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ORIGINAL RESEARCH

Association of 6-Minute Walk Performance and Physical Activity With Incident Ischemic Heart Disease Events and Stroke in Peripheral Artery Disease

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***Background*—**We determined whether poorer 6-minute walk performance and lower physical activity levels are associated with higher rates of ischemic heart disease (IHD) events in people with lower extremity peripheral artery disease (PAD).

***Methods and Results*—**Five hundred ten PAD participants were identified from Chicago-area medical centers and followed prospectively for 19.0±9.5 months. At baseline, participants completed the 6-minute walk and reported number of blocks walked during the past week (physical activity). IHD events were systematically adjudicated and consisted of new myocardial infarction, unstable angina, and cardiac death. For 6-minute walk, IHD event rates were 25/170 (14.7%) for the third (poorest) tertile, 10/171 (5.8%%) for the second tertile, and 6/169 (3.5%) for the first (best) tertile (P=0.003). For physical activity, IHD event rates were 21/154 (13.6%) for the third (poorest) tertile, 15/174 (8.6%) for the second tertile, and 5/182 (2.7%) for the first (best) tertile (P=0.001). Adjusting for age, sex, race, smoking, body mass index, comorbidities, and physical activity, participants in the poorest 6-minute walk tertile had a 3.28-fold (95% CI 1.17 to 9.17, P=0.024) higher hazard for IHD events, compared with those in the best tertile. Adjusting for confounders including 6-minute walk, participants in the poorest physical activity tertile had a 3.72-fold (95% CI 1.24 to 11.19, P=0.019) higher hazard for IHD events, compared with the highest tertile.

***Conclusions*—**Six-minute walk and physical activity predict IHD event rates in PAD. Further study is needed to determine whether interventions that improve 6-minute walk, physical activity, or both can reduce IHD events in PAD. **(*J Am Heart Assoc*. 2015;4: e001846 doi: 10.1161/JAHA.115.001846)**

Key Words: intermittent claudication • peripheral vascular disease

Lower extremity peripheral artery disease (PAD) affects 8 million people in the United States and >200 million people worldwide.[1,2] People with PAD have higher cardiovascular event rates compared with people without PAD, even after adjustment for confounders.[3,4] People with PAD have poorer 6-minute walk performance, lower physical activity levels, and faster decline in the 6-minute walk test than do people without PAD.[5–8] The prognostic significance of poorer 6-minute walk performance and lower physical activity levels among people with PAD is not fully delineated.

We studied associations of 6-minute walk performance and physical activity levels with ischemic heart disease (IHD) events in people with PAD. We hypothesized that poorer 6-minute walk performance and lower physical activity levels at baseline, respectively, would be associated with higher rates of IHD events in people with PAD. We also studied whether poorer 6-minute walk was associated with increased rates of IHD events, even after controlling for physical activity, and whether lower physical activity levels were associated with increased rates of IHD events, even after adjustment for 6-minute walk performance.

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Methods

Overview of the BRAVO Study

Methods of the BRAVO (Biomarker Risk Assessment in Vulnerable Outpatients) Study have been reported.[9] The

primary aim was to determine whether hemostatic and inflammatory biomarker levels increase acutely during the weeks and months leading up to an IHD event. In the BRAVO Study, a cohort of men and women with PAD were recruited and followed prospectively for up to 3 years to identify new IHD events. The current analyses focus on associations of baseline 6-minute walk and physical activity levels with subsequent rates of IHD events.

The institutional review board at Northwestern University and all participating sites approved the protocol. All participants provided written, informed consent. Enrollment occurred between September 2009 and September 2012. Follow-up continued through January 2013.

Recruitment

We identified patients with mild to severe PAD from lists of consecutive patients diagnosed with PAD in noninvasive vascular laboratories or vascular surgery practices from the following 6 medical centers in Chicago: Northwestern Medical Center, Rush Medical Center, University of Chicago Medical Center, Mount Sinai Hospital, Saint Joseph Hospital, and Jesse Brown Veterans Affairs Medical Center. Potential participants with PAD received a mailed recruitment letter, after permission to contact them was granted by their physician. We telephoned potential participants who did not respond to recruitment mailings and invited them to participate.

Inclusion and Exclusion Criteria

The inclusion criterion was an ankle-brachial index (ABI) <0.90. Individuals with an ABI ≥0.90 at baseline with evidence of PAD from an accredited noninvasive vascular laboratory or documentation of lower extremity revascularization for PAD were also eligible. Exclusion criteria and justification for each criterion have been reported[9] and are summarized briefly here. Potential participants with an IHD or cerebrovascular event within 6 months before enrollment and those with a history of inflammatory arthritis, recently diagnosed cancer, or recent unintentional weight loss were excluded. People unable to return for follow-up testing, with significant communication difficulty or cognitive impairment, and those living >40 miles from the medical center who refused regular medical center visits were excluded. Potential participants with heart transplant surgery, major surgery in the previous 3 months, and those enrolled in clinical trials were excluded.

Baseline and Follow-up Data Collection

Baseline measures included the ABI, medical history, phlebotomy, a resting 12-lead electrocardiogram (ECG), and height and weight for calculating body mass index (BMI). After baseline testing, we asked participants to return every 2 months. At each follow-up visit, participants underwent an ECG and questionnaire administration to identify new hospitalizations. We made home visits to participants unwilling or unable to attend a follow-up visit. If a home visit was refused, we called participants to obtain information about hospitalizations.

Baseline Measures

Baseline comorbidities

We ascertained and confirmed baseline comorbidities using patient-report obtained from questionnaire administration, medical record review, medication use, and results of a primary care physician questionnaire. We entered these data into comorbidity algorithms, developed and validated by the Women's Health and Aging Study,[10] to ascertain and confirm the presence of baseline comorbidities including diabetes, angina, heart failure, pulmonary disease, history of myocardial infarction (MI), and cancer. Symptomatic angina at baseline was defined as exertional chest pain that did not begin at rest, that resolved within 10 minutes of rest, or that resolved with nitroglycerin.

Ankle-brachial index

We used a hand-held Doppler probe (Nicolet Vascular Pocket Dop II) to measure systolic blood pressures after the participant rested supine for 5 minutes. Measured pressures were right brachial, dorsalis pedis, and posterior tibial arteries and left dorsalis pedis, posterior tibial, and brachial arteries. Each pressure was measured twice. The ABI was calculated by dividing average pressures in each leg by the average of the 4 brachial pressures.[8,9,11]

Six-minute walk test

We measured the 6-minute walk distance at baseline. Following a standardized protocol,[12–14] participants walked up and down a 100-foot hallway for 6 minutes after instructions to cover as much distance as possible. Participants were allowed to stop, but timing continued while they were stopped. The total distance completed during the 6 minutes was recorded. Available evidence suggests there is not a learning effect for the 6-minute walk among people with PAD.[12]

Physical activity

Physical activity level was obtained at baseline, using a questionnaire derived from the Harvard Alumni Activity Survey and validated in the Cardiovascular Health Study and the Women's Health and Aging Study.[15–17] The physical activity

questionnaire asked, "During the last week, how many city blocks or their equivalent did you walk? Let 12 city blocks equal 1 mile."[18,19]

IHD Events

The primary outcome was the combined outcome of fatal and nonfatal IHD events. Nonfatal IHD events were defined as hospitalization for acute MI, hospitalizations for unstable angina, or new ECG findings consistent with MI obtained during study visits. We obtained medical records for hospitalizations reported during follow-up. Two adjudicators reviewed medical records that mentioned angina or chest pain, reported elevated coronary enzymes, or had a discharge diagnosis consistent with angina or MI. When the 2 primary adjudicators disagreed, a third adjudicator reviewed the case, and the outcome was determined by discussion and consensus.

Adjudicating hospitalizations for MI or unstable angina

Hospitalization for MI was adjudicated using criteria established by the Atherosclerosis Risk In Communities (ARIC) and Multi-Ethnic Studies of Atherosclerosis (MESA) studies.[20,21] We required 2 of the following 3 criteria for hospitalized acute MI: (1) chest pain, (2) abnormal ECG consistent with an MI (ST-segment elevation, new left bundle branch block, new Q waves), and (3) abnormal cardiac enzymes (troponin >2 times the upper limit of normal) consistent with an MI.

We used criteria from the MESA and Lifestyle Interventions and Independence for Elders (LIFE) studies [21,22] to adjudicate unstable angina. Unstable angina was defined as "nonelective admission to the hospital for acute angina that is not codable as definite or probable MI." Hospital admission for IHD symptoms was required with at least 1 of the following: (1) treatment with nitrates, heparin, or β-blockers; (2) coronary revascularization during the hospital stay; (3) ≥70% obstruction of any coronary artery identified during the hospital stay; (4) an ECG showing horizontal or down-sloping ST depression or abnormal ST elevation >1 mm and these findings were present only during chest pain; and (5) a cardiac stress test consistent with ischemia.

Adjudicating IHD deaths

IHD death consisted of definite fatal MI, definite coronary heart disease death, and possible coronary heart disease death.[9] All 3 types of death required the absence of known nonischemic or noncardiac causes of death.

Adjudicating silent MIs

All participants underwent an ECG at each follow-up visit (ie, every 2 months). Two board-certified cardiologists reviewed each ECG to identify new Q waves using methods from the Cardiovascular Health Study (CHS).[23] Participants with new Q waves on their ECG during follow-up (definite or probable) were classified as an IHD event. Discrepancies were resolved by discussion with a third board-certified cardiologist.

Adjudication of stroke

We used criteria from the MESA and LIFE studies to adjudicate stroke.[21,22] Stroke was defined as a hospitalization with the following criteria: (1) acute onset of neurologic impairment not attributable to intracranial mass, (2) neurologic symptoms persisting >24 hours, and (3) a new finding on CT or MRI consistent with the neurologic symptoms.

Statistical Analyses

We compared baseline characteristics between PAD participants with versus those without an IHD during follow-up and across baseline tertiles of 6-minute walk performance and physical activity level, respectively, using general linear models for continuous variables and χ^2 tests for categorical variables. We selected tertiles for study rather than smaller groups of participants (ie, quartiles or quintiles) because of the relatively small number of outcomes. We performed proportional hazards analyses to compare IHD event rates across baseline tertiles of 6-minute walk performance, after adjustment for age, sex, race, comorbidities (diabetes, cancer, pulmonary disease, angina, MI, heart failure and stroke), cigarette smoking status, and BMI. We repeated these analyses with additional adjustment for physical activity. Similarly, we performed proportional hazards analyses to compare IHD event rates across baseline tertiles of physical activity, after adjustment for age, sex, race, comorbidities (diabetes, cancer, pulmonary disease, angina, MI, heart failure, and stroke), cigarette smoking, and BMI. We repeated these analyses with additional adjustment for 6-minute walk. We repeated each set of analysis for the combined outcome of IHD plus stroke and separately for the outcome of stroke. Analyses were repeated, entering the 6-minute walk and physical activity level as continuous variables.

Some PAD participants had an ABI >0.90 at baseline but were eligible for the study because they had a history of lower extremity revascularization or evidence of PAD from an accredited noninvasive vascular laboratory. To determine the relative associations of 6-minute walk, physical activity level, and ABI with IHD events, we repeated analyses among participants with a baseline ABI <0.90. Associations were also repeated among PAD participants with versus without a history of coronary heart disease at baseline.

Analyses were performed using SAS statistical software (version 9.4, SAS Institute Inc).

Table 1. Characteristics of Participants With PAD According to Whether They Experienced an IHD Event During Follow-up

	Total (N=510)	Participants Without IHD Events (n=469)	Participants With IHD Events (n=41)	*P* Value
Age, y	68.8 (10.1)	68.8 (10.0)	69.3 (11.2)	0.760
Ankle-brachial index*	0.65 (0.14)	0.66 (0.14)	0.60 (0.14)	0.036
Body mass index, kg/m^2	29.4 (5.9)	29.3 (5.8)	31.0 (6.6)	0.082
Male sex, %	65.3	65.5	63.4	0.792
African American race, %	34.1	33.7	39.0	0.490
Current/former smoker, %	86.5	87.0	80.5	0.243
Diabetes, %	42.8	42.4	46.3	0.627
Angina, %	23.1	21.9	36.6	0.033
Myocardial infarction, %	18.0	16.8	31.7	0.018
Stroke, %	19.0	18.6	24.4	0.361
Hypertension, %	88.8	87.9	100.0	0.009
Cancer, %	18.8	18.8	19.5	0.906
Pulmonary disease, %	37.7	36.9	46.3	0.231
6-Minute walk (ft) baseline	1168.2 (368.0)	1187.8 (362.3)	943.2 (361.5)	<0.0001
Physical activity level (blocks walked in the past week)	24.1 (35.8)	25.2 (36.6)	11.9 (21.2)	0.022

PAD indicates peripheral artery disease; IHD, ischemic heart disease; ABI, ankle-brachial index.
*ABI comparisons were performed within the 361 PAD participants with ABI values <0.90. The remaining PAD participants were eligible based on a medical record–documented history of lower extremity revascularization or evidence of PAD from an accredited noninvasive vascular laboratory.

Results

Of 595 participants enrolled in the BRAVO Study, 510 (86%) completed the 6-minute walk at baseline and were included in analyses. Of the remainder, 14 (2.4%) were lost to follow-up, 7 (1.2%) refused the 6-minute walk because of insufficient time at their visit, 34 (5.7%) were unable to complete the test due to health problems or safety concerns, 12 (2.0%) had an amputation, severe paralysis, or were wheelchair bound, 7 (1.2%) developed dyspnea or chest pain during the walk and did not complete the test, and 11 (1.8%) were missing 6-minute walk data or other missing data for an unknown reason at baseline. Of the 510 PAD participants, 361 (70.8%) had an ABI at baseline <0.90 and the remainder were eligible for the BRAVO Study based on medical record evidence of lower extremity revascularization or evidence of PAD from an accredited noninvasive vascular laboratory.

Of the 510 PAD participants, 41 (8.0%) developed an IHD event and 9 (1.8%) developed a stroke during a mean follow-up of 19.0±9.5 months. PAD participants with an IHD event during follow-up had a higher baseline prevalence of hypertension, MI, and angina and had poorer baseline 6-minute walk, lower physical activity, and a lower ABI value than those who did not experience an IHD event during follow-up (Table 1).

The correlation coefficient for the association of 6-minute walk with blocks walked during the past week was 0.376 (P<0.001). Table 2 shows characteristics of participants according to their baseline 6-minute walk and physical activity level. Participants with poorer 6-minute walk were older and included a higher prevalence of women, African Americans, and patients with diabetes, hypertension, stroke, or pulmonary disease. Participants with poorer 6-minute walk had lower ABI values and higher BMI values compared with those with better 6-minute walk performance.

Participants with lower physical activity levels at baseline were older and included a higher prevalence of women, African Americans, and patients with diabetes, angina, hypertension, stroke, or pulmonary disease. Participants with lower physical activity levels had lower ABI values and higher BMI values compared with those with higher physical activity levels at baseline. Those with lower physical activity levels also had poorer 6-minute walk performance compared with those with higher physical activity levels at baseline.

Rates of IHD events were 25 (14.7%) of 170 for the third (poorest) 6-minute walk tertile, 10 (5.8%) of 171 for the second tertile, and 6 (3.5%) of 169 for the first (best) 6-minute walk tertile (P<0.001). Figure 1A shows associations of baseline 6-minute walk performance with IHD event rates during follow-up, after adjustment for age, sex, race, comorbidities, smoking, and BMI. Poorer 6-minute walk performance at baseline was associated with higher rates of IHD events (P_{trend}=0.009). Compared with the highest (best) tertile of

Table 2. Characteristics of Study Participants According to Baseline (A) 6-Minute Walk Performance and (B) Baseline Physical Activity Level

Group	6-Minute Walk Tertiles			
	Tertile 1 Best tertile (1360 to 2064 ft) (n=169)	Second Tertile (1032 to 1358 ft) (n=171)	Tertile 3 worst tertile (100 to 1022 ft) (n=170)	P_{trend} Value
Age, y	66.0 (9.5)	68.7 (9.3)	71.7 (10.6)	<0.0001
Ankle-brachial index	0.69 (0.12)	0.67 (0.13)	0.61 (0.15)	<0.0001
Body mass index, kg/m^2	28.4 (4.8)	29.2 (6.0)	30.8 (6.5)	<0.001
Male sex, %	77.5	63.7	54.7	<0.0001
African American race, %	27.2	32.2	42.9	0.002
Current/former smoker, %	81.7	91.2	86.5	0.198
Diabetes, %	32.0	46.2	50.0	0.001
Angina, %	17.8	20.5	31.2	0.004
Myocardial infarction, %	19.5	13.5	21.2	0.691
Stroke, %	9.5	18.1	29.4	<0.0001
Hypertension, %	85.2	87.1	94.1	0.010
Cancer, %	16.6	18.1	21.8	0.222
Pulmonary disease, %	23.1	43.3	46.5	<0.0001
6-Minute walk (ft)	1556.0 (168.7)	1200.0 (87.7)	750.7 (212.2)	<0.0001
Physical activity level (blocks walked in the past week)	39.6 (46.3)	22.2 (31.5)	10.8 (17.3)	<0.0001

Group	Physical Activity Tertiles			
	Tertile 1 best tertile (20 to 300 Blocks) (n=182)	Second Tertile (5 to 18 Blocks) (n=174)	Tertile 3 worst tertile (0 to 4 Blocks) (n=154)	P_{trend} Value
Age, y	66.9 (9.1)	69.0 (10.3)	70.9 (10.5)	<0.001
Ankle-brachial index	0.67 (0.14)	0.66 (0.14)	0.63 (0.15)	0.05
Body mass index, kg/m^2	28.5 (5.3)	29.0 (5.9)	31.0 (6.2)	<0.001
Male sex	73.6	62.1	59.1	0.005
African American race, %	23.6	30.5	50.7	<0.0001
Current/former smoker, %	86.3	85.6	87.7	0.724
Diabetes, %	37.4	41.4	50.7	0.016
Angina, %	18.7	21.8	29.9	0.017
Myocardial infarction, %	19.2	14.4	20.8	0.771
Stroke, %	12.6	19.0	26.6	0.001
Hypertension, %	84.1	90.2	92.9	0.011
Cancer (%)	16.5	23.0	16.9	0.859
Pulmonary disease, %	31.9	37.4	44.8	0.015
6-Minute walk (ft)	1366.7 (302.8)	1154.8 (324.4)	948.7 (356.9)	<0.0001
Blocks walked	56.6 (43.7)	10.0 (3.3)	1.7 (1.4)	<0.0001

6-minute walk, those in the lowest (worst) tertile of 6-minute walk had a 4.23-fold higher rate of IHD events during follow-up (95% CI 1.56 to 11.47, P=0.005). This association was slightly attenuated after additional adjustment for baseline physical activity level (Figure 1A). After additional adjustment for physical activity, the hazard ratio for the poorest versus highest tertile of baseline 6-minute walk was 3.28 (95% CI 1.17 to 9.17, P=0.024) (Figure 1A). We observed similar results for the association of 6-minute walk performance with the combined outcome of IHD and stroke (Figure 1B). Results for

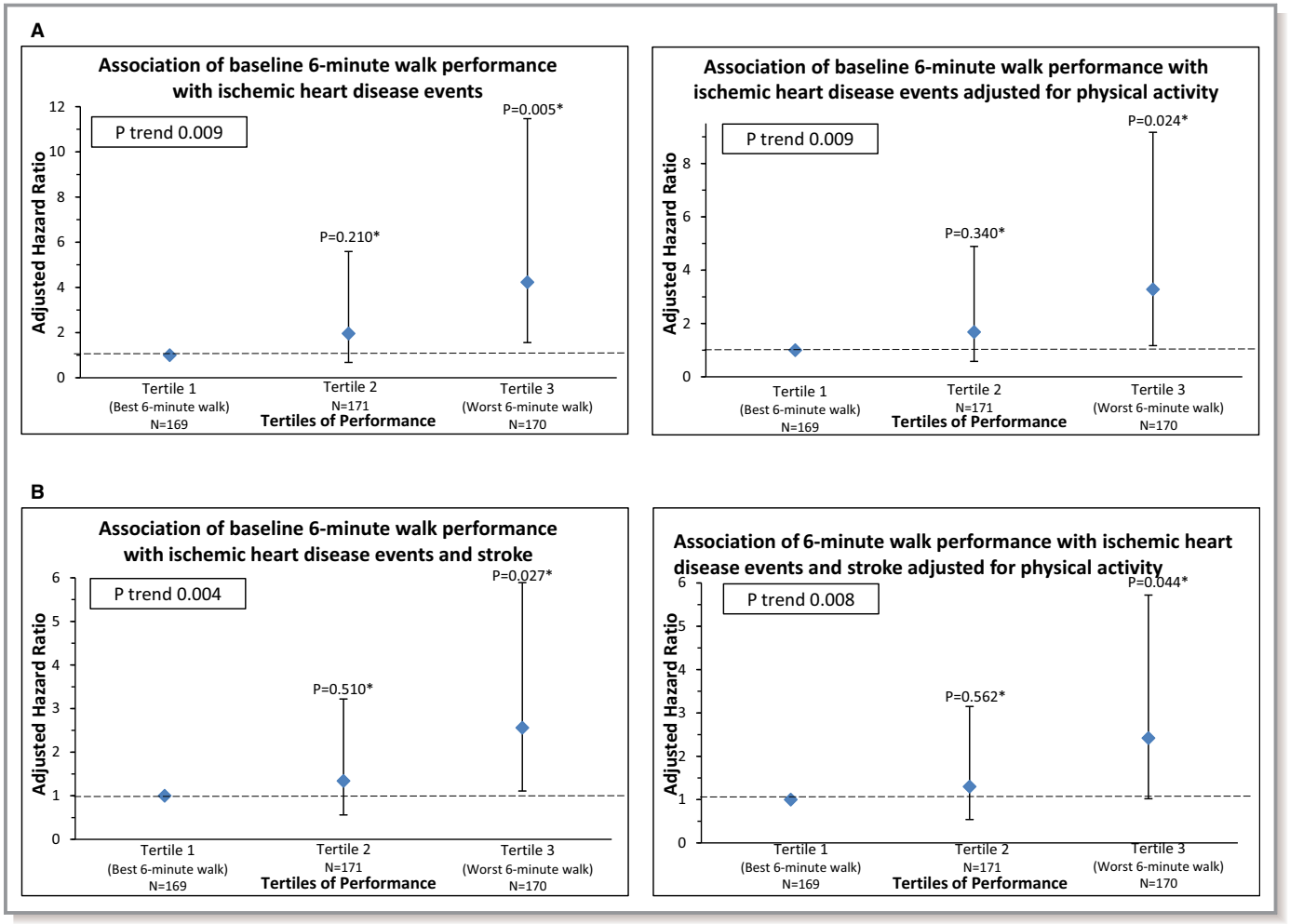

Figure 1. A, Associations of baseline 6-minute walk with ischemic heart disease events. B, Associations of baseline 6-minute walk with ischemic heart disease events and stroke. Models are adjusted for age, sex, race, body mass index, smoking status, and comorbidities (diabetes, cancer, pulmonary disease, and cardiovascular diseases). *Pairwise *P* values based on group comparison with referent (tertile 1).

associations in which the 6-minute walk was entered as a continuous variable are shown in Table 3.

Rates of IHD events were 21 (13.6%) for the third (poorest) physical activity tertile, 15 (8.6%) of 174 for the second tertile, and 5 (2.7%) of 182 for the first (best) physical activity tertile (P=0.001). Figure 2A shows associations of baseline physical activity level with IHD event rates during follow-up, after adjustment for age, sex, race, comorbidities, smoking, and BMI. Lower physical activity levels at baseline were associated with higher IHD event rates (P_{trend}=0.036). Compared with the highest (best) physical activity tertile, those in the lowest (worst) physical activity tertile had a 5.25-fold higher rate of IHD events during follow-up (95% CI 1.85 to 14.93, P=0.002). The overall association of physical activity with IHD events was attenuated after additional adjustment for 6-minute walk (P_{trend}=0.171). After additional adjustment for 6-minute walk performance, the hazard ratio for the poorest versus highest tertile of physical activity level at baseline was 3.72 (95% CI 1.24 to 11.19, P=0.019). We observed similar results for the association of baseline physical activity level with the combined outcome of IHD and stroke (Figure 2B). Results for associations in which physical activity was entered as a continuous variable are shown in Table 3.

To determine whether associations of the 6-minute walk with IHD events remained statistically significant even after adjustment for the ABI, we repeated analyses in the 361 PAD participants with baseline ABI values <0.90 and performed analyses with and without adjustment for the baseline ABI. In the 361 PAD participants with baseline ABI values <0.90, poorer 6-minute walk performance was associated with higher rates of IHD events (P_{trend}=0.006), after adjustment for age, sex, race, BMI, smoking, and comorbidities (model 1, Table 4). After additional adjustment

Table 3. Associations of 6-Minute Walk and Physical Activity With Ischemic Heart Disease Events and Stroke

	N	No. of Events	Hazard Ratio (95% CI)	P_{trend} Value
Association of baseline 6-minute walk with subsequent ischemic heart disease events				
Model 1*	510	41	0.851 (0.773 to 0.936)	<0.001
Model 2†	510	41	0.874 (0.790 to 0.967)	0.009
Association of baseline 6-minute walk with subsequent ischemic heart disease events or stroke				
Model 1*	510	50	0.880 (0.805 to 0.961)	0.004
Model 2†	510	50	0.883 (0.805 to 0.968)	0.008
Association of baseline physical activity level with subsequent ischemic heart disease events				
Model 1*	510	41	0.901 (0.817 to 0.993)	0.036
Model 2‡	510	41	0.936 (0.852 to 1.029)	0.171
Association of baseline physical activity with subsequent ischemic heart disease events or stroke				
Model 1*	510	50	0.972 (0.918 to 1.029)	0.324
Model 2‡	510	50	0.993 (0.942 to 1.047)	0.793

Results for the 6-minute walk are reported per 100 ft. Results for physical activity are reported per 5 blocks of walking.
*Model 1 adjusts for age, sex, race, body mass index, smoking, and comorbidities.
†Adjusts for variables in model 1 and physical activity level.
‡Adjusts for variables in model 1 and 6-minute walk.

for ABI, the association was attenuated but remained statistically significant (P_{trend} = 0.025) (model 2, Table 4). In the 361 PAD participants with baseline ABI values <0.90, poorer 6-minute walk performance was associated with higher rates of IHD events (P_{trend}=0.040), after adjustment for age, sex, race, BMI, smoking, comorbidities, and physical activity (model 3, Table 4). However, when model 3 was additionally adjusted for the ABI, the association of 6-minute walk performance with IHD events was no longer statistically significant (model 4, Table 4). The ABI was not associated significantly with IHD event rates in either model 3 (hazard ratio −0.806/0.10 unit ABI, *P*=0.131) or in model 4 (hazard ratio −0.805/0.10 unit ABI, *P*=0.119).

To determine whether associations of physical activity with IHD events remained statistically significant even after adjustment for the ABI, we repeated analyses in the 361 PAD participants with baseline ABI values <0.90 and performed analyses with and without adjustment for the baseline ABI. Among the 361 PAD participants with a baseline ABI <0.90, lower physical activity levels were associated with higher rates of IHD events (P_{trend}=0.042), after adjustment for age, sex, race, BMI, smoking, and comorbidities. In these analyses, the second and third physical activity tertiles had higher IHD event rates compared with the first (best) physical activity tertile (Model 1, Table 5). After additional adjustment for ABI, these associations were not substantially changed (model 2, Table 5). Among the 361 PAD participants with a baseline ABI <0.90, the third (lowest) tertile of physical activity was associated with higher IHD rates, compared with the first (highest) tertile of physical activity, after adjustment for age, sex, race, BMI, smoking, comorbidities, and 6-minute walk performance (model 3, Table 5). When model 3 was additionally adjusted for the ABI, the association of physical activity with IHD events was not substantially changed (model 4, Table 5). The ABI was significantly associated with IHD event rates in model 3 (hazard ratio −0.765/0.10 unit ABI, *P*=0.049) but not in model 4 (hazard ratio −0.818/0.10 unit ABI, *P*=0.163).

Results were not substantially different when analyses were performed separately among participants with versus without a history of coronary heart disease at baseline (data not shown). We did not find a threshold effect for the association of 6-minute walk or physical activity with ischemic heart disease events in this PAD population.

Discussion

Among 510 PAD participants in the BRAVO cohort, those with poorer 6-minute walk performance at baseline and lower physical activity levels at baseline, respectively, had higher rates of IHD events and stroke during a mean follow-up of 19.0 months, after adjustment for confounders. Participants in the lowest 6-minute walk tertile at baseline had a 4.23-fold higher rate of IHD events, compared with those in the highest tertile for 6-minute walk at baseline. Participants in lowest (worst) tertile of physical activity level at baseline had a 5.25-fold higher rate of IHD events compared with those in the highest (best) tertile for physical activity at baseline. Associations of 6-minute walk with IHD events were attenuated but

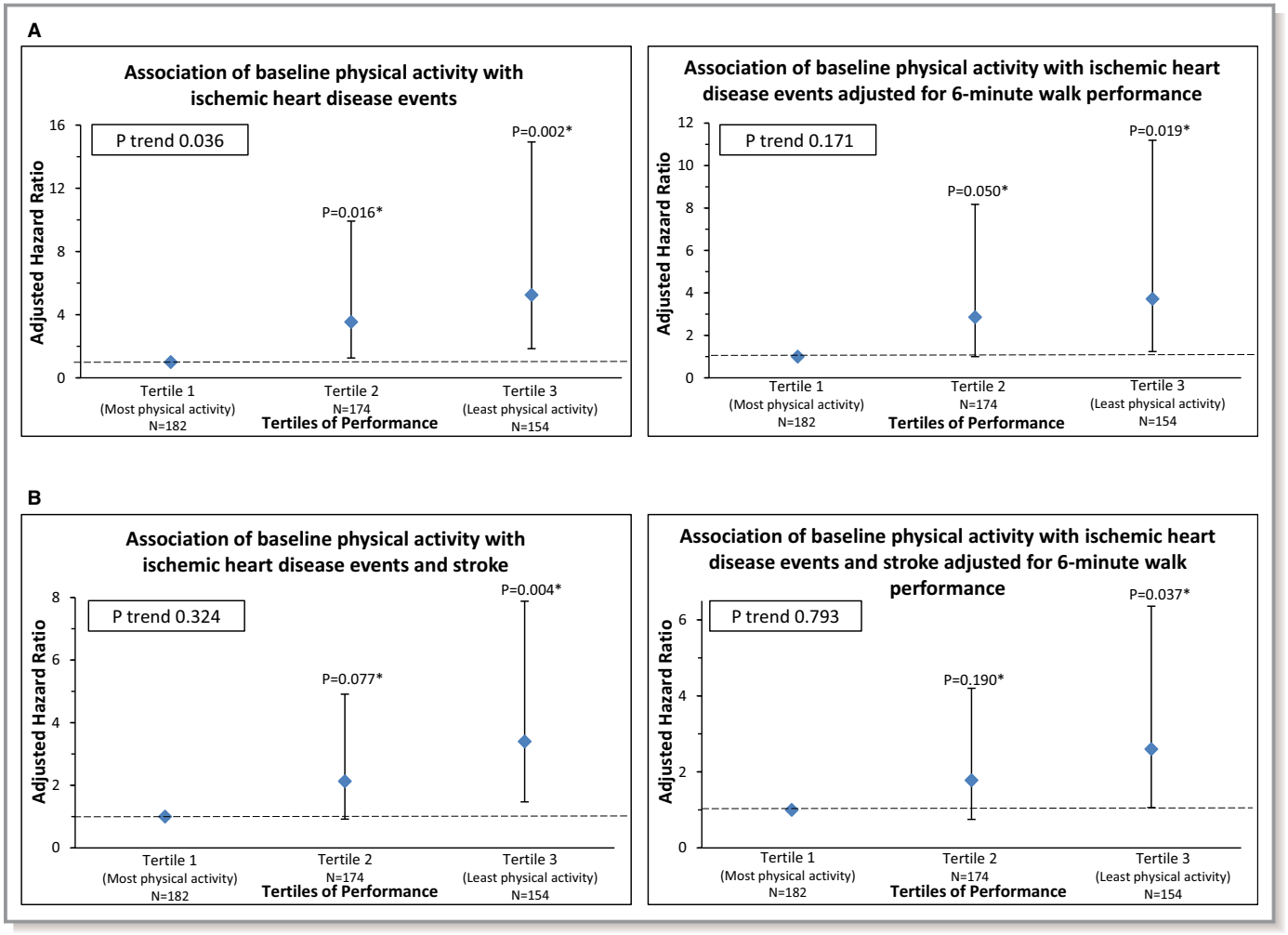

Figure 2. A, Associations of baseline physical activity level with ischemic heart disease events. B, Associations of baseline physical activity level with ischemic heart disease events and stroke. Models are adjusted for age, sex, race, body mass index, smoking status, and comorbidities (diabetes, cancer, pulmonary disease, and cardiovascular diseases). *Pairwise *P* values based on group comparison with referent (tertile 1).

remained statistically significant after additional adjustment for physical activity. Similarly, associations of physical activity with IHD events were attenuated but remained statistically significant after additional adjustment for 6-minute walk. Associations of 6-minute walk with IHD events were attenuated somewhat after additional adjustment for the ABI. In contrast, associations of physical activity with IHD events were largely unchanged after additional adjustment for the ABI.

To our knowledge, no prior studies have assessed the association of 6-minute walk performance or physical activity levels with rates of IHD events or stroke in people with PAD. Among 3075 community dwelling men and women aged 70 to 79 without PAD participating in the Health ABC Study, poorer performance on the 400-m walk test at baseline was associated with a higher rate of incident cardiovascular events at 4.9-year follow-up.[24] In Health ABC, each additional minute required to complete the 400-m walk was associated with an adjusted hazard of 1.29 for all-cause mortality and an adjusted hazard of 1.20 for cardiovascular events.[24] Among people with PAD, McDermott et al[13,14] reported that poorer 6-minute walk performance at baseline was associated with higher all-cause mortality (hazard ratio 2.36), cardiovascular mortality (hazard ratio 5.59), and mobility loss (hazard ratio 9.65), after adjustment for confounders. Leeper et al[25] reported that poorer treadmill-measured exercise capacity was associated with increased mortality among PAD patients at 11-year follow-up. Each additional MET was associated with an 18% lower rate of all-cause mortality. However, Leeper et al did not adjust for comorbidities or other potential confounders. Also among people with PAD, Garg et al[18,19] reported that lower physical activity levels were associated with increased all-cause and cardiovascular mortality in PAD, with hazard ratios of 3.48 and 2.10, respectively.

Results reported here include new and important findings. First, no prior studies have assessed the prognostic association of walking performance for nonfatal IHD events or

Table 4. Associations of 6-Minute Walk With Ischemic Heart Disease Events With and Without Adjustment for the ABI

Six-Minute Walk Tertiles	N	No. of Events	Hazard Ratio (95% CI)	Pairwise *P* Value	P_{trend} Value
Model 1: adjusts for age, sex, race, body mass index, smoking, comorbidities					
First tertile	118	4	1.0 (Reference)	NA	0.006
Second tertile	118	7	1.76 (0.49 to 6.27)	0.385	
Third tertile	125	16	3.19 (0.94 to 10.76)	0.062	
Model 2: adjusts for age, sex, race, body mass index, smoking, comorbidities, and ABI					
First tertile	118	4	1.0 (Reference)	NA	0.025
Second tertile	118	7	1.68 (0.47 to 6.03)	0.423	
Third tertile	125	16	2.61 (0.74 to 9.15)	0.135	
Model 3: adjusts for age, sex, race, body mass index, smoking comorbidities, and physical activity					
First tertile	118	4	1.0 (Reference)	NA	0.040
Second tertile	118	7	1.37 (0.38 to 4.97)	0.632	
Third tertile	125	16	2.29 (0.67 to 7.90)	0.188	
Model 4: adjusts for age, sex, race, body mass index, smoking comorbidities, physical activity, and ABI					
First tertile	118	4	1.0 (Reference)	NA	0.137
Second tertile	118	7	1.29 (0.35 to 4.69)	0.702	
Third tertile	125	16	1.83 (0.51 to 6.60)	0.356	

Analyses are limited to participants with an ABI <0.90. ABI indicates ankle-brachial index; first tertile, 1304 to 1972 feet; second tertile, 1002 to 1300 feet; third tertile, 100 to 1000 feet; NA, not applicable.

stroke in PAD patients. Results reported here primarily consisted of nonfatal cardiovascular events, a less severe outcome than mortality. Second, our results show that associations of 6-minute walk with IHD events are independent of physical activity level and comorbidities that include diabetes and history of IHD. Although results were somewhat

Table 5. Associations of Physical Activity Level With Ischemic Heart Disease Events With and Without Adjustment for the ABI

Physical Activity Tertiles	N	No. of Events	Hazard Ratio (95% CI)	Pairwise *P* Value	P_{trend} Value
Model 1: adjusts for age, sex, race, body mass index, smoking, comorbidities					
First tertile	119	2	1.0 (Reference)	NA	0.042
Second tertile	119	10	5.39 (1.15 to 25.26)	0.033	
Third tertile	123	15	7.04 (1.53 to 32.31)	0.012	
Model 2: adjusts for age, sex, race, body mass index, smoking, comorbidities, and ABI					
First tertile	119	2	1.0 (Reference)	NA	0.045
Second tertile	119	10	5.77 (1.22 to 27.32)	0.0271	
Third tertile	123	15	6.97 (1.50 to 32.35)	0.0132	
Model 3: adjusts for age, sex, race, body mass index, smoking, comorbidities, and 6-minute walk					
First tertile	119	2	1.0 (Reference)	NA	0.113
Second tertile	119	10	4.57 (0.96 to 21.84)	0.0571	
Third tertile	123	15	5.12 (1.06 to 24.68)	0.0420	
Model 4: adjusts for age, sex, race, body mass index, smoking comorbidities, 6-minute walk, and ABI					
First tertile	119	2	1.0 (Reference)	NA	0.103
Second tertile	119	10	5.01 (1.04 to 24.08)	0.0445	
Third tertile	123	15	5.40 (1.11 to 26.31)	0.0367	

Analyses are limited to the PAD participants with baseline ABI values <0.90. ABI, ankle-brachial index; first tertile, 18 to 300 blocks walked in the past week; second tertile, 6 to 16 blocks walked in the past week; third tertile, 0 to 5 blocks walked in the past week; NA, not applicable; PAD, peripheral artery disease.

attenuated after additional adjustment for the ABI, the ABI was not significantly associated with IHD events in models that included the 6-minute walk. Similarly, our results show that associations of physical activity with IHD events are independent of the 6-minute walk and comorbidities that include IHD. In addition, associations of physical activity with IHD events remained statistically significant even after adjustment for the ABI. Third, the measures of walking endurance and physical activity that we studied are relatively easy to obtain. The 6-minute walk can be obtained in a clinical office setting. Physical activity level was obtained with patient-report. Thus, clinicians can readily obtain the measures of walking endurance and physical activity that we used for prognostic assessment.[26]

Our data do not allow us to identify the biologic pathway(s) by which poorer 6-minute walk performance and lower physical activity levels are associated with increased IHD event rates in people with PAD. However, the 6-minute walk and physical activity level are likely to be sensitive measures of overall health and severity of comorbidities. Even after adjustment for comorbidities, associations of 6-minute walk and physical activity with IHD events and stroke remained statistically significant. Our results did not meaningfully change after adjustment for symptomatic angina at baseline.

Our study has limitations. First, follow-up duration was ≈19 months. Our data cannot determine whether poorer 6-minute walk and lower physical activity levels are associated with increased IHD events or stroke over longer-term follow-up. Second, the BRAVO Study is observational. Causal inferences of associations reported here cannot be made. Third, because of the observational study design, there may be residual confounding by unmeasured variables. Fourth, study participants in BRAVO were required to return to the medical center every 2 months for follow-up. Our findings might not be generalizable to individuals unwilling or unable to participate every 2 months in study visits. Fifth, our measure of physical activity consisted of 1 question related to 1 aspect of physical activity (blocks walked in the past week). Stronger associations of physical activity with IHD events might be observed with objective and more precise measures of physical activity.[26]

Conclusion

Poorer 6-minute walk performance and lower physical activity levels are associated with higher IHD event rates among people with PAD. Further study is needed to determine the mechanism of these associations. The 6-minute walk test and the measure of physical activity reported here can be obtained relatively quickly and for minimal cost and provide important prognostic information. Because 6-minute walk performance and physical activity levels in people with PAD can be improved with exercise interventions,[27,28] further study is needed to determine whether interventions that improve 6-minute walk and/or physical activity reduce IHD rates in people with PAD.

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None.

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