Ankle-Arm Index as a Predictor of Cardiovascular Disease and Mortality in the Cardiovascular Health Study

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Abstract—Peripheral arterial disease (PAD) in the legs, measured noninvasively by the ankle-arm index (AAI) is associated with clinically manifest cardiovascular disease (CVD) and its risk factors. To determine risk of total mortality, coronary heart disease, or stroke mortality and incident versus recurrent CVD associated with a low AAI, we examined the relationship of the AAI to subsequent CVD events in 5888 older adults with and without CVD. The AAI was measured in 5888 participants ≥65 years old at the baseline examination of the Cardiovascular Health Study. All participants had a detailed assessment of prevalent CVD and were contacted every 6 months for total mortality and CVD events (including CVD mortality, fatal and nonfatal myocardial infarction, congestive heart failure, angina, stroke, and hospitalized PAD). The crude mortality rate at 6 years was highest (32.3%) in those participants with prevalent CVD and a low AAI ($P<0.9$), and it was lowest in those with neither of these findings (8.7%, $P<0.01$). Similar patterns emerged from analysis of recurrent CVD and incident CVD. The risk for incident congestive heart failure (relative risk [RR]=1.61) and for total mortality (RR=1.62) in those without CVD at baseline but with a low AAI remained significantly elevated after adjustment for cardiovascular risk factors. Hospitalized PAD events occurred months to years after the AAI was measured, with an adjusted RR of 5.55 (95% CI, 3.08 to 9.98) in those at risk for incident events. A statistically significant decline in survival was seen at each 0.1 decrement in the AAI. An AAI of <0.9 is an independent risk factor for incident CVD, recurrent CVD, and mortality in this group of older adults in the Cardiovascular Health Study. **(*Arterioscler Thromb Vasc Biol.* 1999;19:538-545.)**

Key Words: peripheral vascular diseases ■ ankle-arm index ■ ankle-brachial pressure index ■ cardiovascular diseases, epidemiology

Epidemiological studies have demonstrated that subclinical cardiovascular disease in one vascular bed is associated with the presence of clinical disease in another bed,[1–5] as well as with subsequent cardiovascular and total mortality.[6–12] Degrees of peripheral arterial disease (PAD) in the legs, as measured noninvasively, are common in older adults without overt signs and symptoms of PAD.[5,13] Among the elderly, an index of subclinical atherosclerosis with the use of several noninvasive measures that include carotid stenosis and wall thickness by duplex scanning, ECG and echocardiographic abnormalities, a positive Rose questionnaire[14] for angina, and an ankle-arm index (AAI) of <0.9 has been shown to be a strong predictor of total and cardiovascular morbidity and mortality in those without prior history of clinical cardiovascular disease at the baseline examination.[15] PAD in the legs, as measured by progressive decrements in the AAI, was associated with a stepwise increase in cardiovascular risk factor levels as well as in the prevalence of myocardial infarction (MI), stroke, and congestive heart failure (CHF).[5] Past prospective studies of the cardiovascular disease (CVD) risk associated with the presence of PAD have not distinguished between recurrent and incident CVD; thus, the increased risk of mortality may be partly because of the correlation of PAD with prevalent clinical CVD.

The goal of the present study was to evaluate the risk of cardiovascular morbidity and mortality associated with a marker of PAD, the presence of a low AAI (AAI <0.9). Follow-up data of 5888 older adults enrolled in the Cardiovascular Health Study (CHS) were examined for risk of subsequent cardiovascular events and mortality. We hypothesized that the presence of a low AAI in participants without clinical CVD would be associated with a degree of risk for cardiovascular events similar to that found in those with a low AAI and known clinical CVD.

Methods

The CHS is an ongoing observational study of 5888 adults ≥65 years old, including 2495 men and 3393 women. The initial cohort of CHS

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participants was recruited from a defined sample of Medicare-eligible persons between April 1989 and May 1990. Participants were recruited from 4 US communities: Forsyth County, NC; Sacramento County, Calif; Washington County, Md; and Pittsburgh, Pa. Detailed descriptions of the CHS have been published.[16,17] The original sample of 5201 participants was primarily white: 148 (3%) were black women and 96 (1.8%) were black men. A second cohort of 687 black participants (431 women and 256 men) was enrolled between June 1992 and June 1993, 3 years after the enrollment of the original CHS cohort, to allow sample sizes sufficient for subgroup analysis.

All of the CHS participants underwent a baseline medical history and examination that included ECG, AAI, and pulmonary function testing. During this examination, participants were classified in accordance with the presence or absence of 6 preexisting CVDs: MI, angina, CHF, stroke, transient ischemic attack (TIA), and intermittent claudication. Participants with any of these 6 conditions were classified as having prevalent CVD.

The methods of ascertainment of these conditions have been described elsewhere.[18–21] Briefly, baseline disease status was ascertained from the medical history and confirmed by either the ECG, appropriate prescription medication, hospital record review, or physician questionnaire. Participants with a history of coronary angioplasty, carotid endarterectomy, or bypass surgery were also considered to have prevalent CVD. Prevalent PAD was defined as a positive Rose questionnaire[14] for intermittent claudication or a history of lower-extremity bypass surgery, angioplasty, or amputation.

Descriptive variables from the baseline examination were chosen for this analysis on the basis of associations with AAI as reported in a prior cross-sectional analysis.[5] These variables were age, sex, race, cigarette use (current or past versus never), history of treated hypertension or history of diabetes, systolic and diastolic blood pressure (mm Hg), total cholesterol (mg/dL), HDL cholesterol (mg/dL), triglycerides (mg/dL), fasting glucose (mg/dL), fasting insulin (μU/mL), serum creatinine (mg/dL), and fibrinogen (mg/dL). All blood was collected and analyzed at the time of baseline examination according to laboratory methods previously reported.[5] Major ECG abnormalities were determined by the CHS ECG Reading Center according to a standard protocol and included ventricular conduction defects, 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, or first-degree atrioventricular block.

All participants underwent duplicate resting measurements of the blood pressures used to create the AAI. The AAI is the ratio of the ankle systolic blood pressure to the arm systolic blood pressure and is >1.0 in normal adults.[22] The AAI was measured by trained technicians according to a standard protocol, previously described.[5] Briefly, the participant was asked to lie flat on an examination table, and after 5 minutes of rest, standard arm blood pressure cuffs were applied to the right arm and to each ankle (with the lower end of the bladder within 3 cm of the malleoli). After palpation of the brachial and posterior tibial arteries, ultrasound gel was applied, and a Doppler stethoscope (8 MHz, Huntleigh Technology, Inc) and a standard mercury manometer were used to assess systolic blood pressure in the right brachial artery and in each posterior tibial artery in rapid succession. Measurements have been shown to be reliable between observers, stable over time, and highly correlated between left and right legs.[11] We excluded 31 participants (0.5%) with AAI ≥1.5 in both legs at baseline because previous analyses[5] indicated that this is a falsely high level caused by noncompressible vessels in the legs. One hundred and forty-three participants did not have AAI data. Thus, 5714 participants of the total 5888 are included in this analysis.

CHS methods for surveillance and ascertainment of CVD events are described in detail in previous articles[15,23] and are summarized as follows. Participants were contacted by the CHS clinical centers every 6 months in regard to subsequent hospitalizations and outpatient visits for specific cardiovascular diagnoses including MI, angina, CHF, stroke, TIA, and PAD. Total mortality included all deaths and was documented by death certificates, inpatient records, nursing home or hospice records, physician questionnaires, and autopsy reports.

CVD mortality was defined to include death from CHD, MI, sudden death, or stroke. Nonfatal events (whether a new or a repeat event for a participant) were evaluated by review of all hospital records (all ICD-9-CM codes), history and physical exams, discharge summaries, and diagnostic and therapeutic procedures. Outpatient records and physician questionnaires were evaluated for outpatient MI, CHF, and stroke. Incident PAD events were defined by a review of all inpatient hospitalizations on the face sheet for diagnosis. All records with an ICD-9 code of 440.2 or 443.9 or a mention of peripheral vascular disease or claudication on the face sheet or in the discharge summary were reviewed. A hospitalized PAD event required the presence of ischemic leg pain and a consistent invasive or noninvasive diagnostic test. Outpatient reports of PAD were confirmed with the use of the AAI and thus were not independent of the predictor variable. Therefore, only hospitalized PAD was used in these analyses, because these diagnoses were made independently of the CHS AAI measurement. Adjudication of each event was reached by consensus.

For this analysis, the following categories of events were evaluated: total mortality, CVD mortality (CHD and stroke), MI, angina, CHF, stroke, and hospitalized PAD. Data through 6 years of follow-up (mean, 5.1 years) for the original CHS cohort and 2 years of follow-up for the black cohort (mean, 22 months) are reported here.

Statistical Analysis

Participants were classified according to the presence or absence of prevalent clinical CVD at baseline. Participants were also classified as having a low AAI if the AAI was <0.9 in either leg. We chose this cut point based on previous analyses in this population[5] and in other published articles.[10–12] Associations of follow-up events with baseline disease and of AAI groups were assessed by crude event rates, Kaplan-Meier life tables, and Cox proportional hazards models with an adjustment for age, gender, and other CVD risk factors. The factors were those associated with a low AAI in previous cross-sectional analyses[5] and included race, past smoking, pack-years of smoking, diabetes, total cholesterol, HDL cholesterol, triglyceride level, fasting glucose, insulin, fibrinogen level, factor VII, and body mass index. Cox proportional hazards models were used to assess independent associations between an AAI <0.9 and various end points. Cox models also were used to assess whether any interaction between a low AAI and covariates was significant after all main effects for the risk factors in the Cox models were included. Associations were considered to be significant at $P<0.01$. All analyses were performed with Statistical Analysis System software.[24]

Results

At the baseline examination, 768 of 5714 participants (13.4%) had an AAI of <0.9. This includes the added cohort of 687 blacks whose baseline examination was 3 years after the original cohort. Participants with a low AAI were older and more likely to be male or black. In addition, those with a low AAI were approximately twice as likely to have a history of CVD at the baseline examination (46.7% versus 22%, Table 1).

At 6 years of follow-up, crude and age- and gender-adjusted event rates were calculated for total mortality as well as for recurrent and incident CVD events. Rates were calculated separately for those with and without CVD at baseline. The total mortality rate was highest in participants with prevalent disease and a low AAI (32.3%) and lowest in those with neither of these findings (8.7%, $P<0.01$, Table 2). Of note, for those without prevalent CVD but with a low AAI, the mortality rate was quite high (25.4%).

The 1446 participants with CVD at baseline were at a higher risk for subsequent events than those without such

TABLE 1. Characterstics of the CHS Cohort by AAI (n=5714)

	AAI<0.9 (n=768)		AAI≥0.9 (n=4946)	
Characteristic	n	%	n	%
Age, y				
65–69	141	18.4	1836	37.1
70–74	211	27.5	1608	32.5
75–79	200	26.0	956	19.3
80–84	141	18.4	407	8.2
85+	75	9.8	139	2.8
Gender				
Male	360	46.9	2072	41.9
Female	408	53.1	2874	58.1
Race				
Black	189	24.6	691	14.0
White	568	74.0	4223	85.4
Other	11	1.4	32	0.7
Prevalent CVD				
Yes	359	46.7	1087	22.0
No	409	53.3	3859	78.0

history. However, within this high-risk group, a low AAI showed age- and gender-adjusted risk ratios of 1.50 for mortality, 2.04 for CVD mortality, and 1.61 for MI (Table 2). Thus, within this higher-risk subgroup of CHS participants with CVD at baseline, the 3 factors of AAI, age, and male gender distinguished risk of total mortality, CVD mortality, total MI, CHF, and PAD. After adjustment for other CVD risk factors, risk ratios for total mortality, MI, and CHF were attenuated and CIs widened to include 1. The majority (74.7%) of the CHS cohort had no history of CVD at the baseline examination (Table 1). The relative risk (RR) and absolute risk for CVD events and mortality were significantly higher in those participants with a low AAI and no prevalent CVD for all events except stroke (Table 2). The RR of a low AAI for CVD mortality was higher than for total mortality (RR of 2.86 and 2.44, respectively, for CVD and total mortality), although CIs overlapped.

Compared with the use of history of CVD as a predictor of cardiovascular events, in those with no history of CVD the AAI is less sensitive but more specific. For total mortality, the sensitivity and specificity of an AAI <0.9 are 24% and 92%, respectively, compared with 44% sensitivity and 77% specificity for a history of CVD. A similar pattern is found when CVD mortality is used as the outcome event: a low AAI has 30% sensitivity and 91% specificity compared with 64% sensitivity and 77% specificity for history of CVD.

The rate of new clinical PAD events in the legs was significantly associated with the presence of a low AAI at the baseline examination in both groups (Table 2). Although the rate of PAD events was 6- to 11-fold higher in participants with low AAI, the absolute risk of the development of symptomatic PAD (11.7% in those with prevalent CVD versus 6.6% in those with no CVD) was less than or similar to that of other CVD events (including angina and stroke) and was much less than the risk for total mortality (32.3% of those with prevalent CVD, 25.4% for those without CVD).

To further evaluate the relationship of a low AAI to mortality, we focused on the 4268 participants with no CVD

TABLE 2. Cardiovascular Disease Morbidity and Mortality After 6 Years: The CHS

	AAI<0.9*		AAI≥0.9*		RR of Event Given Low AAI (95% CI) Age-Gender Adjusted		RR of Event Given Low AAI (95% CI) Multivariate Adjustment	
Event	n (%)	n/1000 Person Years	n (%)	n/1000 Person Years	n	CI	n	CI
Prevalent CVD at baseline								
Total mortality	116 (32.3)	78.4	229 (21.1)	44.9	1.50‡	(1.20, 1.89)	1.26	(0.96, 1.64)
CVD mortality	68 (18.9)	46.0	104 (9.6)†	20.4	2.04‡	(1.05, 2.79)	1.52‡	(1.05, 2.22)
Total MI	62 (17.3)	45.7	126 (11.6)†	26.5	1.61‡	(1.18, 2.19)	1.20	(0.84, 1.72)
Angina	28 (18.3)	49.9	70 (17.7)	44.4	1.07	(0.69, 1.68)	1.06	(0.63, 1.79)
CHF	63 (22.0)	56.7	137 (15.0)†	33.8	1.47	(1.08, 1.98)	1.28	(0.90, 1.82)
Stroke	32 (11.3)	29.1	78 (8.4)	18.6	1.42	(0.93, 2.15)	1.39	(0.85, 2.25)
PAD	31 (11.7)	31.6	24 (2.3)†	5.0	6.52‡	(3.77, 11.28)	6.04‡	(3.23, 11.28)
No prevalent CVD at baseline								
Total mortality	104 (25.4)	59.3	337 (8.7)†	17.4	2.44‡	(1.94, 3.08)	1.62‡	(1.24, 2.12)
CVD mortality	28 (6.9)	16.0	67 (1.7)†	3.5	2.86‡	(1.79, 4.55)	2.03‡	(1.22, 3.37)
Total MI	33 (8.1)	20.0	169 (4.4)†	9.0	2.02‡	(1.37, 2.98)	1.40	(0.90, 2.17)
Angina	51 (12.5)	31.8	353 (9.2)	19.3	1.64‡	(1.21, 2.22)	1.31	(0.94, 1.83)
CHF	57 (13.9)	34.9	212 (5.5)†	11.3	2.30‡	(1.69, 3.12)	1.61‡	(1.14, 2.29)
Stroke	35 (8.6)	21.2	171 (4.4)	9.1	1.61	(1.10, 2.35)	1.12	(0.74, 1.70)
PAD	27 (6.6)	16.4	36 (0.9)†	1.9	10.59‡	(6.25, 17.96)	5.55‡	(3.08, 9.98)

*For prevalent CVD at baseline, n=1446 (AAI<0.9, n=359; AAI≥0.9, n=1087); for no prevalent CVD at baseline, n=4268 (AAI<0.9, n=409; AAI≥0.9, n=3859).
†$P<0.01$, continuity-adjusted χ^2 for difference between AAI<0.9 versus AAI≥0.9.
‡$P<0.01$, Cox proportional hazards models.

TABLE 3. CVD Mortality in CHS Participants With a Low AAI by Presence or Absence of CVD Risk Factors: Participants Without Prevalent CVD at Baseline

	AAI<0.9			AAI≥0.9			RR Age-Gender	
Risk Factor	N	Deaths	%	N	Deaths	%	Adjusted*	95% CI
Age								
>75 y	219	73	33.3	1085	173	15.9	2.09	(1.6, 2.8)
≤75	190	31	16.3	2774	164	5.9	3.37	(2.3, 5.0)
Gender								
Male	162	59	36.4	1486	185	12.5	2.59	(1.9, 3.5)
Female	247	45	18.2	2373	152	6.4	2.27	(1.6, 3.2)
Race								
Black	105	18	17.1	531	20	3.8	3.65	(1.9, 7.2)
White	298	84	28.2	3302	315	9.5	2.29	(1.8, 2.9)
Treated hypertension								
Yes	229	58	25.3	1602	150	9.4	2.65	(1.8, 3.3)
No	172	43	25.0	2204	180	8.2	2.15	(1.6, 3.3)
Diabetes								
Yes	71	22	31.0	340	41	12.0	2.74	(1.6, 4.7)
No	336	82	24.4	3517	296	8.4	2.26	(1.7, 2.9)
Current smoking								
Yes	85	22	25.9	427	48	11.2	2.46	(1.5, 4.1)
No	316	81	25.3	3380	286	8.5	2.20	(1.7, 2.9)
Cholesterol >240 mg/dL								
Yes	118	32	27.1	807	57	7.1	4.04	(2.6, 6.4)
No	285	69	24.7	3026	276	9.1	2.03	(1.5, 2.7)
Creatinine >1.5								
Yes	37	23	62.2	138	36	26.1	2.69	(1.6, 4.6)
No	361	76	21.1	3684	296	8.0	2.17	(1.7, 2.8)
ECG: any major abnormality								
Yes	139	46	33.1	837	105	12.5	2.16	(1.5, 3.1)
No	268	58	21.6	3016	232	7.7	2.46	(1.8, 3.3)

*RR of mortality for those with an AAI <0.9 after adjustment for age and gender.

at baseline and looked at the mortality rates by AAI in those with and without several important risk factors (Table 3). For each risk factor, the mortality rates were significantly higher in those with a low AAI than in those with a normal AAI. Whether the risk factor was present or absent, the RR of mortality was >2-fold higher in those with a low AAI. For example, those with diabetes and a low AAI had a 31% mortality rate, whereas those with diabetes but a normal AAI had only a 12% mortality rate. Thus, within diabetics, the RR of mortality for those with a low AAI was only slightly higher than the RR of mortality in nondiabetics with a low AAI.

The proportion of blacks with a low AAI and no history of CVD was 16.5% (105 of 636) compared with 8.2% (298 of 3600) in the white participants. Although the majority of the black participants were from the new cohort, which was followed for only 2 years from the baseline examination, the presence of a low AAI was strongly related to subsequent mortality in those 636 black participants free of CVD at baseline (Table 3). Compared with white participants, the RR of mortality even with shorter follow-up time appears higher, although the CIs are wide. These stratified analyses gave similar results when CVD mortality and MI were evaluated.

Participants with an elevated serum cholesterol (>240 mg/dL) and a low AAI had a death rate similar to those with a cholesterol <240 and a low AAI (27.1% versus 24.7%). The relative risk of mortality in those with a low AAI was higher in the high-cholesterol subgroup (4.04 versus 2.03) and may be related to the lower mortality rate (7.1%) in those with a higher cholesterol but a normal AAI.

To further evaluate the independence of association between a low AAI and subsequent cardiovascular events in those without prevalent CVD, models were constructed that included the AAI and all variables associated univariately with a low AAI at baseline (Table 4). There were no significant interactions between a low AAI and covariates for any of the outcomes evaluated. For total mortality, the RR of a low AAI was attenuated somewhat at 1.62. Older age, male gender, higher serum creatinine, major ECG abnormality, and lower forced vital capacity were all associated with mortality independent of its association with a low AAI. Results were similar for CVD mortality. For incident CVD morbidity, we had sufficient numbers of events to evaluate only CHF and PAD. A low AAI was associated with a 1.61-fold increase in the risk of incident CHF. Age, male gender, hypertension,

TABLE 4. Cox Proportional Hazards Model for Various End Points: RR, Significance, and CI for Independent Predictors in Participants Without Prevalent CVD at Baseline

	Total Mortality		CVD Mortality		CHF		PAD Claudication	
Risk Factor	RR	CI	RR	CI	RR	CI	RR	CI
AAI<0.90	1.62	(1.24, 2.12)	2.03	(1.22, 3.37)	1.61	(1.14, 2.29)	5.55	(3.08, 9.98)
Age/y	1.09	(1.07, 1.12)	1.12	(1.08, 1.17)	1.07	(1.04, 1.10)		
Male	2.20	(1.60, 3.01)	2.67	(1.39, 5.13)	1.97	(1.32, 2.94)	2.39	(1.01, 5.65)
Current smoker							4.98	(2.07, 11.99)
Hypertension					1.51	(1.15, 2.02)		
Creatinine (0.1 mg/dL)	2.19	(1.63, 2.95)			2.06	(1.36, 3.13)		
Major ECG abnormality	1.33	(1.07, 1.66)	1.92	(1.23, 2.98)	2.08	(1.60, 2.72)		
Forced vital capacity (L)	0.65	(0.55, 0.77)	0.54	(0.39, 0.76)	0.63	(0.51, 0.78)		

Other covariates in model that were not independently associated with events were race, body mass index, diabetes, fasting insulin, glucose, fibrinogen, factor VII, cholesterol level, HDL, triglyceride level, history of cigarette use in the past, and pack-years of cigarette use.

higher serum creatinine, major ECG abnormality, and lower forced vital capacity were also associated with incident CHF.

The risk for PAD remained quite high after adjustment, 5.55 (CI, 3.08 to 9.98), which suggested that the majority of those with an incident PAD event had a low AAI by screening for months to years before significant clinical manifestations. Current smoking and male gender were also strongly associated with incident PAD.

For all analyses, specification of the AAI as a continuous versus categorical variable in the model yielded consistent results.

In a previous study, we showed cross-sectionally that CVD and its risk factors were associated with a stepwise decrease in the AAI below 1.0.[5] In the present study, we were able to evaluate the relationship of a decrease in AAI to total mortality in those with and without prevalent CVD at baseline (Figures 1 and 2). A striking increase in mortality was seen early in follow-up in the prevalent disease group at an AAI of <0.9. For participants with no prevalent disease at baseline, mortality rates were similar for those with an AAI <0.8 to those with an AAI of 0.8 to <0.9 after several years of follow-up. In addition, for those with no prevalent disease at baseline and a normal AAI, almost 80% of these older adults survived without cardiovascular morbidity (Figure 3). For each 0.1 decrement in the AAI below 1.0, event rates increased, which indicated a lack of a threshold for predicting mortality.

Discussion

The majority of total and cardiovascular deaths in older adults occur in those with either clinical or subclinical CVD. Although easily documented by the presence of a low AAI, PAD is quite often asymptomatic in older adults. Even in participants without a history of CVD and without symptoms of claudication, ≈10% of men and women >65 years old had an AAI <0.9.[5] Thus, the AAI, as a marker of PAD, can provide important information about subclinical atherosclerosis.

Clearly, participants with a history of prevalent, clinically manifested CVD would be at highest risk for mortality and recurrent events. Even within this group, a low AAI was associated with increased age- and gender-adjusted risk of total and CVD mortality and remained independently associated with CVD mortality but not with total mortality or MI with multivariate adjustment. Regardless of clinical manifestation, participants with a reduction of the AAI of <0.9 are likely to have diffuse, advanced atherosclerosis.

The magnitude of the risk related to a low AAI is similar to that found with the classification of participants with a more extensive battery of noninvasive tests, including echocardiography and carotid ultrasound.[15] Cross-sectional analysis in the Atherosclerosis Risk in Communities Study (ARIC) cohort shows that the prevalence of an AAI <0.9 (low AAI) is uncommon in middle-aged and younger people.[26] The associations with clinical and subclinical disease and the comparisons with angiography indicate that those with a low AAI have advanced significant atherosclerosis.[6–12]

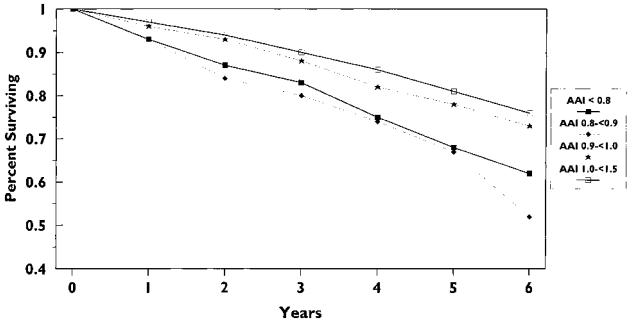

Figure 1. Kaplan-Meier survival for 1446 CHS participants with prevalent CVD, by categories of AAI level (AAI <0.8, n=258; AAI 0.8 to <0.9, n=101; AAI 0.9 to <1.0, n=193; AAI 1.0 to <1.5, n=894).

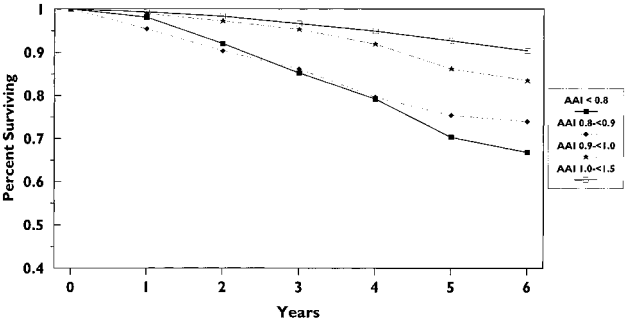

Figure 2. Kaplan-Meier survival for 4268 CHS participants at risk for incident CVD, by categories of AAI level (AAI <0.8, n=213; AAI 0.8 to <0.9, n=196; AAI 0.9 to <1.0, n=536; AAI 1.0 to <1.5, n=3323).

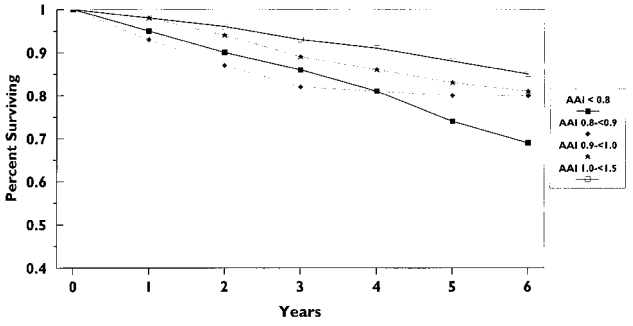

Figure 3. Kaplan-Meier survival from death or CVD morbidity for 4268 participants at risk for incident CVD at baseline by categories of AAI (AAI <0.8, n=213; AAI 0.8 to <0.9, n=196; AAI 0.9 to <1.0, n=536; AAI 1.0 to <1.5, n=3323).

The strong associations (2- to 3-fold hazard ratio) of a low AAI with total and CVD mortality, even in those without a history of CVD, confirm this.

Thus, the AAI is not a useful screening test for early disease; rather, it is a very specific test for advanced disease. Its sensitivity and specificity for CVD mortality are 30% and 91%, respectively. This compares with a sensitivity and specificity of 43% and 70%, respectively, for left ventricular hypertrophy by echocardiogram as a predictor of CVD events.[28] When calcium scores by electron-beam CT scan of the coronary arteries were reviewed to measure their ability to predict coronary events, a score threshold of 160 resulted in a sensitivity of 89% and specificity of 77%.[29] In CHS, participants with a low AAI had a >2-fold risk of total and CVD mortality, even after the exclusion of those with clinical CVD. The risk was attenuated somewhat but still statistically significant with adjustment for traditional risk factors. A low AAI is not highly sensitive for outcomes, but its predictive value is roughly comparable to having a history of prior CVD.

It has been suggested that the AAI might be used to screen and target older adults for more aggressive risk factor intervention. Clearly, it cannot be considered in isolation because an AAI >0.9 does not rule out the presence of atherosclerosis. One potential role for the AAI is its use in the elimination of ≈10% of those >65 years old with no history of CVD from undergoing more expensive and sensitive test procedures. Alternatively, it may be useful to combine it with information from the ECG and electron-beam CT scan; the combination of information about several vascular beds may be the most sensitive and specific method to describe the anatomic extent of disease. The AAI is essentially a screening-level assessment for anatomic PAD in the legs, and when <0.9, it is quite sensitive and specific for obstruction compared with a full vascular laboratory evaluation.[30] As a continuous variable, it must be remembered that AAI is a ratio of blood pressures and may also capture physiological information about systolic blood pressure and vascular stiffness. Nevertheless, when the AAI is used in older adults as a screening test with a cut point of 0.9, it also identifies a subgroup at higher risk for total and CVD mortality and is much less expensive and easier to interpret than methods that rely on vascular imaging, such as carotid duplex scanning.

The presence of a low AAI was associated with an increase in risk for all incident CVD morbidity and mortality except for stroke. In those at risk for incident CVD, the risk remained significantly elevated for total and CVD mortality, as well as CHF and PAD, but not for MI, angina, or stroke after multivariate adjustment. It may be that with longer follow-up, events would increase and CIs would narrow for other morbid events. It is also possible that the risk is highest in the short term and would attenuate with additional follow-up. These issues will be explored with further follow-up.

The association with CHF is interesting and may suggest that much of the CHF is related to atherosclerosis and perhaps myocardial ischemia. However, because the AAI is a ratio of systolic blood pressures, it may also be related to CHF as a measure of vascular stiffness. The diagnosis of CHF in the CHS cohort has been problematic in that it is often found in participants hospitalized for other reasons, such as chronic lung disease, pneumonia, arrhythmia, or postoperatively. Nevertheless, a preliminary report of CHF in this cohort shows that CHF is associated with myocardial ischemia, as well as left ventricular hypertrophy.[31]

The ability of a low AAI to predict hospitalization for symptomatic PAD is not surprising, because it is a screening test for atherosclerotic obstruction in the legs. Of note, the majority of these events occurred in those with a low AAI, yet some occurred in those with an AAI ≥0.9 at baseline. It is possible that obstruction developed over the years of follow-up or that occlusion occurred more suddenly. In addition, the cut point of 0.9 is arbitrary and will misclassify some participants with more mild atherosclerosis. Further analysis of the change over time and the types of procedures and symptoms in these individuals is ongoing. Caution must be used in the interpretation of these data, because only severe PAD identified by hospital records is included. Outpatient diagnoses of PAD in CHS included use of the AAI; thus, we could not make an unbiased assessment of its predictive value for outpatient events. Sensitivity and specificity of the AAI for PAD may be reduced if milder degrees of PAD had been included in the analyses.

The risk ratio for mortality in those with a low AAI was higher in blacks than whites, although the follow-up time was only ≈2 years for the majority of blacks in the CHS cohort. The black participants in CHS have been found to have more extensive clinical and subclinical atherosclerosis by multiple measures.[32] The relative merits of different risk classification strategies in this group will require longer follow-up.

Previous studies have demonstrated the relationship between PAD by various measures and mortality in populations including subjects with hyperlipidemia or systolic hypertension.[6–12] The RRs are similar in all of these studies. Previous studies, however, have not distinguished the risk of a low AAI for incident as opposed to recurrent CVD. Although the presence of a low AAI is strongly related to the presence of other clinical manifestations of CVD, a substantial proportion of older adults have no other clinical manifestations of CVD. The data demonstrate that the increased risk of CVD in those with low AAI is not solely related to the association of the AAI with clinically manifest CVD in these individuals. In addition, although a low AAI is associated with other cardiovascular risk factors,[5] its association with CVD events is strong regardless of the presence or absence of these other risk factors.

Although symptoms of claudication do not occur until the AAI is ≈0.8,[22] mortality risk appears to increase substantially

at an AAI <0.9. The majority of the participants in this study had moderate reductions in the AAI (0.8 to 0.9) that would not be identified by medical history or other components of a routine physical examination, such as pulse palpation. Of note, those with an AAI ≥1.0 were at low risk of death or cardiovascular morbidity. Nevertheless, CVD cannot be excluded by the presence of a normal AAI. The AAI is reduced when there is obstruction to blood flow in the legs; thus, it is essentially a marker of fairly advanced atherosclerosis. As an initial screen, it is quite specific for subsequent CVD or mortality in older adults. Sensitivity may be improved by a combination of risk factors and measures of subclinical atherosclerosis.[25] Follow-up of the CHS cohort for additional cardiovascular events will explore strategies that optimize the identification of older adults at high risk of CVD morbidity and mortality.

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