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Leg Symptom Categories and Rates of Mobility Decline in Peripheral Arterial Disease

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Abstract

Objectives—To determine whether asymptomatic lower extremity peripheral arterial disease (PAD) and leg symptoms other than intermittent claudication (IC) in PAD are associated with faster functional decline compared to people with both PAD and IC.

Design—Prospective, observational study.

Setting—Chicago-area medical center.

Participants—415 men and women with PAD followed annually for up to seven years.

Measurements—At baseline, PAD patients were categorized into symptom categories including IC, leg pain on exertion and rest, pain/carry on (participants walk through exertional leg pain), and always asymptomatic (participants who never experience exertional leg pain, even during the six-minute walk). Outcomes included mobility loss (becoming unable to walk ¼ mile or walk up and down one flight of stairs without assistance) and becoming unable to complete the six minute walk without stopping. Analyses adjust for age, sex, comorbidities, the ankle brachial index (ABI) and other confounders.

Results—Always asymptomatic PAD participants (hazard ratio (HR)=2.94, 95% Confidence Interval (CI)= 1.34-5.42, p=0.005) and those with leg pain on exertion and rest (HR=2.89, 95% CI=1.47-5.68, p=0.002) had increased mobility loss compared to participants with IC. PAD participants with leg pain/carry on were less likely (p=0.047) to become unable to walk for six minutes continuously without stopping, compared to participants with IC.

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Author Contributions:

Mary McDermott; Luigi Ferrucci; Kiang Liu; Jack M. Guralnik; and Michael H. Criqui: Study concept and design, acquisition of subjects and/or data, analysis and interpretation of data, and preparation of manuscript.

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Conclusion—The ABI identifies asymptomatic PAD patients and those with atypical leg symptoms who are at risk for greater mobility decline than participants without PAD and PAD participants with IC.

Keywords

intermittent claudication; peripheral vascular disease; physical functioning

Introduction

Intermittent claudication (IC) is the most classic symptom of lower extremity peripheral arterial disease (PAD) and is characterized by exertional calf pain that does not begin at rest and resolves within 10 minutes of walking cessation (1). However, most men and women with an ankle brachial index (ABI) < 0.90, consistent with PAD, do not report intermittent claudication symptoms (2,4,5). Many patients with PAD report no exertional leg symptoms (i.e. are asymptomatic). Others have exertional leg symptoms that are atypical for intermittent claudication (2,4,5).

Previous cross-sectional studies demonstrate that certain types of atypical leg symptoms in PAD are associated with greater or lesser functional impairment, compared to those with classic symptoms of intermittent claudication, independently of the ABI (3,4). For example, in cross-sectional analysis PAD patients with exertional leg pain that sometimes begins at rest (i.e. pain on exertion and rest) have greater functional impairment, while those who continue walking through exertional leg pain (i.e. leg pain/carry on) have less functional impairment compared to PAD persons with intermittent claudication (4). PAD patients who never develop leg symptoms, even during a six-minute walk test, have poorer functional performance and more adverse calf muscle characteristics compared to PAD patients with intermittent claudication (4). However, associations of asymptomatic PAD or of atypical leg symptoms in PAD with mobility decline over long-term follow-up are unknown.

We studied associations of asymptomatic PAD and of leg symptoms other than classic intermittent claudication with rates of mobility decline and mobility loss in men and women with PAD. For these analyses, mobility decline is defined as becoming unable to walk for six minutes continuously without stopping or as $\geq$ a 20% decline in six-minute walk performance. Mobility loss is defined as loss of the ability to walk up and down a flight of stairs or to walk ¼ mile without assistance. Rates of mobility decline and mobility loss are compared between PAD participants who are asymptomatic or who have specific leg symptoms other than intermittent claudication with a) PAD participants with IC and b) participants without PAD. Based on a previous cross-sectional study (5), we hypothesized that PAD patients who are always asymptomatic would have more rapid rates of mobility loss or decline, compared to PAD patients with classic IC and compared to men and women without PAD. We also hypothesized that, independent of the ABI, PAD participants with leg pain on exertion and rest would have faster rates of mobility loss or decline and that PAD participants with leg pain/carry on would have slower rates of mobility loss or decline, compared to PAD participants with intermittent claudication.

Methods

Study Overview

The institutional review boards of Northwestern University and Catholic Health Partners Hospital approved the protocol. Participants gave written informed consent. Participants were part of the Walking and Leg Circulation Study (WALCS), a prospective, observational study designed to identify predictors of functional decline in participants with PAD (3,5,6).

Participants underwent baseline assessment and returned for up to seven annual follow-up visits. Participants unable to return for follow-up were interviewed by telephone for the mobility outcome measure.

Participant Identification

Participants with PAD were identified from among consecutive patients age 55 and older diagnosed with PAD in three Chicago-area non-invasive vascular laboratories (3,5,6). Participants without PAD were identified from among patients with normal lower extremity arterial studies at the three non-invasive vascular laboratories and from among consecutive patients with appointments in a large general internal medicine practice at Northwestern (3,5,6). Participants from general internal medicine who had a low ABI at their study visit were included among PAD participants. Exclusion criteria for the WALCS have been reported (3,5,6) and include dementia, recent major surgery, above or below knee amputations, nursing home residence, and wheelchair confinement. Non-English-speaking patients were excluded because investigators were not fluent in non-English languages. Participants with baseline ABI > 1.30 were excluded (7,8).

Ankle Brachial Index Measurement

A hand-held Doppler probe (Nicolet Vascular Pocket Dop II; Nicolet Biomedical Inc, Golden, Colo) was used to obtain systolic pressures in the right and left brachial, dorsalis pedis, and posterior tibial arteries (4,5,9). Each pressure was measured twice. The ABI was calculated by dividing the mean of the dorsalis pedis and posterior tibial pressures in each leg by the mean of the 4 brachial pressures (9). Zero values for the dorsalis pedis and posterior tibial pulses were set to missing for the ABI calculation. Average brachial pressures in the arm with highest pressure were used when 1 brachial pressure was higher than the opposite brachial pressure in both measurement sets and the 2 brachial pressures differed by 10 mm Hg or more in at least one measurement set, since in such cases subclavian stenosis was possible (10). The lowest leg ABI was used in analyses. PAD was defined as an ABI < 0.90, while absent PAD was defined as an ABI of 0.90 to 1.30.

Leg Symptom Groups

Among participants with PAD, leg symptoms were characterized into one of six mutually exclusive groups using the San Diego claudication questionnaire, according to previous studies (4,11). Four groups had exertional leg symptoms (4): 1) Intermittent claudication (IC) (exertional calf pain that does not begin at rest, causes the participant to stop walking, and resolves within ten minutes of rest); 2) Leg pain on exertion and rest: (exertional leg pain that sometimes begins at rest); 3) Atypical exertional leg pain/carry on (exertional leg symptoms that do not begin at rest and do not stop the individual from walking); 4) Atypical exertional leg pain/stop (exertional leg symptoms that do not begin at rest, stop the individual from walking, and do not involve the calves or resolve within ten minutes of rest).

PAD participants who were asymptomatic (i.e. had no exertional leg pain) were further categorized into two groups (always asymptomatic vs. sometimes asymptomatic) according to whether they developed leg symptoms during the six-minute walk test (4). Always asymptomatic PAD participants were those who reported no exertional leg symptoms and did not develop leg symptoms during the six minute walk. Sometimes asymptomatic PAD participants were those who reported no exertional leg pain but developed exertional leg symptoms during the six-minute walk. These leg symptom categories have been validated in cross-sectional analyses (4).

Outcomes

Our primary outcomes were mobility loss and becoming unable to walk for six-minutes continuously without stopping (5,12,). These outcomes were assessed annually at each follow-up visit and were selected because they represent clearly defined, discrete endpoints. These outcomes avoid a possible “floor” effect that may occur with annual rates of distance achieved in the six-minute walk, for example, when a participant becomes unable to walk but cannot further deteriorate in functional performance. A secondary outcome measure was a $\geq 20\%$ decline in six-minute walk performance (13,14). This secondary outcome measures mobility decline in the context of baseline functional performance and accounts for the fact that a 100 foot decline in six-minute walk distance has different implications in an individual whose baseline six-minute walk performance is 1000 feet, compared to one whose baseline six-minute walk distance is 200 feet (13,14).

Six-minute walk

The six-minute walk was administered at baseline and at each annual follow-up visit. Following a standardized protocol (13-16), participants walk up and down a 100-foot hallway for six minutes after instructions to cover as much distance as possible. The interviewer administering the test recorded whether the participant stopped during the six-minute walk.

Mobility Measures

Based on previous studies, mobility loss was defined as becoming unable to walk up and down one flight of stairs or walk $\frac{1}{4}$ mile without assistance among those without mobility impairment at baseline (13,14,17). At baseline and at each follow-up visit, participants were asked to indicate whether they were able to walk $\frac{1}{4}$ mile and whether they could climb up and down one flight of stairs a) on their own; b) with assistance; or c) not at all (13,14,17).

Comorbidities

Comorbidities assessed were diabetes, angina, myocardial infarction, heart failure, cancer, chronic lung disease, lower extremity arthritis, spinal stenosis, spinal disk disease, and stroke. Disease-specific algorithms that combine data from patient report, medical record review, medications, laboratory values, and a questionnaire completed by the participant's primary care physician were used to document baseline comorbidities other than knee and hip arthritis, using previously developed criteria (18). American College of Rheumatology criteria were used to document presence of knee and hip osteoarthritis (19,20).

Peripheral Neuropathy—A monofilament assessed sensation on the dorsal and ventral surface of each foot in specific locations (21,22). Participants were classified according to the percent of locations with sensation.

Other Measures

Height and weight were measured at the study visit. Body mass index (BMI) was calculated as weight (kilograms)/(height (meters))². Cigarette smoking history was determined with patient report. Participants were asked to bring all medications to their baseline visit and medications were recorded. The principal investigator (MMM) identified statin, pentoxifylline, and cilostazol use, blinded to other participant characteristics. Walking exercise frequency was ascertained using patient report. Participants were classified according to whether they walked for exercise $<$ three times per week or $\geq$ three times per week (23). At each follow-up visit, we used patient report, a primary care physician questionnaire, and medical record review to identify lower extremity revascularizations each year.

Statistical Analyses

Baseline characteristics of PAD and non-PAD participants were compared using general linear models for continuous variables and chi-square tests for categorical variables. Among participants with PAD, baseline characteristics of participants in each atypical or asymptomatic symptom category were compared to participants with intermittent claudication using general linear models for continuous variables and chi-square tests for categorical variables. Rates of each outcome were compared between participants with vs. without PAD, adjusting for age, sex, race, and baseline values for comorbidities, smoking, walking exercise frequency, neuropathy score, use of statins, cilostazol, and pentoxifylline, and BMI.

Two sets of Cox regression analyses were performed to assess associations of leg symptom categories in PAD participants with rates of functional decline, adjusting for age, sex, race, comorbidities, smoking, walking exercise frequency, neuropathy score, use of statins, cilostazol, and pentoxifylline, and BMI. Analyses restricted to PAD participants were additionally adjusted for the ABI. In these Cox regression analyses, leg symptom categories were entered as dummy variables. First, analyses were performed involving participants with and without PAD. In these analyses, each leg symptom category among PAD participants was compared to participants without PAD. Second, each leg symptom category among participants with PAD was compared to the reference group of PAD participants with IC. Participants who met relevant primary outcome definitions at baseline (mobility impairment or inability to walk for six-minutes without stopping) were excluded from these respective analyses. Person-time was calculated as the number of months from the baseline visit to the date of the most recent visit (last seen) or the date of the visit during which each functional outcome of interest was first reported, whichever came first. Participants who died before experiencing an outcome measure or underwent lower extremity revascularization during follow-up were censored at the date of their last visit prior to these events. We tested the proportional hazards assumption for mobility loss, the stop during the six-minute walk outcome, and the 20% decline in six-minute walk outcomes using martingale residuals based methods and we did not find any significant deviation from the proportional hazards assumption (24). Analyses were performed using SAS statistical software (version 9.1, SAS Institute Inc, Cary, NC).

Results

Of 731 men and women who completed baseline testing for WALCS and had a baseline ABI < 1.30, 698 (95%) completed at least one follow-up visit. Of these, 18 were excluded because they had a normal baseline ABI with a history of lower extremity revascularization and therefore could not be clearly classified with vs. without PAD. Of the remaining 680 participants included in analyses, 492 (279 with PAD) completed the six-minute walk test at baseline without stopping and were included in analyses of becoming unable to walk for six minutes without stopping. In addition, 623 participants (395 with PAD) were free of mobility impairment at baseline and were included in analyses of mobility loss. Finally, 600 (374 with PAD) were included in analyses for the outcome of a 20% percent decline in six-minute walk performance. Mean follow-up was 43 ± 28.7 months.

Table 1 shows characteristics of participants with and without PAD. Compared to participants without PAD, those with PAD were older, had a lower BMI, had a poorer baseline six-minute walk performance, and included a higher proportion of men, current cigarette smokers, participants with diabetes mellitus, participants taking statins, and participants with a history of cardiovascular disease.

Table 2 shows characteristics of each asymptomatic or atypical leg symptom category, compared to PAD participants with intermittent claudication. PAD participants with leg pain on exertion and rest had a higher average ABI value, had a poorer baseline six-minute walk performance and poorer neuropathy score, and included higher proportions of women, African-Americans, and participants with diabetes mellitus, spinal stenosis, disk disease, and pulmonary disease, compared to PAD participants with intermittent claudication (Table 2). PAD participants with leg pain/carry on had higher ABI values and better six-minute walk performance than those with intermittent claudication. PAD participants with atypical exertional leg symptoms had better six-minute walk performance at baseline. PAD participants who were sometimes asymptomatic had higher ABI values and those who were always asymptomatic were older, had higher ABI values, and were more likely to report walking exercise ≥ 3 times per week than PAD participants with intermittent claudication.

Overall, the hazard ratio for mobility loss was 1.42 (95% Confidence Interval = 0.95 -2.12, $p=0.09$) for PAD participants compared to those without PAD, adjusting for age, sex, race, comorbidities, smoking, BMI, walking exercise frequency, neuropathy score, use of statins, cilostazol, and pentoxifylline, and smoking. In fully adjusted analyses, the hazard ratios for becoming unable to walk for six-minutes continuously and for $\geq 20\%$ decline in six-minute walk performance were 1.95 (95% CI = 1.33-2.85, $p=0.007$) and 1.46 (95% CI = 1.07-2.00, $p=0.018$) for PAD participants compared to those without PAD, respectively.

Figure 1 shows associations of baseline leg symptom categories with mobility loss among all participants with and without PAD and among participants with PAD, respectively, adjusting for age, sex, race, BMI, walking exercise frequency, neuropathy score, use of statins, cilostazol, and pentoxifylline, smoking, and comorbidities. Analyses of PAD participants only were additionally adjusted for the ABI. Compared to the reference group of participants without PAD, those with pain on exertion and rest (Hazard Ratio =2.62, 95% CI=1.58-4.35, $p<0.001$) and those who were always asymptomatic (Hazard Ratio =2.70, 95% CI=1.43-5.11, $p=0.002$) had higher rates of mobility loss. Compared to PAD participants with intermittent claudication, those with pain on exertion and rest (HR=2.89, 95% CI=1.47-5.68) and those who were always asymptomatic at baseline (HR=2.94, 95% CI = 1.39-6.19) had greater mobility loss.

Figure 2 shows associations of baseline leg symptom categories with becoming unable to walk for six-minutes continuously during follow-up among all participants with and without PAD and among participants with PAD, respectively, adjusting for age, sex, race, BMI, smoking, walking exercise frequency, neuropathy score, use of statins, cilostazol, and pentoxifylline, and comorbidities. Analyses of PAD participants only were additionally adjusted for ABI. Compared to the reference group of participants without PAD, those with pain on exertion and rest (Hazard Ratio =2.34, 95% CI=1.36-4.03, $p=0.002$) and those with intermittent claudication (Hazard Ratio =2.53, 95% CI=1.54-4.15, $p<0.001$) were more likely to become unable to walk for six-minutes continuously during follow-up. Compared to PAD participants with intermittent claudication, those with leg pain/carry were less likely to become unable to walk for six-minutes continuously during follow-up (HR=0.45, 95% CI=0.20-0.99, $p=0.047$).

Figure 3 shows associations of baseline leg symptom categories with experiencing $\geq 20\%$ decline in six-minute walk performance among all participants and among participants with PAD, respectively, adjusting for age, sex, race, BMI, smoking, walking exercise frequency, neuropathy score, use of statins, cilostazol, and pentoxifylline, and comorbidities. Analyses involving PAD participants only were additionally adjusted for ABI. Compared to the reference group of participants without PAD, those with pain on exertion and rest (Hazard Ratio =2.09, 95% CI=1.33-3.26, $p=0.001$) were more likely to experience $\geq 20\%$ decline

and those with intermittent claudication (Hazard Ratio = 1.48, 95% CI=1.00-2.19, $p=0.053$) were nearly more likely to experience $\geq$ a 20% decline in six-minute walk performance. Compared to PAD participants with intermittent claudication, those with leg pain on exertion and rest were more likely to experience a $\geq$ 20% decline in six-minute walk performance during follow-up (HR=1.72, 95% CI=1.06-2.77, $p=0.027$).

Discussion

Findings reported here demonstrate that specific types of leg symptoms are associated with different rates of mobility decline and mobility loss among men and women with PAD. PAD participants who are always asymptomatic and those with exertional leg pain that sometimes begins at rest have higher rates of mobility loss as compared to participants without PAD and PAD participants with classic symptoms of intermittent claudication, respectively. PAD participants with leg pain on exertion and rest and those with intermittent claudication were more likely to become unable to walk for six-minutes continuously and PAD participants with leg pain on exertion and rest were more likely to experience a $\geq$ 20% decline in six-minute walk performance during follow-up, compared to participants without PAD. As compared to PAD participants with intermittent claudication, those with pain on exertion and rest were more likely to experience a $\geq$ 20% decline in six-minute walk performance. In contrast, those with exertional leg pain/carry on were less likely to become unable to walk for six-minutes continuously at follow-up. Together, findings reported here suggest that PAD patients who walk at an intensity that provokes exertional leg symptoms and PAD patients who walk through exertional leg symptoms are more likely to preserve their mobility over time.

PAD is common in primary care medical practices, affecting 25% to 30% of men and women in primary care medical practices who are either age 70 and older or age 50-69 with a history of diabetes or smoking (1). Because most people with PAD do not have classic intermittent claudication, the American Diabetes Association and the American Heart Association recommend that patients at high risk for PAD should be screened with the ABI (25,26). However, screening for PAD is uncommon (1). Screening for PAD with the ABI will help identify asymptomatic PAD patients and those with pain on exertion and rest who have even faster rates of mobility decline than patients with intermittent claudication, but may not otherwise come to the physician's attention. These individuals could be offered exercise therapy in effort to prevent mobility decline (27). However, it is important to point out that no clinical trials have assessed whether screening for PAD with the ABI improves outcomes.

The reason for absence of exertional leg symptoms, even during a six-minute walk test, among PAD participants who were always asymptomatic is unclear. One possibility is that PAD participants who are always asymptomatic may slow their walking speed to avoid exertional leg symptoms, even during a six-minute walk test. Consistent with this hypothesis, prior cross-sectional study shows that PAD participants who are always asymptomatic have smaller calf muscle area and lower calf muscle density, compared to PAD participants with intermittent claudication (4). In contrast, PAD participants with leg pain on exertion and rest have a poorer neuropathy score and a higher prevalence of comorbidities, such as disk disease, spinal stenosis, and lower extremity arthritis that may also contribute to the character of leg symptoms.

This study has limitations. First, sample sizes of leg symptom subgroups were small, limiting statistical power. Second, the observational study design prevents us from concluding that slowing walking speed to avoid exertional leg symptoms or that walking through exertional leg symptoms are causally associated with mobility decline. Third,

characteristics of exertional leg symptoms in PAD are likely influenced in part by factors other than leg ischemia, such as self-efficacy and comorbidities. Our data do not allow us to discern reasons for different types of leg symptoms observed in PAD. However, since PAD participants in this study were identified from a medical center, associations reported here are relevant to PAD patients encountered by clinicians.

Our findings demonstrate that PAD patients who are always asymptomatic and those with leg pain on exertion and rest have faster mobility decline and greater mobility loss compared to PAD patients with intermittent claudication. In contrast, PAD patients who walk through their leg symptoms have slower rates of adverse mobility outcomes decline than PAD patients with intermittent claudication. While these findings underscore the importance of using the ABI to screen for PAD patients who may be asymptomatic or have atypical symptoms, further study is needed to determine whether screening for PAD with the ABI improves outcomes.

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Figure 2. Adjusted Associations of baseline Leg Symptom Categories with becoming unable to Walk for Six Minutes Continuously Among Men and Women with and without Peripheral Arterial Disease (N=492)

Analyses adjust for age, sex, race, comorbidities, smoking, body mass index, walking exercise frequency, neuropathy score, use of statins, cilostazol, and pentoxifylline, and ankle brachial index (for analyses of peripheral arterial disease participants only).

Figure 3. Adjusted Associations of Leg Symptom Categories with Experience $\geq$ a 20% Decline in Six-Minute Walk Performance among Men and Women with and without Peripheral Arterial Disease (N=600)

Analyses adjust for age, sex, race, comorbidities, smoking, body mass index, walking exercise frequency, neuropathy score, use of statins, cilostazol, and pentoxifylline, and ankle brachial index (for analyses of peripheral arterial disease participants only).

Table 1
Characteristics of Study Participants According to Presence vs. Absence of Lower
Extremity Peripheral Arterial Disease*

	PAD (N=415)	NONPAD (N=237)	P value
Age (years)	71.8 (8.4)	69.3 (8.1)	0.002
Ankle brachial index	0.65 (0.14)	1.09 (0.10)	<0.001
Body mass index (kg/meters ²)	27.2 (4.8)	28.4 (5.6)	0.004
Male Sex (%)	59.0	49.8	0.022
African-American Race (%)	15.4	19.8	0.15
Current smoker (%)	20.0	7.6	<0.001
Diabetes (%)	30.4	19.4	0.002
Angina (%)	36.4	22.9	<0.001
Myocardial infarction (%)	27.5	14.8	<0.001
Stroke (%)	11.3	4.2	0.002
Heart failure (%)	26.0	18.6	0.042
Hip arthritis (%)	3.4	3.0	0.77
Knee arthritis (%)	9.9	11.8	0.44
Disk disease (%)	30.0	31.7	0.64
Spinal stenosis (%)	10.8	31.7	<0.001
Cancer (%)	14.9	16.5	0.61
Pulmonary disease (%)	30.8	34.6	0.32
Six-minute walk performance at baseline (feet)	1,147.6 (366.6)	1,430.5 (413.2)	<0.001
Statin therapy	47.5%	28.7%	<0.001
Walking for exercise $\geq$ 3 times per week	34.0%	39.2%	0.18
Neuropathy score	82%	84%	0.12

* Data shown are means (standard deviations).

Table 2
Characteristics of Participants with Peripheral Arterial Disease According to Leg Symptoms*

	Pain on Exertion and Rest	Atypical Exertional Leg Pain	Leg Pain/Carry on	Sometimes Asymptomatic	Always Asymptomatic	Intermittent Claudication
N	74	88	41	33	45	134
Age (years)	71.5 (8.3)	71.3 (8.8)	72.0 (7.7)	72.8 (8.5)	76.5 (7.1) ¹	70.4 (8.4)
Ankle brachial index	0.67(0.16) ⁶	0.64 (0.14)	0.70 (0.11) ²	0.68 (0.13) ⁹	0.70 (0.13) ²	0.62 (0.14)
Body mass index (kg/m ²)	28.9 ³ (6.1)	26.5 (4.7)	26.5 (3.3)	26.7 (3.4)	27.2 (4.9)	27.2 (4.7)
Male sex (%)	41.9 ²	53.4	73.2	63.6	68.9	63.4
African-American Race (%)	25.7 ²	13.6	7.3	18.2	20.0	11.2
Current smoker (%)	24.3	19.3	12.2	21.2	11.1	23.1
Diabetes (%)	47.3 ²	27.3	24.4	33.3	26.7	25.4
Angina (%)	40.5	34.1	29.3	36.4	28.9	40.3
Myocardial Infarction (%)	28.4	26.1	19.5	27.3	24.4	31.3
Stroke (%)	12.2	10.2	7.3	15.2	13.3	11.2
Heart Failure (%)	29.7	20.5	24.4	27.3	26.7	26.1
N	74	88	41	33	45	134
Knee Arthritis (%)	12.2	10.2	4.9	0.0 ⁸	8.9	12.7
Disk Disease (%)	43.2 ⁷	28.4	29.3	18.2	26.7	27.6
Spinal Stenosis(%)	21.6 ¹	13.6	9.8	0.0	11.1	6.0
Cancer (%)	17.6	14.8	7.3	18.2	15.6	14.9
Pulmonary Disease (%)	47.3 ⁵	25.0	17.1	18.2	37.8	30.6
Six-minute walk performance (feet).	910 ± 357 ¹	1,267 ± 280 ¹	1,438 ± 346 ¹	1,175±334	1,149±377	1,099±344
N	74	88	41	33	45	134
Peripheral Neuropathy Score (%) (higher score is better)	75 ¹	86	80	76	82	85
Statin use (%)	46	47	46	52	42	50
Pentoxifylline use (%)	4	7	5	6	2	12
Walking exercise ≥3 times per week	23	32	46	27	53 ⁴	33

* Data shown are means (standard deviations).

- 1 p<0.001;
- 2 p<0.01;
- 3 p=0.013;
- 4 p=0.014;
- 5 p=0.017;
- 6 p=0.019;
- 7 p=0.022;
- 8 p=0.026;
- 9 p=0.027