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A Propensity-Matched Study of the Association of Peripheral Arterial Disease with Cardiovascular Outcomes in Community-Dwelling Older Adults

Wilbert S. Aronow, MD, **Mustafa I Ahmed, MD**, **O. James Ekundayo, MBChB, DrPH**, **Richard M. Allman, MD**, and **Ali Ahmed, MD, MPH**
New York Medical College, Valhalla, NY (WSA), University of Alabama at Birmingham, Birmingham, AL (AA, MIA, OJE, RMA), and VA Medical Center, Birmingham, AL (AA, RMA)

Abstract

The association between peripheral arterial disease (PAD) and outcomes has not been studied in a propensity-matched population of community-dwelling older adults. We analyzed the public-use copy of the Cardiovascular Health Study (CHS) datasets to test the hypothesis that baseline PAD is associated with increased all-cause mortality and cardiovascular morbidity. Of the 5795 CHS participants, 5630 had data on baseline ankle-brachial index (ABI) and 767 had PAD defined as ABI <0.9. Propensity scores for PAD were calculated for each participant using 66 baseline covariates and were used to match 679 pairs of participants with and without PAD. Matched Cox regression models were used to estimate associations of PAD with outcomes during a median follow up of 7.5 years. Overall, 55% of matched participants died from all causes during 9958 person-years of follow-up. All-cause mortality occurred in 61% (rate, 8710/100,000 person-years) and 55% (rate, 6503/100,000 person-years of follow up) of participants respectively with and without PAD (matched hazard ratio {HR} when PAD was compared with no-PAD, 1.47; 95% confidence interval {CI}, 1.23–1.76; P<0.0001). Pre-match unadjusted, multivariable-adjusted and propensity-adjusted HR (95% CI) for PAD-associated all-cause mortality were 2.90 (2.61–3.21; P<0.0001), 1.53 (1.36–1.71; P<0.0001) and 1.57 (1.39–1.78; P<0.0001) respectively. Matched HR and 95% CI for PAD for incident heart failure and symptomatic PAD were respectively 1.32 (1.00–1.73; P=0.052) and 3.92 (3.92–7.21; P<0.0001). In conclusion, in a propensity-matched well-balanced population of community-dwelling older adults, baseline PAD was associated with increased all-cause mortality and cardiovascular morbidity.

Keywords

Peripheral artery disease; mortality; propensity score

Peripheral arterial disease (PAD) is a manifestation of systemic atherosclerosis and has been shown to be associated with poor outcomes.[1–5] However, most of these studies were based on a small number of select high risk patients and used traditional regression-based risk-

Correspondence: Ali Ahmed, MD, MPH, University of Alabama at Birmingham, 1530 3rd Avenue South, CH-19, Suite 219, Birmingham AL 35294-2041. Telephone: 1-205-934-9632; Fax: 1-205-975-7099; aahmed@uab.edu.

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adjustments. We used a public-use copy of the Cardiovascular Health Study (CHS) data obtained from the National Heart, Lung and Blood Institute (NHLBI) to test the hypothesis that baseline PAD is associated with increased all-cause mortality and cardiovascular morbidity in a propensity-matched population of community-dwelling older adults.

METHODS

CHS is an NHLBI-funded ongoing, community-based, epidemiologic study of 5888 participants, ≥65 years, from four counties in North Carolina, California, Maryland, and Pittsburgh, Pennsylvania. The details of the rationale, design and implementation of the CHS have been previously reported.[6] Briefly, a recruitment of 5201 participants (1989–1990) was supplemented by a second cohort of 687 African-Americans (1992–1993). The objective of the CHS was to study cardiovascular morbidity and mortality in older adults. Of the 5888 original CHS participants, 5795 consented to be included in the de-identified public-use copy of the dataset, and of these 5630 with valid data on ankle-brachial index (ABI) were included in the current analysis.

Baseline PAD, defined by an ABI of <0.9, was present in 767 participants. Baseline seated blood pressure was measured with a random-zero sphygmomanometer.[7] Data on socio-demographic, clinical, sub-clinical, and laboratory variables were collected at baseline and have been previously described in details.[6,8] Missing values for continuous variables were imputed based on values predicted by age, sex and race. The primary outcome for the current analysis is all-cause mortality. Secondary outcomes included various cardiovascular morbidities. The detail of the process of adjudication of cardiovascular events in CHS is well-documented in the literature.[9,10]

Propensity scores for baseline PAD were estimated for each of the 5630 participants using a non-parsimonious multivariable logistic regression model using 66 baseline covariates displayed in Figure 1.[11,12] We matched 679 pairs of participants with and without PAD using a greedy matching protocol described elsewhere.[13,14] Absolute standardized differences for all 66 covariates were estimated to assess pre-match imbalances and post-match balances achieved and results were presented as Love plot.[13] An absolute standardized differences of 0% indicates no bias, and values <10% suggest inconsequential bias.[13,15] Matched Cox proportional hazard analyses were used to determine the association of PAD with outcomes during 7.5 years of median follow up. Homogeneity of the association of PAD and all-cause mortality was assessed by subgroup analyses. All statistical tests were two-sided, and tests with p-value <0.05 were considered significant. SPSS for Windows (Version 15) was used for all data analysis.[16]

RESULTS

Overall, matched participants had a mean (±SD) age of 76 (±6) years, 54% were women, and 25% were non-whites. Imbalances in baseline characteristics before matching and balances achieved after matching between patients with and without PAD are displayed in Table 1 and Figure 1. After matching, absolute standardized differences for all measured covariates were <10% (most were <5%), suggesting substantial significant covariate balance across the groups (Figure 1). Of the 679 participants with PAD, 666 had mild to moderate PAD (ABI 0.40–0.89) and only 13 had severe PAD (ABI <0.40).

During 9958 person-years of follow-up 753 (55%) participants died from all causes. All-cause mortality occurred in 61% (rate, 8710/100,000 person-years) and 50% (rate, 6503/100,000 person-years of follow up) of participants respectively with and without PAD (matched HR, 1.47; 95% CI, 1.23–1.76; P<0.0001; Figure 2 and Table 2). When ABI was

used as a continuous variable, every one-tenth of an increase in ABI (e.g. from 0.7 to 0.8 or from 1.3 to 1.4) was associated with a decreased all-cause mortality (HR, 0.94; 95% CI, 0.91–0.97; P<0.0001). The association between PAD and all-cause mortality was homogeneous across a wide spectrum of participants (Figure 3). Associations of PAD with other outcomes in the matched cohort are displayed in Table 2.

In the pre-match cohort of 5630 participants, 2001 (36%) died from all causes, with 63% and 31% respectively in those with and without PAD (unadjusted HR, 2.90; 95% CI, 2.61–3.21; P<0.0001). Multivariable-adjusted and propensity-adjusted hazard ratios for all-cause mortality were respectively 1.53 (95% CI, 1.36–1.71; P<0.0001) and 1.57 (95% CI, 1.39–1.78; P<0.0001; Table 3). Associations of PAD with other outcomes in the pre-match cohort are displayed in Table 3.

DISCUSSION

The findings from the current analysis demonstrate that the prevalence of PAD in community dwelling older adults was relatively high, that PAD was mostly mild to moderate in severity and asymptomatic in nature, and that baseline PAD was associated with all-cause mortality and cardiovascular morbidity. To the best of our knowledge, this is the first demonstration of such associations in a large population of propensity matched, community dwelling older adults in which participants with and without PAD were well balanced in 66 measured baseline covariates.

The observed associations between PAD and poor outcomes can be explained by a direct effect of PAD, a confounding by measured covariates such comorbidities associated with PAD, or a confounding by an unmeasured covariate. PAD is a manifestation of systemic atherosclerosis and as such patients with PAD are more likely to have other manifestations of atherosclerosis.[17] In fact, before matching, more participants with PAD had coronary artery disease, hypertension, diabetes, heart failure and stroke (Table 1). However, after matching, participants with and without PAD were well-balanced in 66 measured baseline covariates including all of the above cardiovascular comorbidities and risk factors. Therefore, the increased PAD-associated mortality observed in the current analysis may not be explained by differences in baseline prevalence of atherosclerotic diseases. However, it is possible that atherosclerosis was more widespread and severe in those with PAD than in those without. Among patients undergoing coronary angiography for suspected coronary artery disease, compared to those without PAD, those with PAD had a higher prevalence of obstructive coronary artery disease including left main and 3- or 4-vessel disease.[18] It is also possible that atherosclerosis in participants with PAD progressed at much faster rate than in those without PAD. Therefore, increased PAD-associated mortality may have mediated via atherosclerotic diseases in other vascular beds.

Except for incident symptomatic PAD, among our matched participants, PAD was not associated with incident cardiovascular morbidity. However, directions of these associations were generally positive. The lack of statistically significant associations was likely due to the small sample size of the matched cohort. Further, propensity matching generally provides more conservative estimates than those obtained from multivariable-adjusted or propensity-adjusted models. In fact, the multivariable-adjusted or propensity-adjusted associations of PAD with all incident cardiovascular morbidity were significant in our pre-match cohort. This suggests that increased PAD-associated mortality was at least in part mediated via increased atherosclerotic cardiovascular morbidity. Further, the incident cardiovascular morbidity does not include fatal cases, and it is possible that those with PAD may have experienced more fatal cardiovascular atherosclerotic events.

To the best of our knowledge this is the first report of an association of PAD with all-cause mortality and cardiovascular morbidity in a propensity-matched population of community-dwelling older adults. There are several important clinical and public health implications of these findings. These findings suggest that although PAD is a marker of systemic atherosclerosis, its presence may indicate more severe and widespread atherosclerosis and an eventual association with increased mortality. This is important as PAD was asymptomatic in over 90% of community-dwelling older adults, and thus may be considered a silent killer often unappreciated by clinicians and public health experts. Asymptomatic PAD is known to be associated with poorer functional performance, poorer quality of life, and more adverse calf muscle characteristics compared with persons with intermittent claudication.[19] However, our findings suggest that it also has an independent association with all-cause mortality and major cardiovascular morbidity. These findings also highlight the importance of prevention, early detection and treatment of PAD in older adults.

Several limitations of our study must be acknowledged. We had no data on the extent and severity of PAD. Large-vessel, but not small-vessel PAD has been shown to be associated with increased mortality.[3,20] This may have underestimated the association of PAD and mortality in our study. Patients without PAD at baseline may have developed PAD during follow up. This regression dilution may also have underestimated the PAD-mortality association observed in our study.[21] We were able to match 89% of participants with PAD and any effects due to loss of participants during matching are likely to be minimal. Further, we were able to replicate our key findings using traditional risk-adjustment approaches in the pre-match cohort. Confounding due to unmeasured covariate is possible. However, for an unmeasured covariate to become a confounder it must be near-perfect predictor of mortality, must not be strongly correlated with any of the 66 covariates used in our study, and also be associated with PAD. In conclusion, we demonstrate that among community-dwelling older adults, PAD is an asymptomatic disease associated with high prevalence of other atherosclerotic cardiovascular comorbidities. However, when all of these differences were balanced after rigorous propensity matching, baseline PAD was independently associated with increased mortality. Ankle-brachial index should be routinely assessed in community-dwelling older adults to identify those with PAD, and these patients should be appropriately treated.[22,23]

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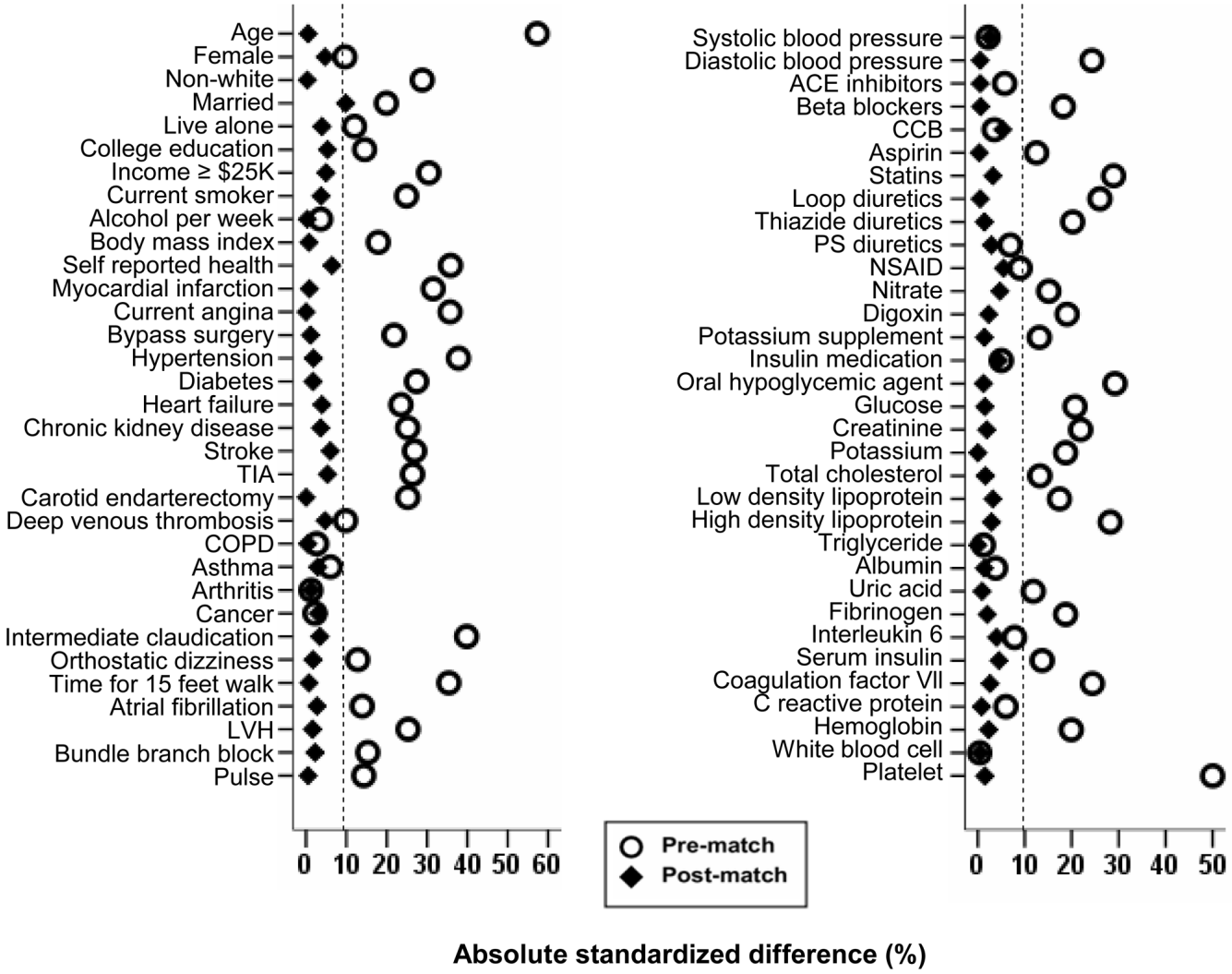

Figure 1.

Love plot for absolute standardized differences for 66 covariates before and after propensity score matching between participants with and without peripheral arterial disease. ACE= angiotensin-converting enzyme; CCB=calcium channel blocker; COPD=chronic obstructive pulmonary disease; LVH= left ventricular hypertrophy; NSAID=non-steroidal anti inflammatory drug; PS=potassium- sparing; TIA=transient ischemic attack

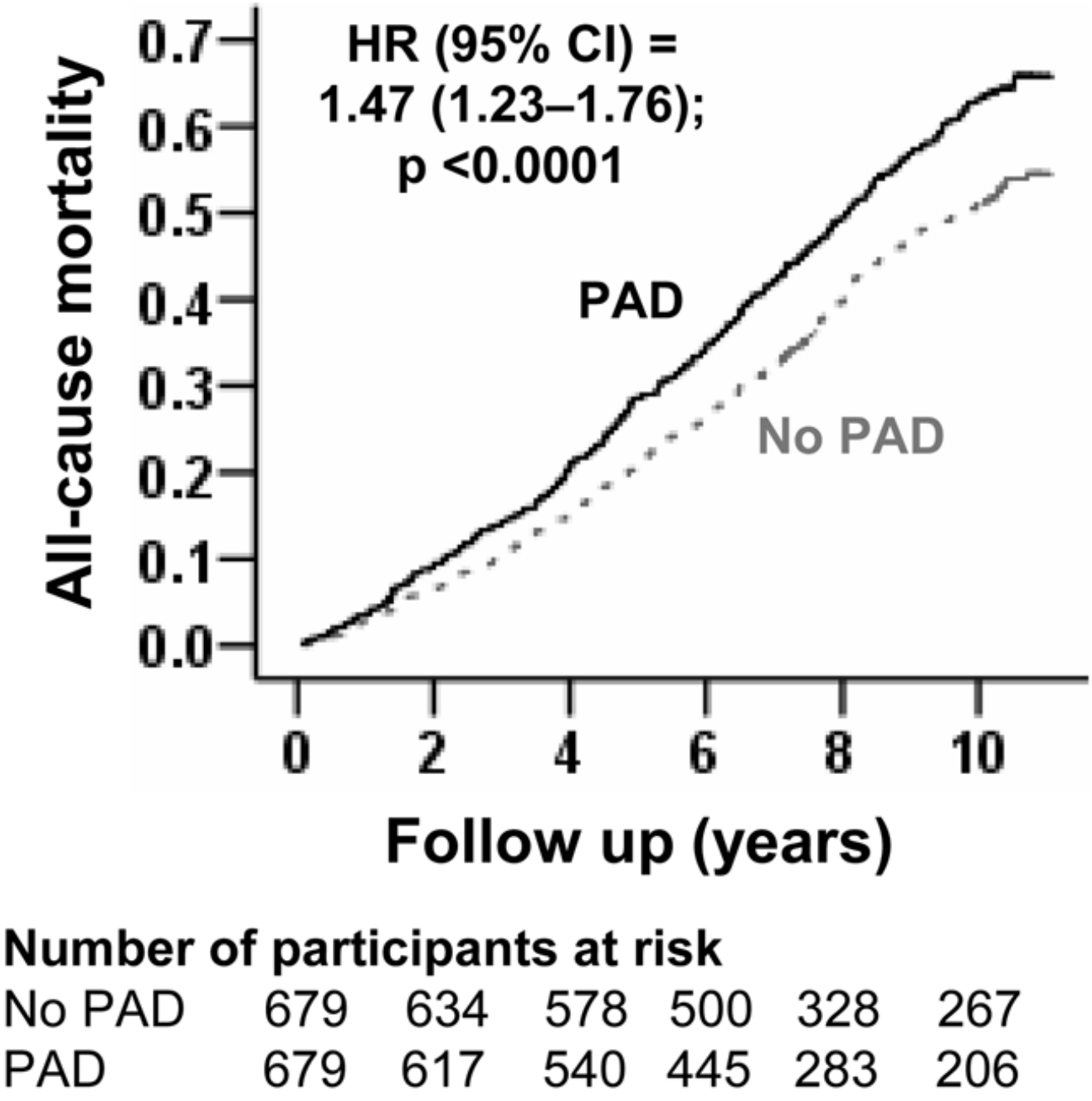

Figure 2.
Kaplan-Meier plot for all-cause mortality by peripheral arterial disease (PAD)

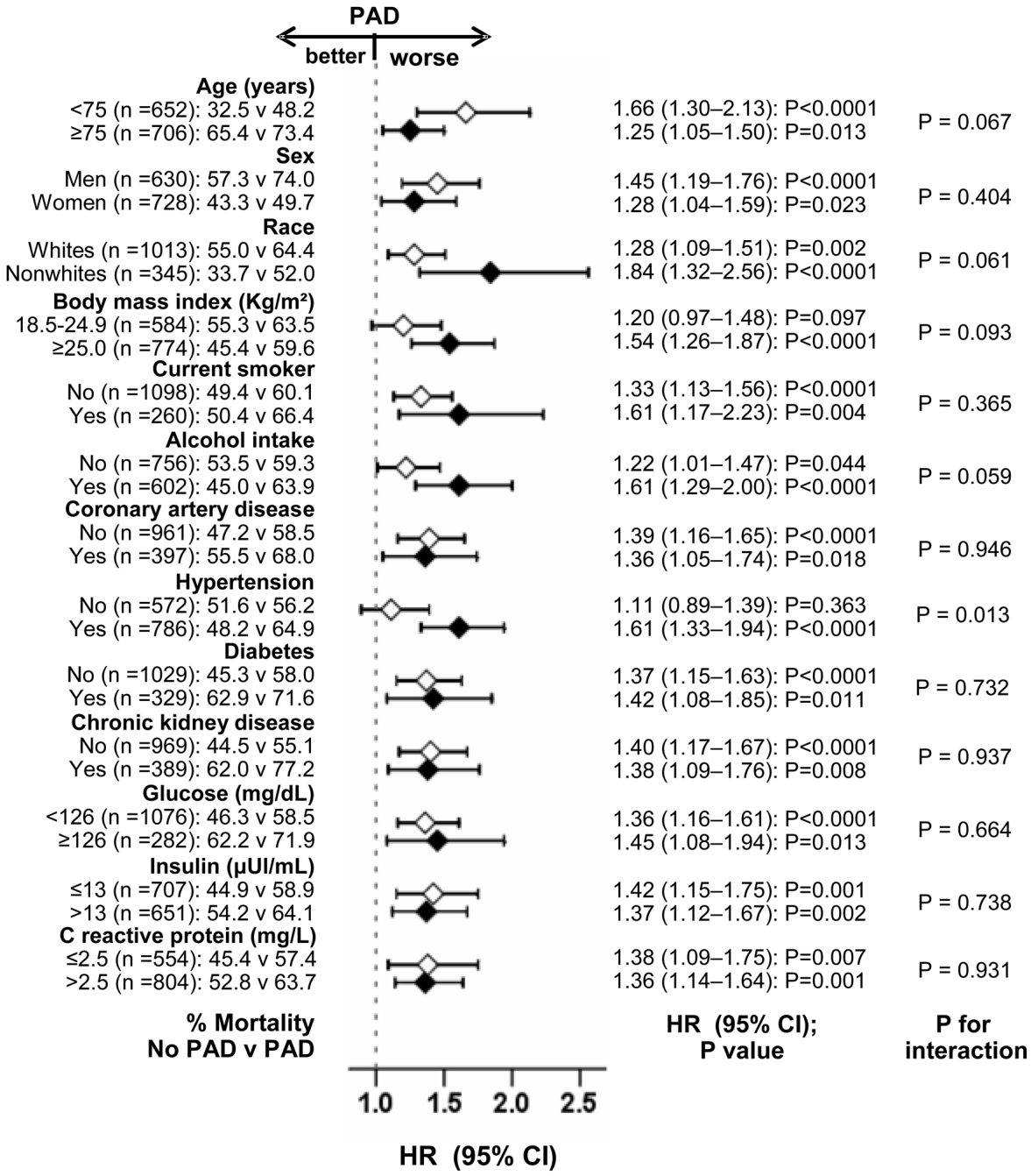

Figure 3.

Hazard ratio (HR) and 95% confidence interval (CI) for all-cause mortality associated with peripheral artery disease (PAD) in subgroups of patients. ACE=angiotensin-converting enzyme; HF=heart failure

Table 1

Baseline characteristics, by peripheral artery disease (PAD)*, before and after propensity score matching

n (%) or mean (±SD)	Before matching			After matching		
	No PAD (n = 4863)	PAD (n = 767)	p value	No PAD (n = 679)	PAD (n = 679)	p value
Age, years	73 (±5)	76 (±6)	<0.0001	76 (±6)	76 (±6)	0.924
Female	2,807 (58%)	406 (53%)	0.013	372 (55%)	356 (52%)	0.414
Non-white	700 (14%)	198 (26%)	<0.0001	172 (25%)	173 (26%)	0.950
Married	3,298 (68%)	447 (58%)	<0.0001	365 (54%)	398 (59%)	0.080
Living alone	583 (12%)	124 (16%)	0.002	119 (18%)	109 (16%)	0.469
College or higher education	2,132 (44%)	282 (37%)	<0.0001	228 (34%)	245 (36%)	0.362
Income ≥ $25 thousand	1,850 (38%)	185 (24%)	<0.0001	153 (23%)	167 (25%)	0.372
Current smoker	525 (11%)	151 (20%)	<0.0001	135 (20%)	125 (18%)	0.491
Alcohol, drinks per week	2.5 ± 6.3	2.3 ± 6.8	0.345	2.2 ± 6.4	2.2 ± 6.8	0.963
Body mass index, kg/m^2	27 (±4)	26 (±4)	<0.0001	26 (±4)	26 (±4)	0.902
Self-reported fair to poor general health	1099 (23%)	298 (39%)	<0.0001	269 (40%)	248 (37%)	0.264
Prior myocardial infarction	392 (8%)	143 (19%)	<0.0001	109 (16%)	111 (16%)	0.883
Current angina pectoris	825 (17%)	246 (32%)	<0.0001	195 (29%)	195 (29%)	1.000
Heart failure	177 (4%)	72 (9%)	<0.0001	47 (7%)	54 (8%)	0.469
Hypertension	2,032 (42%)	463 (60%)	<0.0001	390 (57%)	396 (58%)	0.783
Diabetes mellitus	708 (15%)	195 (25%)	<0.0001	167 (25%)	162 (24%)	0.752
Atrial fibrillation by EKG	110 (2%)	37 (5%)	<0.0001	36 (5%)	32 (5%)	0.622
LVH by EKG	188 (4%)	79 (10%)	<0.0001	56 (8%)	59 (9%)	0.771
Transient ischemic attack	235 (5%)	93 (12%)	<0.0001	65 (10%)	76 (11%)	0.374
Stroke	156 (3%)	75 (10%)	<0.0001	48 (7%)	59 (9%)	0.270
Intermittent claudication	34 (0.7%)	70 (9.1%)	<0.0001	31 (5%)	36 (5%)	0.534
Chronic obstructive pulmonary disease	631 (13%)	93 (12%)	0.562	85 (13%)	84 (12%)	0.935
Chronic kidney disease	956 (20%)	234 (31%)	<0.0001	200 (30%)	189 (28%)	0.548
Cancer	697 (14%)	104 (14%)	0.617	97 (14%)	90 (13%)	0.637
Medications						
ACE inhibitors	344 (7%)	100 (13%)	<0.0001	84 (12%)	79 (11.6%)	0.677
Beta blockers	610 (13%)	112 (15%)	0.117	100 (15%)	102 (15%)	0.879

n (%) or mean (±SD)	Before matching			After matching		
	No PAD (n = 4863)	PAD (n = 767)	p value	No PAD (n = 679)	PAD (n = 679)	p value
Calcium channel blockers	594 (12%)	163 (21%)	<0.0001	136 (20%)	129 (19%)	0.633
Aspirin	162 (3%)	48 (6%)	<0.0001	41 (6%)	34 (5%)	0.409
Statin	98 (2%)	25 (3.3%)	0.033	26 (4%)	21 (3%)	0.463
Loop diuretics	296 (6%)	87 (11%)	<0.0001	70 (10%)	66 (10%)	0.719
Thiazide diuretics	514 (11%)	111 (15%)	0.002	91 (13%)	93 (14%)	0.874
Potassium sparing diuretics	39 (0.8%)	9 (1.2%)	0.290	7 (1%)	8 (1%)	0.803
NSAID	454 (12%)	237 (16%)	<0.0001	88 (13%)	88 (13%)	1.000
Pulse, beats per minute	68 ± 11	69 ± 12	<0.0001	69± 12	69 ± 12	0.925
Average blood pressure (mm Hg)						
Systolic	135 ± 21	146 ± 23	<0.0001	144 ± 24	145 ± 23	0.787
Diastolic	71 ± 11	71 ± 13	0.912	71 ± 12	71 ± 13	0.936
Serum creatinine, mg/dL	0.95 ± 0.35	1.08 ± 0.57	<0.0001	1.06 ± 0.49	1.06 ± 0.52	0.828
Serum glucose, mg/dL	109 ± 34	118 ± 46	<0.0001	117 ± 43	116 ± 45	0.789
Serum insulin, mcU/ml	15 ± 23	20 ± 27	<0.0001	21 ± 38	21 ± 45	0.956
Serum potassium, mEq/L	4.16 ± 0.37	4.18 ± 0.41	0.177	4.19 ± 0.39	4.18 ±0.41	0.422
Total cholesterol, mg/dL	210 ± 38	216 ± 43	<0.0001	214 ± 41	214 ± 42	0.795
Triglyceride, mg/dL	138 ± 75	145 ± 85	0.015	148 ± 95	143 ± 79	0.315
Albumin, g/dL	3.99 ± 0.29	3.98 ± 0.29	0.077	3.99 ± 0.29	3.98 ± 0.29	0.592
Fibrinogen, mg/dL	317 ± 72	337 ± 84	<0.0001	334 ± 81	334 ± 83	0.932
C reactive protein, mg/dL	4.5 ± 8	6.1 ± 9	<0.0001	5.9 ± 11	5.9 ± 9	0.917
Hemoglobin, gram/dL	14.03 ± 1.40	13.94 ± 1.50	0.132	13.96 ± 1.81	13.97 ± 1.49	0.926
White blood cells, $10^3/\mu L$	6.22 ± 1.93	6.82 ± 2.88	<0.0001	6.59 ± 2.35	6.59 ± 1.87	0.927
Platelets, $10^3/\mu L$	244 ± 64	245 ± 80	0.530	243 ± 68	245 ± 82	0.639

*PAD was defined as ankle brachial index <0.9

ACE=angiotensin converting enzyme, EKG=electrocardiography, LVH=left ventricular hypertrophy, MI=myocardial infarction, NSAID=non-steroidal anti-inflammatory drug

Table 2

Peripheral artery disease (PAD)* and outcomes in the matched cohort

Outcomes	Rate, per 100,000 person-years (Events/total follow up years)		Absolute rate difference** (per 100,000 person-years)	Matched hazard ratio (95% confidence interval)	P value
	No PAD (n = 679)	PAD (n = 679)			
All-cause mortality	6503(337/5182)	8710 (416/4776)	+ 2207	1.47 (1.23–1.76)	<0.0001
Incident symptomatic PAD	527(27/5124)	1447 (65/4492)	+ 920	3.92 (2.13–7.21)	<0.0001
Incident heart failure	2971(145/4880)	4152 (180/4335)	+ 1181	1.32 (1.00–1.73)	0.052
Incident acute myocardial infarction	1423(71/4989)	1995 (91/4561)	+ 572	1.26 (0.88–1.80)	0.206
Incident angina pectoris	2064(100/4845)	2581 (114/4417)	+ 517	1.18 (0.85–1.63)	0.321
Incident stroke	1860(92/4946)	2401 (108/4498)	+ 541	1.35 (0.96–1.89)	0.088
Incident transient ischemic attack	510(26/5094)	514 (24/4670)	+ 4	1.00 (0.54–1.86)	1.000

* PAD was defined as ankle brachial index <0.9

** Absolute rate differences were calculated by subtracting the rates of events in the non-PAD group from those in the PAD group (before values were rounded)

Table 3

Peripheral artery disease* and outcomes in the pre-match cohort

Outcomes	Hazard ratio (95% confidence interval)	P value
All-cause mortality		
Unadjusted	2.90 (2.61–3.21)	<0.0001
Propensity-adjusted	1.57 (1.39–1.78)	<0.0001
Multivariable-adjusted	1.53 (1.36–1.71)	<0.0001
Incident symptomatic peripheral artery disease		
Unadjusted	6.40 (4.73–8.65)	<0.0001
Propensity-adjusted	3.78 (2.63–5.42)	<0.0001
Multivariable-adjusted	3.94 (2.84–5.46)	<0.0001
Incident heart failure		
Unadjusted	2.83 (2.43–3.31)	<0.0001
Propensity-adjusted	1.59 (1.32–1.91)	<0.0001
Multivariable-adjusted	1.49 (1.26–1.71)	<0.0001
Incident acute myocardial infarction		
Unadjusted	2.18 (1.75–2.72)	<0.0001
Propensity-adjusted	1.65 (1.28–2.13)	<0.0001
Multivariable-adjusted	1.72 (1.35–2.17)	<0.0001
Incident stroke	1.35 (0.96–1.89)	0.088
Unadjusted	2.12 (1.74–2.58)	<0.0001
Propensity-adjusted	1.36 (1.08–1.71)	0.009
Multivariable-adjusted	1.30 (1.06–1.60)	0.013

* Peripheral artery disease was defined as ankle brachial index <0.9

** Absolute rate differences were calculated by subtracting the rates of new-onset heart failure in the high serum uric acid group from the rate of new-onset heart failure in the normal serum uric acid group (before values were rounded)