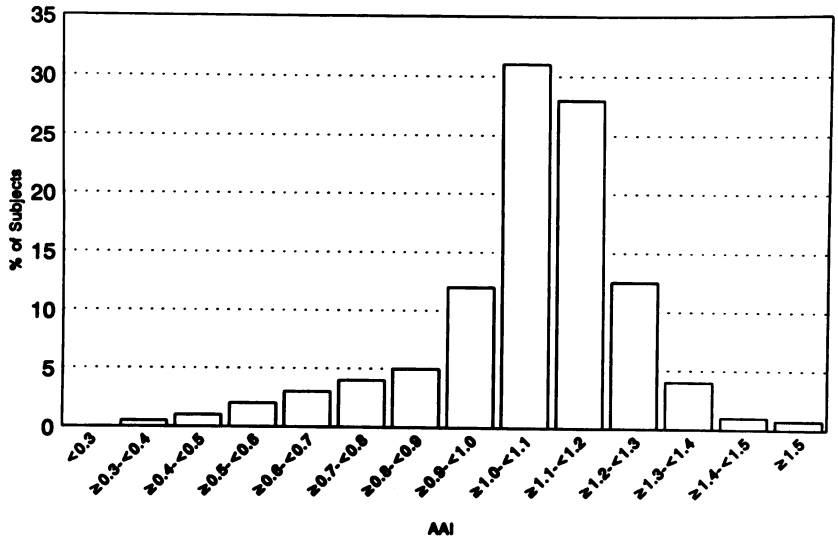

FIG 1. *Bar graph showing frequency distribution of the ankle-arm index (AAI) in the Cardiovascular Health Study population.*

clinical and subclinical atherosclerosis and its risk factors is unknown. To determine this, we examined the relation between the AAI and cardiovascular disease in a community-based group of older adults. The Cardiovascular Health Study is a population-based, observational study of heart disease and stroke in 5201 adults ≥65 years old, specifically designed to evaluate risk factors and noninvasive measures and to describe and predict atherosclerotic events in older adults.

Methods

Between June 1989 and May 1990, 5201 individuals ≥65 years old were recruited from a stratified random sample of Medicare recipients from four US communities: Washington County, Maryland; Pittsburgh (Allegheny County), Pennsylvania; Forsyth County, North Carolina; and Sacramento County, California. The sampling method and study design are fully described in an earlier publication.[19] Data on lower-extremity arterial disease were obtained on 5084 participants who form the population for this analysis. There were 2214 men (44%) and 2870 women (56%), with 1803 (35%) 65 to 69 years old, 1580 (31%) 70 to 74 years old, 1035 (20%) 75 to 79 years old, 482 (10%) 80 to 84 years old, and 184 (4%) ≥85 years old. Those who enrolled were somewhat healthier and better educated than the general population. All completed a medical history questionnaire, the Rose questionnaire for intermittent claudication,[20] and underwent lower-extremity noninvasive testing limited to duplicate resting measurements of the AAI in both legs. The AAI is the ratio of the ankle systolic blood pressure to the arm systolic blood pressure and is usually >1.0 in normal adults.[21-24] Participants were categorized with respect to disease on the basis of the lower of the left or right AAI.

The AAI was measured according to a standard protocol by trained technicians. All observers were first trained and certified in standard research sphygmomanometry with a regular stethoscope. This was followed by training in the measurement of the systolic blood pressure with a Doppler stethoscope (8 MHz, Huntleigh Tech, Inc). Trainees were certified after completing all steps of the protocol under observation, including obtaining Doppler pressures within 2 mm Hg on repeated measures, observed via a double-headed stethoscope. A standard mercury manometer was used. Standard arm blood pressure cuffs were used on the lower extremities, just above the malleoli, and a cuff of appropriate size on the right arm. The systolic blood pressures in the right arm and both legs were measured in rapid succession and repeated immediately with the subject lying flat on an exam table after at least 5 minutes of rest. The cuff was inflated rapidly to 20 mm Hg above the palpated systolic pressure and deflated at 2 mm Hg/s. The first reappearance sound was recorded as the systolic pressure. The ratio or index was calculated as the ratio of the average of two blood pressure measurements in each extremity. The correlations for each duplicate blood pressure were left leg, 0.97; right leg, 0.97; and right arm, 0.95.

Because of a protocol deviation, ankle blood pressure measurements were performed with a pediatric instead of an adult cuff in 363 participants. To adjust those readings, ankle blood pressure readings were performed with both adult and pediatric cuffs on 36 subsequent participants. From this sample, a regression equation was estimated to predict adult cuff reading from pediatric reading. This equation was then used to adjust the blood pressure measurements obtained with the pediatric cuff. Each ankle blood pressure measurement was adjusted independently. The mean difference between adjusted and unadjusted ankle blood pressures was 23 mm Hg for the right leg and 31.5 mm Hg for the left. Preliminary analyses were the same with these adjusted readings included or excluded.

Other epidemiological studies have used various cutoff points to indicate an abnormal AAI. To determine whether there was an inverse dose-response relation between cardiovascular disease (CVD) risk and AAI, we looked at the disease and risk factor relations within categories of an AAI <1.0. An AAI of 1.0 to 1.5 was used as the reference group. Participants with AAI measurements <1.0 were categorized into three levels: ≥0.9 to <1.0, ≥0.8 to <0.9, and <0.8. Relative risks were calculated for each of these levels compared with the group with AAI of ≥1.0 to <1.5 to assess trends in mean risk factor level and relative risk as the AAI decreased. We excluded the 29 participants (0.6%) with

an AAI >1.5. Clinical studies[20] have indicated that these individuals are not "normal" in that they have arterial rigidity preventing arterial occlusion, yielding falsely high ankle blood pressure values. On the basis of preliminary analyses that suggested that these participants had a higher prevalence of clinical CVD than participants with AAI measurements between 1.0 and 1.5, we excluded them from further analysis. This was somewhat arbitrary, since the small number of subjects would have little effect on the analysis. Clinical CVD was defined to include reported history of myocardial infarction (MI), angina, congestive heart failure (CHF), history of atrial fibrillation, coronary angioplasty, other heart surgery, valve disease, pacemaker, bypass surgery, stroke, transient ischemic attack (TIA), or use of nitrates, digitalis, or class 1A antiarrhythmics.

Duplex ultrasonography of the extracranial carotid arteries was performed with a Toshiba SSA-270A (Toshiba America Medical Systems, Tustin, Calif) equipped with a 5.0-MHz transducer. Real-time (B-mode) imaging was used to measure arterial intimal-medial thickness and the presence of focal atherosclerotic plaque bilaterally. Pulsed Doppler sonography was used to record Doppler spectra at the site of maximum blood flow in the internal carotid arteries. The percent of maximal stenosis was calculated from the Doppler velocity, and the maximum of the left or right was used as the independent variable in this analysis. A lesion severity score was calculated from the real-time image and the Doppler-derived velocities and was expressed as percent lumen diameter stenosis in the following categories: 0%, 1% to 24%, 25% to 49%, 50% to 74%, 75% to 99%, and 100%.[24] The final two categories were collapsed into one (75% to 100%) because of small numbers. Stenosis was also dichotomized for this analysis to rate a person as having plaque present (stenosis ≥1%) in either carotid or not.[25]

M-mode, two-dimensional, and Doppler echocardiographic examinations were performed with the Toshiba SSH-160-A (Toshiba Medical Systems) equipped with 2.5-MHz and 3.75-MHz transducers. For this analysis, the presence of definite qualitative global or regional wall motion abnormalities was used as a marker for atherosclerotic cardiac disease.[26]

Twelve-lead ECGs were obtained on all participants using the MAC PC-DT ECG recorder (Marquette Electronics, Inc, Milwaukee, Wis). "Major ECG abnormality" was defined to include ventricular conduction defect, major Q or QS abnormalities, minor Q or QS with ST-T-wave abnormalities, left ventricular hypertrophy, isolated major ST-T-wave changes, atrial fibrillation, and first-degree atrioventricular block.

Fasting serum chemistry analyses were performed on the Kodak Ektachem 700 analyzer (Eastman Kodak Corp, Rochester, NY). Fasting lipids were measured on an Olympus Demand system under the Centers for Disease Control and Prevention proficiency program. Plasma fibrinogen levels were measured by a modified clot-rate method with a BBL fibrometer. Serum insulin levels were measured by solid-phase immunoassay (Diagnostic Products Corp, Los Angeles, Calif). Pulmonary function testing included a forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV_1), measured with a water-sealed Collins II spirometer.

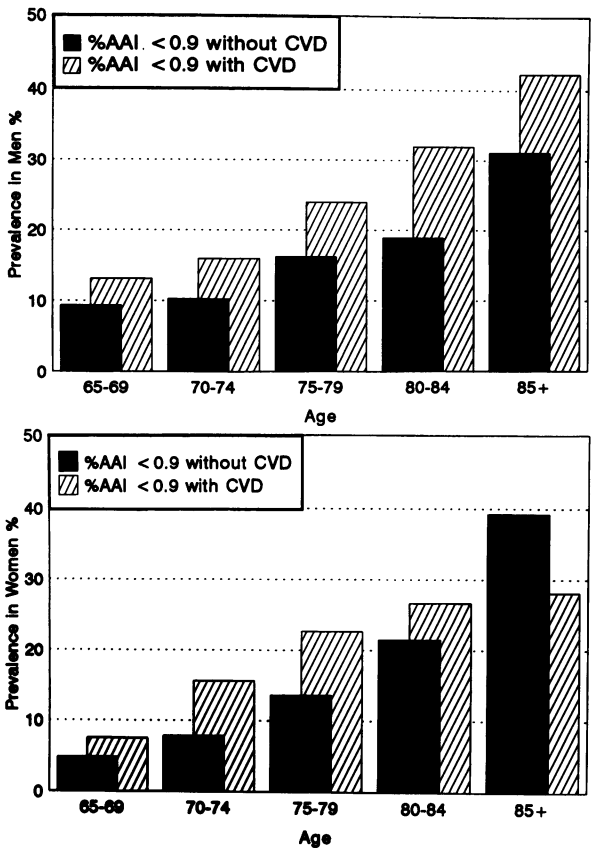

FIG 2. *Bar graphs showing prevalence of low ankle-arm index (AAI) in men and women with and without clinical cardiovascular disease (CVD).*

Statistical Methods

Bivariate associations between the AAI and discrete variables were evaluated with the χ^2 test. The χ^2 test for trend was used to test for a dose-response relation of clinical CVD, subclinical disease, and CVD risk factors between AAI categories. Analysis of covariance was used to adjust mean levels of continuous variables for age and sex. Relative risk estimates were adjusted for age and sex by Mantel-Haenszel methods. Independence of associations was assessed by multiple logistic regression. All variables included in bivariate analysis were considered in a stepwise multivariate regression analysis except for current blood pressure and other noninvasive measurements. We used an AAI cutoff point of 0.9 to define a low AAI in the regression model because this level of AAI was significantly associated with most risk factors and measures of atherosclerosis.

Results

The mean AAI for the 5084 participants with an AAI measurement was 1.07 (SD, 0.17) (Fig 1). There were 375 participants (7.4%) with an AAI <0.8, 629 (12.4%) with an AAI <0.9, and 1198 (23.6%) <1.0. In contrast, the frequency of a positive Rose questionnaire for intermittent claudication was 2%. The mean AAI in this group with intermittent claudication was 0.8, compared with 1.09 for those without intermittent claudication ($P<.001$). Fig 2 shows the prevalence of an AAI of less than the 0.9 cutoff point for men and women according to age and the presence or absence of prevalent clinical

TABLE 1. Number and Percent of Participants With Clinical Cardiovascular Disease in Subgroups With Decreasing Ankle-Arm Index

	Ankle-arm index				
	≥1.0 to <1.5 N*=3835	≥0.9 to <1.0 N*=566	≥0.8 to <0.9 N*=252	<0.8 N*=371	P (trend)†
Myocardial infarction					
n (%)	264 (7.3)	49 (9.4)	35 (15.0)	74 (21.8)	
RR (adj)‡	1	1.3§	2.0§	2.7§	<.0001
Angina					
n (%)	416 (11.5)	76 (14.6)	41 (17.4)	88 (26.5)	
RR (adj)	1	1.3§	1.4§	2.1§	<.0001
CHF					
n (%)	60 (1.6)	8 (1.4)	10 (4.0)	22 (6.0)	
RR (adj)	1	0.9	2.1§	3.1§	<.0001
Stroke					
n (%)	78 (2.1)	11 (2.0)	19 (7.7)	20 (5.6)	
RR (adj)	1	1.0	3.6§	2.6§	<.0001
TIA					
n (%)	47 (1.2)	11 (2.0)	6 (2.4)	14 (3.8)	
RR (adj)	1	1.5	1.6	2.4§	<.01

*Actual N varies for each cell because possible cases were excluded. Definite myocardial infarction, angina, congestive heart failure (CHF), stroke, and transient ischemic attack (TIA) were confirmed by baseline ECG, medication use, or medical records and compared with those with no disease.

†χ^2 test of trend.

‡RR (adj) means relative risk adjusted for age and sex.

§$P<.05$, Mantel-Haenszel χ^2.

CVD. Three hundred eight men (13.8%) and 326 women (11.4%) had an AAI of <0.9. The striking features of this relation are the strong associations with increasing age ($P\leq.0001$) and baseline CVD status ($P=.0001$) and lack of association with sex ($P=.49$) when accounting for age and CVD. Men with a low AAI were more likely than women to have a diagnosis of clinical CVD (56% vs 40%, $P<.001$). Results were similar at the 0.8 cutoff point.

The age- and sex-adjusted relative risks for MI, angina, CHF, stroke, and TIA are shown in Table 1 for progressively lower AAIs compared with those with an AAI of ≥1.0 to <1.5. Participants with an AAI <0.8 were more than twice as likely as those with an AAI of ≥1.0 to <1.5 to have a history of MI, angina, stroke, or TIA and more than three times as likely to have a history of CHF after adjustment for age and sex. In most cases, the relative risk for clinical disease was progressively and inversely related to the AAI. This is apparent for MI and angina at an AAI <1.0. For congestive heart failure and stroke, this increased risk is noted among persons with an AAI <0.9.

We next examined the relations of risk factors and other noninvasive measures of subclinical atherosclerosis with the AAI in participants free of clinical cardiovascular disease at baseline (n=3372) (Table 2). In participants without clinical CVD, increasing age continues to be strongly associated with decreasing levels of AAI. Male sex was not associated with decreasing AAI in this elderly sample without cardiovascular disease. Nonwhite race, predominantly black in this study, was associated with a low AAI. The persons in the lowest AAI stratum were 3.5 times more likely to be nonwhite than those in the normal stratum. Age- and sex-adjusted means and relative risks for other risk factors are shown in Table 2. Crude means and relative risks differed little from the age-adjusted estimates, and sex-specific estimates showed few differences between men and women (except for cholesterol, discussed below).

Age- and sex-adjusted total and low-density lipoprotein cholesterol increased as the level of AAI decreased. The mean adjusted high-density lipoprotein cholesterol was lower at an AAI of <0.8. Total and low-density lipoprotein cholesterol were the only factors that showed different sex-specific associations with the AAI. In women, the total and low-density lipoprotein cholesterol levels increased significantly (P for trend <.0001) as the AAI decreased, whereas for men, there was no significant trend. Conversely, for both men and women, the mean high-density lipoprotein cholesterol decreased as the AAI decreased. The triglyceride level also increased as the AAI decreased.

Participants with a low AAI were more likely to report hypertension and had a higher baseline systolic blood pressure. The adjusted diastolic blood pressure was not associated with the AAI level. The mean serum creatinine also increased with decreasing level of AAI.

As expected, smoking was clearly related to a low AAI (<0.8) in both current and ex-smokers. The lower the AAI, the more likely a subject was to be a current smoker. Decreased AAI was also associated with past smoking and with reduced FVC and FEV_1. History of diabetes was associated with the level of AAI, as were the actual fasting blood glucose and insulin levels. There was no association in bivariate analysis with body mass index. There was no relation between AAI and factor VII or VIII. An increasing mean fibrinogen level was associated with a decreasing AAI.

Decreased AAI was strongly related to subclinical CVD as measured by carotid ultrasound, ECG, and

TABLE 2. Association of Baseline Characteristics With Ankle-Arm Index in 3372 Participants Without Baseline Cardiovascular Disease

	Ankle-arm index				
	≥1.0 to <1.5	≥0.9 to <1.0	≥0.8 to <0.9	<0.8	*P* (trend)*
N	2690	361	149	172	
Demographics					
Age (years), mean (adj)†	71.7	73.7	75.7	75.5	<.0001
Sex					
% Male	39.8	32.7	34.2	45.9	
RR (adj)‡	1	0.8¶	0.8¶	1.1	.20
Race					
% Nonwhite	4.2	7.2	6.7	14.5	
RR (adj)	1	1.7¶	1.7	3.5¶	<.0001
Lipids					
Total cholesterol (mg/dL), mean (adj)	215.8	218.8	224.8	227.0	<.0001
LDL cholesterol (mg/dL), mean (adj)	133.5	134.9	140.9	144.6	<.0001
HDL cholesterol (mg/dL), mean (adj)	55.4	56.4	55.8	52.4	<.01
Triglycerides (mg/dL), mean (adj)	136.6	141.8	140.3	159.8	<.001
Blood pressure					
Hypertension§					
% Reported	38.4	46.1	52.1	52.4	
RR (adj)	1	1.2¶	1.4¶	1.4¶	<.0001
Systolic blood pressure (mm Hg), mean (adj)	134.0	138.7	140.0	143.7	<.0001
Diastolic blood pressure (mm Hg), mean (adj)	70.5	71.9	69.5	71.3	.97
Creatinine (mg/dL), mean (adj)	1.01	1.03	1.03	1.07	<.01
Smoking and pulmonary function					
Ex-smokers‖					
%	45.8	47.8	39.7	61.2	
RR (adj)	1	1.1¶	1.0	1.5¶	<.0001
Current smokers‖					
%	17.6	27.8	29.8	49.5	
RR (adj)	1	1.8¶	2.3¶	3.5¶	<.0001
FEV_1, mean (adj)	2.13	1.99	1.88	1.83	<.0001
FVC, mean (adj)	3.02	2.90	2.75	2.64	<.0001
Diabetes§					
% Reported	7.2	8.6	18.2	17.8	
RR (adj)	1	1.3	2.9¶	2.6¶	<.0001
Fasting glucose (mg/dL), mean (adj)	107.1	108.6	121.5	114.5	<.0001
Fasting insulin, mean (adj)	15.2	15.4	16.0	22.3	<.0001
Body mass index (kg/m^2), mean (adj)	26.7	25.6	25.7	26.3	.40
Coagulation factors					
Factor VII, mean (adj)	126.9	128.5	125.2	131.3	.25
Factor VIII, mean (adj)	119.9	118.7	124.4	123.2	.10
Fibrinogen, mean (adj)	315.7	324.7	334.2	333.3	<.001

LDL indicates low-density lipoprotein; HDL, high-density lipoprotein; FEV_1, forced expiratory volume in 1 second; and FVC, forced vital capacity.

*χ^2 test for trend, adjusted for age and sex.

†Mean (adj) is adjusted for age and sex.

‡RR (adj) means relative risk adjusted for age and sex.

§Compared with normal participants, excluding borderline cases.

‖Compared with never-smokers only.

¶$P<.05$, Mantel-Haenszel χ^2.

qualitative two-dimensional echocardiography (Table 3). Participants with an AAI of ≥0.8 to <0.9 were more than twice as likely to have regional wall motion abnormalities as those with AAI ≥1.0 to <1.5, whereas those with AAI <0.8 were more than four times as likely. The relative risk for global left ventricular dysfunction was particularly large (5.1) in participants with an AAI of <0.8. AAI was also strongly related to carotid stenosis. We looked at the relative risk for each level of carotid stenosis vs no stenosis at each level of AAI. Fig 3 summarizes these separate 2×4 analyses. For each level of carotid stenosis, there is a strong association with decreasing AAI. This association becomes apparent at carotid stenosis of ≥50%. For carotid stenosis of 50% to

TABLE 3. Noninvasive Measures of Cardiovascular Disease in Participants Without Clinical Cardiovascular Disease by Decreasing Level of Ankle-Arm Index

	Ankle-arm index				
	≥1.0 to <1.5	≥0.9 to <1.0	≥0.8 to <0.9	<0.8	*P* (trend)*
N†	2689	361	149	172	
Carotid plaque‡					
n (% positive)	1592 (59.8)	250 (70.8)	121 (81.8)	144 (87.8)	
RR (adj)§	1	1.2¶	1.3¶	1.4¶	<.0001
Major ECG abnormality					
n (% positive)	443 (16.5)	81 (22.4)	40 (26.9)	52 (30.2)	
RR (adj)	1	1.3¶	1.5¶	1.6¶	<.0001
ECG left ventricular hypertrophy					
n (% positive)	53 (2.0)	10 (2.8)	4 (2.7)	11 (6.4)	
RR (adj)	1	1.2	1.0	2.5¶	.03
Regional wall motion abnormality					
n (% positive‖)	37 (1.4)	6 (1.9)	4 (2.9)	10 (6.3)	
RR (adj)	1	1.4	2.2	4.4¶	<.001
Global wall motion abnormality					
n (% positive‖)	21 (0.9)	5 (1.4)	5 (3.5)	7 (4.5)	
RR (adj)	1	1.9	4.2¶	5.1¶	<.0001

*χ^2 test for trend, adjusted for age and sex.
†Actual N for each cell varies slightly because of missing data.
‡Carotid plaque defined as any plaque in either carotid artery by B-mode scan.
§RR (adj) means relative risk adjusted for age and sex.
‖Percent positive, relative to normal, excluding borderline cases.
¶$P<.05$, Mantel-Haenszel χ^2.

<75% and ≥75%, the age- and sex-adjusted relative risk increased in a graded, stepwise fashion as the AAI decreased (Fig 3).

To further assess independence of these relations, we performed a stepwise multiple logistic regression analysis (Table 4). We chose a cutoff point of 0.9 to categorize participants as having PAD because this level of AAI was generally associated with risk factors in the stratified analysis. All factors considered in bivariate analysis, except for current blood pressure and the other noninvasive measures, were considered in the model. The final model included those variables listed in Table 4 in the order in which they entered the model. Both current smoking and race were associated with a more than twofold increased risk of low AAI. Sex was not related to a low AAI. Age retained its positive association after adjustment of other factors. Obesity was inversely associated with low AAI in this model.

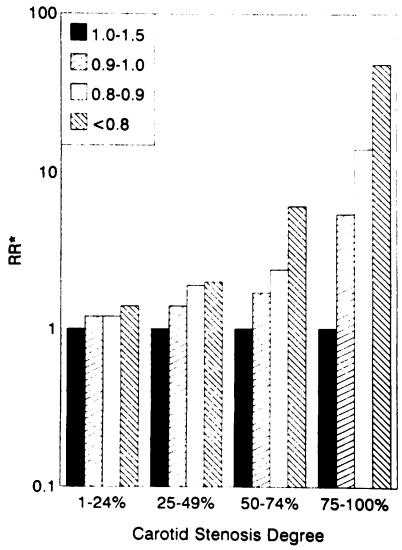

FIG 3. *Relative risk (RR*) of carotid disease associated with a low ankle-arm index. Each category of carotid stenosis is compared independently with those with no stenosis. This figure summarizes these four separate analyses. *Relative risk adjusted for age and sex.*

The sensitivity, specificity, and predictive value of the AAI for carotid stenosis were calculated with different cutoff points for both the AAI and carotid stenosis. An AAI of <0.9 had a sensitivity of 0.51 for >75% carotid stenosis, and the specificity was 0.91. The positive predictive value was 5.4% and the negative predictive

TABLE 4. Independent Risk Factors for Low Ankle-Arm Index (<0.9) by Stepwise Multiple Logistic Regression

Variable	RR	95% CI	*P*
Age (5 years)	1.69	(1.50, 1.92)	<.0001
Race (nonwhite)	2.12	(1.31, 3.44)	.002
Total cholesterol (10 mg/dL)	1.10	(1.06, 1.14)	<.0001
HDL cholesterol (1 mg/dL)	0.99	(0.98, 1.00)	.02
Creatinine (0.1 mg/dL)	1.07	(1.13, 1.12)	.002
Body mass index (kg/m^2)	0.94	(0.91, 0.97)	.0003
FVC (L)	0.63	(0.52, 0.76)	<.0001
Reported diabetes	4.05	(2.789, 5.90)	<.0001
Current smoker	2.55	(1.76, 3.68)	<.0001
Pack years	1.01	(1.01, 1.02)	<.0001
Reported hypertension	1.51	(1.15, 1.99)	.004

RR indicates relative risk; CI, confidence interval; HDL, high-density lipoprotein; and FVC, forced vital capacity.

value, 99.4%. Sensitivity fell with other cutoff points with little change in specificity. An AAI of <0.9 had a sensitivity of 0.23 for echocardiographic wall motion abnormality, with similar specificity (0.90) and predictive values (positive predictive value, 4.0%; negative predictive value, 98.5%) as for carotid stenosis.

Discussion

Although the AAI is used extensively in epidemiological studies and clinical practice, there is no cutoff point that is diagnostic of PAD. Cutoff points for an abnormal AAI were originally developed from studies of patients referred for angiography of the lower extremities. An AAI of <0.8 is strongly predictive of significant obstruction; however, healthy patients without PAD virtually never have an AAI <1.0.[21] Other studies have used a single cutoff point either 0.8 or 0.9 to indicate disease and have shown associations with risk factors.[1,3,9,15,27,28] In our elderly population, we hypothesized that, as a marker of atherosclerosis, a decreasing AAI would show a graded or dose-response relation to risk factors and other noninvasive measures. In general, we found such a trend for clinical cardiovascular disease, CHD risk factors, and noninvasive measures of disease. These findings are strengthened by the large sample of community-dwelling elderly, the validation of clinical history of CVD, the extensive number of risk factors considered, and the comparison of several noninvasive measures of disease in other vascular beds. These data show that the AAI is inversely related to cardiovascular risk factors and represents a marker for atherosclerosis in other vascular beds.

This study also shows that a low AAI is quite prevalent among older persons with and without a history of ischemic heart disease. On the other hand, the prevalence of MI, angina, CHF, stroke, and TIA increased with decreasing levels of AAI. An AAI <0.9 was associated with a twofold increase in risk of prevalent CVD. The AAI was consistently associated with all major manifestations of clinical CVD, suggesting that the AAI is a noninvasive marker of atherosclerosis. This is similar to the findings of the Edinburgh Artery Study,[12] which showed an increased prevalence of CVD in both symptomatic and asymptomatic PAD.

Analysis in participants free of clinical CVD at baseline revealed interesting relations between CVD risk factors and decreasing levels of AAI. The lack of association between decreasing AAI and male sex was somewhat surprising, but it may be explained by the fact that men with a low AAI were more likely to have symptomatic CVD than women. It is also possible that women with CVD are less likely to have been diagnosed as such than men.[29,39] This would create a bias that would show an increased prevalence of a low AAI in women classified as having no clinical CVD at baseline.

We adjusted the bivariate analyses for age and sex but did not find that the means and relative risks were meaningfully changed by this. Risk factor associations did not differ substantially by sex, suggesting that risk factors for subclinical disease are similar in men and women.

Nonwhite race (predominantly black) was significantly associated with decreasing AAI level. This finding remained significant even after adjustment for other risk factors, including diabetes, body mass index, and smoking. The duration and severity of these and other factors are not fully accounted for and may ultimately explain this finding. We know of no other published data with a significant number of nonwhite participants with PAD. However, studies of carotid disease and race show similar results.[31]

A relation between hypercholesterolemia and a low AAI has been shown previously.[3,7,10,11] This study not only confirms this relation but also shows that at least cross-sectionally in women, cholesterol level is inversely related to this AAI. This relation is important because the benefit of risk factor reduction in the elderly may vary according to the degree of atherosclerosis. The finding that increasing cholesterol is associated with a low AAI in women but not in men was also found in a recent study by Vitale et al.[32] As noted by others, the association of triglycerides with the AAI does not hold up in multivariate analysis.[33]

The relation of a low AAI with hypertension and particularly high systolic blood pressure is consistent with other studies.[1,9,34,35] The association with systolic blood pressure may indicate that pulse pressure is widened in those with more advanced atherosclerosis of the peripheral vessels. However, associations of the AAI with current blood pressure may be spurious and artifactual, since the AAI is a ratio of systolic blood pressures and is not independent. Therefore, we did not include current blood pressure in the multivariate model.

The relation of smoking to the level of AAI shows a dose-response pattern for both current smokers and past smokers. Current smoking was inversely associated with the AAI even in this apparently healthy subgroup free of clinical CVD at baseline. This is not necessarily an expected finding in this age group. It is plausible that older adults without clinical CVD represent survivors who are less susceptible to the effects of smoking. These data suggest that smoking continues to be associated with worsening atherosclerosis at advanced ages, even in an apparently healthy population of older adults. The FEV_1 and FVC, which are measures of pulmonary function and perhaps markers of smoking exposure, were related to decreasing AAI level even after adjustment for smoking in the regression model. Pulmonary function has been associated with cardiovascular mortality, but whether this relation is truly independent of smoking is unclear.[36]

The diagnosis of diabetes was related to the level of AAI, as were the fasting blood glucose and fasting insulin levels. This is not surprising, given the high prevalence of PAD in diabetics.[3,4] This relation appears to be independent of obesity as measured by body mass index.

Reunanen et al[37] have shown a similar relation between fibrinogen and PAD using the Rose questionnaire for intermittent claudication to define disease. Fibrinogen level has been shown to be a risk factor for myocardial infarction and stroke.[38-41] Factors VII and VIII were not associated with PAD in our healthy participants, although factor VIII was associated with a decreasing AAI in those with clinical CVD (P for trend <.001). The meaning of these findings in a cross-sectional analysis is not clear and will be followed prospectively.

We also observed a relation of AAI level with noninvasive measures of carotid and cardiac disease. There was a strong inverse relation of AAI with both ECG and echocardiographic markers of coronary heart disease and left ventricular hypertrophy, even in those apparently healthy participants free of clinical CVD at baseline. The relation between AAI and carotid disease was particularly strong. Other investigators have demonstrated an association between AAI and carotid disease[15]; however, we were able to demonstrate that the inverse relation between AAI and carotid disease is graded. Levels of AAI <1.0 are not diagnostic of PAD but are indicative of increased probability of atherosclerosis. The low sensitivity of the AAI for carotid stenosis and echocardiographic wall motion abnormalities would indicate that, although it is an excellent way to group participants with disease, it should not be used as a diagnostic test. Because of its inverse association with clinical and subclinical CVD, we hypothesize that the AAI will be a strong predictor of future events in this group of older adults.

Appendix

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