Circulation

AHA SCIENTIFIC STATEMENT

Optimal Exercise Programs for Patients With Peripheral Artery Disease

A Scientific Statement From the American Heart Association

Peripheral artery disease (PAD) is a progressive atherosclerotic disease that affects >8 million Americans.[1] Symptoms of PAD are caused by insufficient arterial blood flow to the lower extremities, which often results in ischemia-induced, debilitating leg discomfort associated with walking. Claudication, which is cramping, aching, or pain in the calves, thighs, or buttocks, is the classic symptom of PAD. Claudication is defined as a reproducible discomfort or fatigue in the muscles of the lower extremity that occurs with exertion and is relieved within 10 minutes of rest.[2] Most people with PAD do not have classic claudication symptoms but still have significantly greater functional impairment and decline than people without PAD. This significant physical activity limitation results in functional impairment, mobility loss, and decreased quality of life. Improving functioning and quality of life is a major goal in the treatment of individuals with PAD.[3,4]

The evidence supporting the efficacy of exercise therapy for patients with PAD dates back to 1966 when 6 months of unsupervised intermittent walking exercise was demonstrated to improve time walked to onset of pain and peak walking time (PWT).[5] Over the 50 years since that first report, numerous randomized clinical trials and meta-analyses have added to the body of evidence supporting the efficacy of exercise to improve functioning and quality of life in patients with PAD.

SUMMARY OF THE OBJECTIVES OF THIS DOCUMENT

The most recently published American Heart Association/American College of Cardiology (AHA/ACC) guidelines on the management of patients with lower-extremity PAD include 4 recommendations supporting exercise therapy for patients with PAD.[6] The AHA/ACC guidelines gave supervised exercise treadmill training a Class I recommendation supported by a Level of Evidence A on the basis of multiple randomized clinical trials showing the efficacy of supervised exercise treadmill training to improve claudication onset time (COT) or distance (COD), PWT or peak walking distance (PWD), and other clinically meaningful functional outcomes.[6] Current AHA/ACC practice guidelines are summarized in Table 1.

In 2017, the Centers for Medicare & Medicaid Services evaluated the large body of evidence demonstrating the efficacy of exercise to improve symptoms, functioning, and quality of life in patients with PAD. This has resulted in a national coverage determination of supervised exercise therapy (SET) for Medicare beneficiaries with symptomatic PAD.[7]

The purpose of this document is to review and summarize the state of the science related to exercise therapy in patients with PAD. Brief summaries of the epidemiology and functional burden of PAD are presented. Evidence supporting the mechanisms of the exercise training response and selection of outcome measures is included. Discussion of traditional and novel exercise modalities, comparison of

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the outcomes of exercise therapy with other therapeutic interventions, and assessment of the efficacy of exercise in patients with asymptomatic PAD are included. Finally, gaps in the literature and areas needing future research are identified.

LITERATURE SEARCH STRATEGY

MEDLINE, MEDLINE In-Process, CINAHL, and EMBASE databases were used for the initial literature search. The search was limited to articles published in the English language. Broad topics related to this statement, including PAD, exercise, physical functioning, and revascularization, were searched. For PAD, subject headings in MEDLINE included the following: exp peripheral arterial disease (2011–present), exp peripheral vascular diseases (1992–present), and exp intermittent claudication. Key words included peripheral arter* disease*, peripheral vascular disease*, claudication, and (lower extremit*) adj2 (arterial disease*).

For exercise, subject headings included exp exercise therapy/, exp exercise movement techniques/, exp walking/, and exp physical exertion/;exp rehabilitation. Key words included the following: (physical* adj [active or activity or activities]); (stair* or step or steps); ([muscle or muscles or muscular] adj strengthen*); (swim* or swam or jog* or run or running or ran or walk or walking or walked); treadmill*; ([circuit* or resistance or strength* or physical or weight] adj [train or training]); exercise*; (arm* or leg*) adj2 (cycle or cycling or bicycl* or ergomet*); and rehabilitat*.

Physical functioning subject headings included exp physical fitness/ and exp activities of daily living/. Key words included physical* adj function*(function or physical*) adj (status* or limit*).

Subject headings for revascularization included exp angioplasty, exp stents, and exp vascular surgical procedures. Key words included bypass, stent*, and revasculariz*.

SUMMARY OF THE BURDEN OF SYMPTOMATIC PAD

Prevalence of Symptomatic PAD

For the purposes of this statement, clinical evidence of PAD is defined as atherosclerotic arterial disease of the lower extremities. In patients who have not had a prior lower-extremity revascularization, clinical evidence of PAD includes typical limb symptoms with exercise and an ankle-brachial index (ABI) of ≤0.90. However, imaging evidence for significant occlusive disease is now more widely used to make the diagnosis, as are other noninvasive vascular laboratory tests. Some patients who have undergone a prior lower-extremity revascu-

Table 1. 2016 Exercise Therapy Guidelines for Patients With Lower-Extremity PAD

Class of Recommendation	Level of Evidence	Recommendation
I	A	In patients with claudication, a supervised exercise program is recommended to improve functional status and QOL and to reduce leg symptoms.
I	B-R	A supervised exercise program should be discussed as a treatment option for claudication before possible revascularization.
IIa	A	In patients with PAD, a structured community- or home-based exercise program with behavioral change techniques can be beneficial to improve walking ability and functional status.
IIa	A	In patients with claudication, alternative strategies of exercise therapy, including upper-body ergometry, cycling, and pain-free or low-intensity walking that avoids moderate to maximum claudication while walking, can be beneficial to improve walking ability and functional status.

PAD indicates peripheral artery disease; and QOL, quality of life.
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larization will have normal ABIs but still have PAD as the underlying disease. In addition, some patients with PAD have lower-extremity arterial stiffness that results in an abnormally elevated ABI.[8]

The prevalence of PAD rises sharply with increasing age such that it affects a substantial proportion of individuals ≥70 years of age.[9] Looking at 4 age categories, Allison et al[1] estimated the ethnicity-specific prevalence of PAD in the United States by combining data from 7 community-based studies. Included in these studies were 5 ethnic groups: non-Hispanic whites, blacks, Hispanics, Asian Americans, and Native Americans. PAD was defined as an ABI <0.90 or prior revascularization for PAD. The results for men showed that, although uncommon before 50 years of age, PAD rates rose sharply with age, such that by 80 years of age, rates were in the 25% to 30% range in 4 of the 5 ethnic groups. Notably, the rate for blacks was about twice that of non-Hispanic whites at any given age. The data for women reveal a somewhat lower PAD prevalence compared with men but similar trends with age. Native American women had a rate nearly as high as black women, although the data for Native American women came from a single study, the Strong Heart Study. Overall, these data suggested that in the year 2000 there were 8.5 million individuals with PAD in the United States, or ≈7.2% of individuals ≥40 years of age. A recent study by Nehler et al[10] addressed the prevalence of PAD between 2003 and 2008 in an insured US population of

12 million adults ≥40 years of age. PAD was defined as a clinical diagnosis, and the presence of a severe form of PAD, critical limb ischemia, was also estimated. PAD prevalence was 10.7%, and critical limb ischemia prevalence was 1.3%.

Beyond age, the 2 most powerful risk factors for PAD are modifiable: cigarette smoking and diabetes mellitus. Worldwide, cigarette smoking is decreasing. Between 2000 and 2010, cigarette smoking fell in men in 72% of countries and in women in 87% of countries,[11] which should decrease PAD burden, other risks being equal. However, an increase in cigarette smoking is projected in Africa and the eastern Mediterranean.[11] In contrast to cigarette smoking, the prevalence of diabetes mellitus worldwide has more than doubled in the last 20 years,[12] which will likely increase the PAD burden, other risks being equal.

Functional Impairment and Decreased Quality of Life Associated With PAD

Classic claudication, present in about one-third of patients with PAD, along with other exertional limb symptoms, typically significantly curtails the functional independence of patients with PAD.[13,14] However, functional impairment and functional decline are present even in people with PAD who are asymptomatic (ie, they have no exertional leg symptoms).[15,16] A limited ability to walk represents a disability when people are unable to perform their normal personal, social, and occupational activities. The major goals of treatment in people with claudication and other functional limitations resulting from PAD are to improve walking ability by relieving claudication, to improve community-based functional status and health-related quality of life (HRQOL), and to prevent mobility loss. In all patients with PAD, regardless of functional limitation, the other key goal is to treat cardiovascular risk factors and to prescribe antiplatelet and statin medications to reduce the risk of fatal and nonfatal ischemic cardiovascular and limb events.

Assessment of functional impairment and HRQOL in patients with claudication should be incorporated into the evaluation of all treatments for symptomatic PAD. For the purposes of this document, functional status is defined as an individual's ability to perform normal daily activities required to meet basic needs, to fulfill usual roles, and to maintain health and well-being.[17,18] For people with PAD, this includes the ability to walk distances without pain. HRQOL is a multidimensional concept that includes domains related to physical, mental, emotional, and social functioning and focuses on the impact that health status has on quality of life.[19,20]

Patients with PAD have significant functional impairment. Overall, patients with claudication have an ≈50% reduction in peak oxygen consumption ($\dot{V}o_2$) compared with an age-matched healthy cohort.[21] Peo-

ple with PAD also have reduced walking endurance, have a slower walking velocity over 4 m, and are more likely to be unable to walk for 6 minutes without stopping to rest compared with people without PAD.[16,22] These walking limitations are associated with marked impairments in functional status and HRQOL.[20] Individuals with PAD often avoid physical activity, especially walking.[22] Their sedentary lifestyle leads to additional declines in functional status and HRQOL, as well as cardiovascular health.[13,14,23,24] Measures of objective and subjective functioning and HRQOL commonly used in patients with PAD are presented in the Outcome Measures section of this statement.

MECHANISMS OF TRAINING RESPONSE TO EXERCISE IN PATIENTS WITH PAD

The pathophysiological mechanisms underlying the functional impairment and progressive functional decline observed in lower-extremity PAD are complex and incompletely understood.[25] However, current evidence indicates that both anatomic and functional vascular abnormalities, leading to blood flow limitation during exercise and structural and pathophysiological abnormalities in calf skeletal muscle, which cause an impairment of contractile performance, are key contributors. In patients with hemodynamically significant PAD, a drop in peripheral vascular resistance during rest maintains an adequate resting calf muscle blood flow despite a reduction in the arterial pressure distal to the stenosis.[26] However, during exercise, the fixed nature of the stenosis prevents the marked increase in blood flow required to match the metabolic demands of the muscular tissue and leads to muscle ischemia.[26–28] This blunted hemodynamic response is further exacerbated by endothelial dysfunction[29] and the associated defective vasorelaxation of the conduit vessels and microcirculation,[30] possibly mediated by an increased release of the potent vasoconstrictor peptide endothelin-1.[31,32] Surprisingly, limb hemodynamics, such as toe pressure and the ABI, are not well correlated with measures of functional capacity in patients with PAD,[32,33] suggesting that additional mechanisms are involved in the pathogenesis of the functional limitations. It is also possible that toe pressure and ABI measured immediately after exercise may correlate better with functional limitations than resting toe pressure and ABI.

Investigations with computed tomography imaging show that patients with PAD have reduced calf muscle area and higher calf muscle percent fat content compared with people without PAD and that these parameters are inversely and directly related, respectively, to the degree of calf ischemia.[34] In addition, electron microscopy studies indicate that PAD is associated with

distortion and impaired function of mitochondria in the calf muscle,[35–37] which lead to reduced energy production.[38] The damage to the muscle fibers and mitochondria is caused, at least in part, by the occurrence of ischemia during activity of the calf muscle followed by return of adequate blood supply at rest. The cycles of ischemia/reperfusion lead to the generation of reactive oxygen species with oxidative stress[39] and inflammation,[40,41] endothelial activation,[42] mitochondrial dysfunction,[43–45] muscle fiber type switching,[46] activation of apoptosis,[36] and myofiber degeneration.[47] Of interest, arterial insufficiency may be associated with distal motor neuropathy, which may independently affect muscle performance.[48] However, it is possible that motor neuropathy is related to skeletal muscle atrophy, in part from reduced physical activity levels in PAD. These structural and functional changes of the calf muscle appear to have a significant impact on functional outcomes and prognosis in patients with PAD and have been associated with loss of mobility, even after adjustment for risk factors and comorbidities,[34] and increased all-cause and cardiovascular mortality, independently of the ABI.[49]

Contemporary treatment of symptomatic PAD focuses on reducing cardiovascular and limb events and on improving symptoms and HRQOL.[50] The latter can be achieved with exercise training.[51] Several mechanisms underlying the beneficial effects of exercise have been elucidated or proposed. Regular physical activity such as in the standard 12-week SET program leads to reduced levels of inflammatory markers,[52] improved endothelium-dependent vasodilation,[53] increased capillary density of the gastrocnemius muscle,[54] and altered skeletal muscle metabolism through an increase in oxidative enzymes.[55] The plethora of effects of exercise training likely account for its efficacy.

OUTCOME MEASURES

Treadmill exercise performance has been the most common outcome measurement used to measure changes in walking endurance and peak exercise capacity in response to exercise interventions in patients with PAD.[56–59] Treadmill exercise performance has the advantage of being conducted in a standardized setting in which speed and grade of the treadmill start and increase at the same magnitude for each test.[58] Treadmill exercise tests differ from corridor walking tests such as the 6-minute walk test (6-MWT), which appear to more closely simulate walking activity during daily life.[60–68]

Questionnaire measures of functional status and HRQOL assess participants' perceptions of their ability to function in daily life and well-being before and after an exercise intervention. Validated questionnaires are based on subjective assessments and regularly yield dif-

ferent outcomes compared with objective measures in randomized trials of participants with PAD. The following sections summarize testing methods and advantages and disadvantages of both objective and subjective questionnaire measures in people with PAD.

Treadmill Walking Performance

Graded and constant-load treadmill tests are used to measure change in maximal and pain-free treadmill walking distance in response to exercise interventions in PAD.[60] Most studies evaluating walking ability in people with claudication have used treadmill testing as the primary objective measure of changes in performance after a treatment.[58] A graded treadmill exercise test modifies the load during treadmill testing, has better test-retest reliability than constant-load treadmill testing, and is the preferred method of treadmill testing in randomized trials of PAD.[60,69–72] Most graded protocols have a constant speed and increase the grade every 2 to 3 minutes to a symptom-limited maximal (or peak) walking time. The graded Gardner-Skinner treadmill exercise test is a well-accepted modified-load treadmill exercise test that is frequently used in randomized trials of therapeutic interventions in PAD.[73] In this protocol, participants begin walking on the treadmill at 2.0 mph with a grade of zero. The treadmill speed is maintained at 2.0 mph throughout testing, and the treadmill grade is increased by 2% every 2 minutes. Participants with PAD who are unable to walk at 2.0 mph should perform a modified Gardner treadmill test in which the speed begins at 0.5 mph and a grade of zero and speed is increased by 0.5 mph every 2 minutes until 2.0 mph is achieved.[73] When a speed of 2.0 mph is reached, the treadmill grade is increased by 2% every 2 minutes. Participants are asked to continue walking as long as possible until ischemic leg symptoms, fatigue, or other symptoms prevent them from continuing. Treadmill walking PWT or PWD and COT or COD are the typical outcome measures used to assess changes in walking performance in a treadmill exercise test.[60] Of these, PWT or PWD has the greatest reliability.[74] After a treadmill-based SET program, typical changes in PWT, relative to a control group, have been shown to be 3.4 to 4.6 minutes and typical changes in COT have been shown to be 1.65 to 2.2 minutes.[64,66,69]

A limitation of treadmill exercise testing is a learning/placebo effect in which patients with PAD who do not receive an intervention increase their PWD/PWT and COD/COT between baseline and follow-up testing.[58] Recent placebo-controlled drug therapeutic trials in patients with PAD have demonstrated increases in PWT in the placebo or control groups ranging from 17% to 26%.[75–77] This phenomenon may occur because the practice provided by repeated treadmill tests at baseline and follow-up allows patients with PAD to improve

their treadmill walking performance, even without a therapeutic intervention.[58]

The 6-MWT

The 6-MWT is a well-validated measure of walking endurance that does not require sophisticated equipment or extensive training.[57] In people with PAD, the 6-MWT predicts rates of mobility loss and mortality, improves in response to therapeutic interventions, and is not associated with a learning effect when repeated testing is performed.[57,64–67,60,78,79] Declines in 6-MWT performance have been linked to clinically meaningful outcomes in people with PAD.[68,80–82] Clinically meaningful change in the 6-MWT distance has been defined for older people without PAD.[83] A small meaningful change has been defined as 20 m, and a large meaningful change has been defined as 50 m. However, these definitions of meaningful change were not derived specifically from people with PAD.

The 6-MWT is performed in an unobstructed 100-ft hallway with a trained staff member. The staff member reads a script with instructions about the test and uses a stopwatch to time the 6-minute time period. Participants are instructed to walk back and forth along the 100-ft hallway with the goal of completing the greatest distance possible. Participants are allowed to stop and rest and may sit down in a chair while resting, but the stopwatch continues to run while the participant rests. At the end of 6 minutes, the distance walked is recorded. The staff member should also record whether and at what time point during the test the participant rests.[57,64,66] In response to a structured home-based walking exercise (H-BEx) intervention, meaningful improvement in the 6-MWT is observed as early as the 12-week follow-up and ranges from 41 to 53 m in improvement at the 12-week and 6-month follow-up relative to a control group who do not exercise.[65,67]

A structured H-BEx intervention improves the 6-MWT distance more than it improves treadmill-based PWT/PWD, whereas a supervised treadmill exercise intervention improves treadmill walking more than it improves the 6-MWT.[64–67] This conclusion, based on results from randomized trials, may be related to the fact that a supervised treadmill exercise intervention specifically trains the participant with PAD to the treadmill walking measure, whereas a structured H-BEx intervention focuses on over-ground walking.[57,84] Investigators and clinicians should take this phenomenon into account when designing and interpreting randomized trials of exercise in people with PAD.

More recently, activity can be measured using wearable technology such as activity monitors in the form of wristbands or other types of accelerometers.[85] These monitors provide objective data that reflect free-living physical activity in daily life.[85,86] The utility of these de-

vices has not been fully explored in exercise trials in patients with PAD but holds promise.[48,87,88]

Subjective Measures of Functional Status and HRQOL

Measures of walking ability provide excellent objective data, but they do not address subjective assessment of HRQOL. To comprehensively evaluate functional status and HRQOL in people with claudication, valid and feasible questionnaires should be incorporated in addition to objective measures of walking ability. A goal of assessing HRQOL in PAD is to determine whether a specific therapy that is associated with an objective response in exercise performance is also associated with the patient being able to perceive improvement in daily life.

The Walking Impairment Questionnaire (WIQ),[89] Vascular Quality of Life Questionnaire (VascuQoL),[90] Peripheral Artery Questionnaire (PAQ),[91] and Impact of PAD on Quality of Life Questionnaire[20] have been used to measure patient-reported perceptions of their walking ability or HRQOL after exercise interventions. The WIQ, PAQ, VascuQoL, and Impact of PAD on Quality of Life Questionnaire are PAD-specific measures in that they were developed specifically to measure limitations in walking or HRQOL in people with PAD.

The WIQ[89] is a disease-specific questionnaire widely used to assess the ability of patients with claudication to walk defined distances and speeds and to climb stairs. In addition, the questionnaire evaluates claudication severity and the presence of other (nonclaudication) symptoms that could potentially limit walking. The WIQ was validated against treadmill walking in patients with claudication and has been used extensively in these patients to evaluate changes in community-based walking ability resulting from an exercise training program,[92,93] stenting,[94,95] and pharmacological agents. It has also been shown to improve mortality risk prediction models.[96] Scores range from 0 to 100, with higher scores indicating better community-based walking ability.[72] This questionnaire has now been translated into and validated in >50 languages.

The VascuQol[90] is a 25-item questionnaire that assesses pain, activities, symptoms, and emotional and social domains of life. This questionnaire has been widely used in Europe to assess outcomes of interventions for patients with PAD, including exercise and revascularization in patients with claudication and critical limb ischemia. Scores for the VascuQoL are an average of all questions answered and range from 1 (worst quality of life) to 7 (best quality of life). Recently, an abbreviated version of the VascuQoL, the VascuQoL-6 has been validated[97–99] and is seen as especially useful in clinical care.[100,101]

The PAQ is a disease-specific health status questionnaire for patients with PAD that assesses both func-

tional status and HRQOL.[91,102] Currently, several studies are examining the validity of the PAQ, including translation into several languages including a Dutch version.[103] PAQ subscale and summary scores range from 0 to 100, with higher scores reflecting fewer limitations and symptoms and higher satisfaction with treatment. The PAQ has been used to assess outcomes in studies of revascularization and for a study comparing exercise rehabilitation and endovascular procedures.[77] The PAQ and WIQ overlap in assessing claudication-limited physical limitations, but the PAQ also assesses patient perception of the quality of their health care.

The Impact of PAD on Quality of Life Questionnaire[20] is a 38-item questionnaire with 5 subscales that assess the impact of PAD on multiple dimensions of life. These include social relationships and interactions, sense of self and feeling states, symptoms and limitations in physical functioning, fear and uncertainty, and positive adaptation. Scores range from 0 to 100, with higher scores indicating better HRQOL. Although relatively new, this questionnaire has been used to evaluate quality-of-life outcomes after exercise interventions in patients with moderate to severe PAD.[104,105]

The Short-Form (SF)-36[106] or SF-12[107] and the Euro-Qol-5D[108] are the most common general health status or HRQOL questionnaires used to evaluate outcomes of exercise therapy for patients with PAD. The SF-36 and SF-12 are more generic quality-of-life measures that are not specifically focused on walking endurance or speed and are not specifically focused on people with PAD. The SF-36 assesses 8 health concepts: physical functioning, role limitations resulting from physical problems, bodily pain, social functioning, general mental health, role limitations caused by emotional problems, vitality, and general health perceptions. However, exercise studies in patients with PAD have not consistently demonstrated improvements in the role physical, bodily pain, vitality, social, role emotional, and mental health domains.[64,109] Subscales are scored from 0 to 100, with higher scores indicating higher functioning.

The EuroQOL-5D[108,110] was developed to be a generic instrument for describing and attaching value to health states. This questionnaire was designed for use in countries across Europe. It has 5 domains of 5 items each, and scores range from 0 to 1. The EuroQOL was intended to be used in conjunction with other quality-of-life measures. It has been used in trials of revascularization and exercise therapy in patients with PAD.[111,112]

Table 2 summarizes the most commonly used PAD-specific and general HRQOL questionnaires with exercise therapy in patients with PAD. Full descriptions of both PAD-specific and general HRQOL questionnaires have been given elsewhere.[24] The most commonly used objective assessments are the Gardner-Skinner graded exercise test and the 6-MWT. The most commonly used subjective measures are the WIQ and either the SF-12

or SF-36. More recently, the use of PAD-specific HRQOL questionnaires, including the VascuQoL and PAQ, has been increasing.

Questionnaire measures do not always improve even when treadmill walking performance or 6-MWT improves. For example, in the CLEVER randomized trial (Claudication: Exercise Versus Endoluminal Revascularization) of SET, aortoiliac stenting, or neither therapy in people with PAD, SET improved treadmill walking performance significantly more than aortoiliac stenting, whereas aortoiliac stenting improved the WIQ distance score, the WIQ speed score, and several components of the PAQ significantly more than SET.[77] In a randomized trial of structured H-BEx in PAD, the intervention significantly improved 6-MWT distance, PWT, and the WIQ distance and speed scores more than the control but did not improve the SF-12 physical component score more than the control.[65] In a separate study, SET significantly improved treadmill walking performance and the 6-MWT in people with PAD but did not improve either the WIQ or SF-36 physical functioning measures.[64] In summary, these questionnaire measures appear to be important complements to objective measures of improvement after walking exercise interventions.

SUPERVISED EXERCISE TREADMILL TRAINING FOR INDIVIDUALS WITH CLAUDICATION

Over the past 30 years, treadmill-based SET programs have been shown to be consistently beneficial in improving walking ability as assessed by graded treadmill testing[113–119] and to be effective in patients with PAD both with and without classic symptoms of claudication.[64,66] For example, in the 15 studies[51,66,120–132] included in a meta-analysis by Parmenter and colleagues,[133] graded treadmill testing after treadmill-based SET resulted in a significant mean improvement in COD and PWD among the studies that had 12-week interventions. Improvement in COD and PWD was even greater in the studies that had a 24-week intervention (Table 3). Similarly, a meta-analysis by Fakhry et al[56] of 25 randomized trials of SET for people with PAD demonstrated that supervised walking exercise was associated with a statistically significant 180-m (95% CI, 130–238) improvement in PWT and 128-m (95% CI, 92–165) improvement in COT. In addition to improvement in walking ability, some treadmill-based SET programs have improved measures of functional status and HRQOL.[51,77,92,120,134–136]

The majority of studies evaluating SET for patients with claudication have been conducted in a supervised (usually hospital) setting, with walking exercise performed on a treadmill.[51,77,120] Treadmill-based exercise therapy for patients with PAD consists of intermittent bouts of walking exercise to moderate to moderately

Table 2. Examples of Measures of Functional Status Used to Assess Outcomes of Exercise Therapy in Patients With PAD

		Utility	Primary Measure	Detects Treatment Effect	Predicts Outcomes in PAD
Exercise tests					
	Graded Treadmill	Objective measure of peak exercise performance	Peak walking time on a treadmill	Exercise training Pharmacotherapy Revascularization Intermittent pneumatic compression	Mortality[59]
	6-MWT	Objective measure of maximal walking distance, measured in a corridor	Maximal distance walked in 6 min	Exercise training Supplement[78] Intermittent pneumatic compression[79]	Mobility loss All-cause mortality Cardiovascular mortality Cardiovascular events[80–82]
Physical activity monitors					
	Accelerometer	Objective measure of activity during daily life	Wearable device	Exercise training	Mortality Mobility loss[87,88]
General questionnaires					
	MOS SF- 36/MOS SF-12	HRQOL	Physical and mental function	Exercise training Pharmacotherapy Revascularization	
	EQ-5D	Functional status and HRQOL	State of health and function	Exercise training Revascularization	
PAD-specific questionnaires					
	WIQ	Functional status	Distance, speed, stairs, and claudication severity	Exercise training Pharmacotherapy Revascularization	Predicts all-cause and cardiovascular mortality[96]
	VascuQoL	Functional status, HRQOL	Pain, symptoms, activities, emotional, social	Exercise training Revascularization	
	PAQ	Functional status and health satisfaction	Physical function, satisfaction with care	Exercise training Revascularization Medical therapy	
	PADQOL	HRQOL	Symptoms/physical limitations, fear/uncertainty, social interactions, sense of self, feeling states, adaptation	Exercise training	

EQ-5D indicates EuroQOL 5D[95,108,110]; HRQOL, health-related quality of life; MOS, Medical Outcomes Study; PAD, peripheral artery disease; PADQOL, Impact of PAD on Quality of Life Questionnaire[20]; PAQ, Peripheral Artery Questionnaire[91,102]; SF, Short Form; 6-MWT, 6-minute walk test; VascuQoL, Vascular Quality of Life Questionnaire[90]; and WIQ, Walking Impairment Questionnaire.[77,93,94]

severe discomfort followed by short periods of rest until symptoms resolve. These exercise/rest bouts are repeated over a 30- to 60-minute exercise session. Exercise capability is most commonly measured as COT/COD and PWT/PWD. Unlike cardiac rehabilitation, there is no requirement for telemetry during SET for patients with PAD.

The following sections examine the evidence that supports the different components of a treadmill-based SET program. These include intensity, accumulated exercise per session, claudication level during exercise, progression of increasing exercise volume, work-to-rest ratio, frequency of exercise sessions, and program duration.

Table 3. Change in Walking Distance From Baseline After Supervised Exercise Therapy in Patients With PAD

Duration of supervised program, wk	Mean (SD) Change in COD, m	Mean Change in COD, %	Mean (SD) Change in PWD, m	Mean Change in PWD, %
12 (8 studies)[120–126,132]	156.60 (46.97)	103	283.10 (69.32)	79
24–52 (7 studies)[51,66,127–131]	251.23 (75.72)	167	334.06 (78.14)	92
Overall (15 studies)	203.93 (77.93)	128	307.45 (75.58)	82

COD indicates claudication onset distance; PAD, peripheral artery disease; and PWD, peak walking distance.

Intensity

Intensity is defined as the effort of the walking task as a percentage of the measured maximal workload or peak oxygen consumption (peak $\dot{V}o_2$) attained during a standardized treadmill test. One study that investigated the effect of different exercise intensities found no differences between low- and high-intensity exercise based on percent of maximal workload, provided that the total amount of exercise was similar between groups. This suggests that exercise intensity may not be related to the amount of improvement in walking distance.[137] In contrast, intensity of exercise training may be related to improvement in peak $\dot{V}o_2$. A meta-analysis by Parmenter et al[133] suggested an overall greater improvement in peak $\dot{V}o_2$ with interval exercise training consisting primarily of short intervals of exercise at a vigorous intensity (70%–80% $\dot{V}o_2$ peak) compared with intermittent exercise at a moderate intensity. Additional research is required to elucidate whether high-intensity/short-interval exercise is as beneficial in improving walking distance as moderate-intensity exercise.

Duration of Exercise per Session

Few studies have investigated the optimal session duration, and there has been a lack of reporting of actual exercise/rest time in published studies, which limits the understanding of an optimal exercise session duration. A previous meta-analysis found that sessions lasting >30 to 60 minutes were more beneficial.[113] More recent meta-analyses suggest that 30 minutes of exercise results in an improvement in walking distance similar to that of 60 minutes of exercise and that improvement appears to peak at 45 minutes.[56,116,133]

Claudication Severity During Walking Exercise

The majority of supervised exercise treadmill trials have used severity of claudication as a guide to instruct patients when to stop the exercise bout. Depending on the protocol, patients are instructed to walk to onset of or moderate or near-maximal level of claudication. Most protocols specify that exercise is initiated at an intensity that induces onset of claudication within 3 to 5 minutes and moderate to moderately severe claudication within 8 to 10 minutes. Previous meta-analyses and current guidelines suggest that exercise treadmill training should be performed to near-maximal claudication levels.[6,56,113–119,138] However, a recent meta-analysis found no differences in walking exercise in which participants walked to a mild claudication level compared with walking to severe claudication.[139] This suggests that exercise training to either mild or severe levels of claudication may be effective for walking improvement in PAD.[133] To the best of our knowledge, no adequately powered randomized clinical trials have compared the relative effects of walking to different levels (low versus moderate versus severe) of claudication. Treadmill exercise intermittently performed to a level of mild to moderate claudication allows physiological improvement or training adaptation to occur.[140] This also allows patients with claudication to avoid repeated near-maximal claudication that may reduce adherence levels.

Progression of Increasing Volume of Exercise

Exercise volume takes into consideration both duration (minutes) and workload (metabolic equivalents of task) of the exercise performed. No studies were identified that have directly compared different progression schemes of exercise prescription for claudication rehabilitation. In general, it is accepted that progression of exercise should occur gradually throughout the exercise program to allow continued adaptation to the training stimulus. This can be accomplished by manipulating the components of the exercise prescription, which include the duration, workload (determined by the grade and speed of the treadmill), and frequency of exercise, as well as the work-to-rest ratio.[140] The supervising exercise therapist should make the decision on how to progress the exercise prescription on the basis of each individual patient. Most studies increase exercise volume by alternating increases in duration and workload. As exercise becomes easier and individuals can walk a given duration, the workload (grade or speed of the treadmill) is increased, usually initially resulting in shorter exercise bouts, which subsequently become longer with continued training. This pattern is repeated throughout the exercise program. Because no studies have investigated optimal rates of progression of exercise in SET for patients with claudication, it is prudent to increase the exercise volume at a rate no faster than every 1 to 2 weeks, thereby following exercise progression guidelines for older adults with chronic disease.[140]

Work-to-Rest Ratio

No studies were identified that specifically compared exercise bout durations (ie, the time to the prescribed level of claudication) relative to the subsequent rest duration (long versus short duration). Most published studies prescribe the use of intermittent exercise to moderate/moderately severe claudication, interspersed with rest periods until the claudication subsides. Because the time it takes for claudication to subside differs among individuals,[141] it is not possible (or necessary) to standardize rest periods in this population. To

maximize the time spent exercising during each session, the shortest rest period needed to dissipate symptoms is ideal. Current AHA/ACC PAD guidelines suggest that the rest period should be to the point of cessation of claudication (usually occurring within 2–5 minutes).[6] Current AHA/ACC PAD guidelines also state that the exercise workload should be such that onset of claudication levels is reached within 3 to 5 minutes of exercise initiation.[6] This recommendation is based primarily on 2 meta-analyses from 1995 and 2004.[113,116] No original research studies were identified that have directly compared the efficacy of exercise training with different lengths of exercise bouts.

Frequency

Current AHA/ACC PAD recommendations are based on meta-analyses that have shown that the frequency of the SET program should be at least 3 times per week.[6] The evidence suggests that an exercise frequency of 3 sessions per week is associated with better outcomes compared with <3 times per week, but additional sessions do not appear to result in greater benefits.[113,116] To the best of our knowledge, no randomized controlled trials have been specifically designed to investigate the optimal frequency of exercise training on outcomes in walking distance.

Program Duration

Several recommendations about optimal program duration have been reported, ranging from 12 weeks to 6 months of SET.[6,56,113–119,133,138] Current recommendations suggest a minimum of 12 weeks' duration for optimal improvement in treadmill walking ability with a goal of completing at least 6 months of exercise training.[6] The effect of treadmill-based SET on treadmill walking performance has been shown to occur as early as 6 weeks into the program, with a larger response at 12 weeks.[138,142] This effect appears to be maintained over 12 months with an effect size ranging between 0.5 to >0.8 for follow-up periods at 6, 12, 24, and 52 weeks, with the largest effect size occurring at 12 weeks.[56,138,142]

Few studies have specifically investigated the optimal duration of an SET program. Gardner et al[130] showed a significant improvement in treadmill walking outcomes after 2 months of exercise despite much lower total exercise volume than was achieved with longer durations of 3 to 4 and 5 to 6 months. In this study, the greatest improvement in treadmill walking distances occurred during the first 2 months of the exercise training program, and walking distance improved at a much more gradual rate beyond 2 months. This study supports the current recommendations of 3 months of SET followed by ongoing lifestyle changes that include continued

exercise training to maintain achieved benefits of the supervised exercise program.[6] In addition, a Cochrane review and several meta-analyses recently indicated that the largest effect size in treadmill walking performance occurred at 3 months of SET. This improvement was maintained, but was not greater, at 6 months.[56,116,117,130,138] The 6-MWT distance improves more gradually in response to supervised treadmill exercise and is more likely to peak after 6 months of exercise training.[64]

Summary

Although SET programs for patients with PAD should be individualized with regard to duration, intensity, frequency of exercise, and the work-to-rest ratio, currently available evidence suggests parameters for these program elements (Table 4). Exercise sessions should progress up to a target goal of accumulating 30 to 45 minutes of treadmill walking per session. Exercise should be carried out at an intensity that elicits mild claudication pain within 5 minutes and moderate to moderately severe claudication within 10 minutes followed by rest until claudication pain subsides. Randomized trials of SET that demonstrate significant improvement in walking performance have typically asked patients with PAD to walk for exercise 3 times per week.[109]

COMPARISON OF EXERCISE AND REVASCULARIZATION ON FUNCTIONAL OUTCOMES IN PATIENTS WITH PAD

In the last 3 decades, a number of clinical trials have compared the effects of SET programs with various revascularization approaches or medical therapy in patients with claudication[77,136,143–151] (Table 5) .Their study designs were heterogeneous, but they can be grouped into 4 main categories: (1) those comparing SET, revascularization, and the combination of SET and revascularization[143,149,150]; (2) those comparing SET and revascularization[144–146,148]; (3) those comparing SET and SET plus revascularization[147,151]; and (4) the CLEVER study,[77,136] which compared SET, revascularization, and optimal medical therapy. An outline of the design and the main results of these trials are reported in the following paragraphs.

SET Versus Revascularization Versus SET Plus Revascularization

Lundgren et al[143] randomized 75 patients with claudication resulting from above-the-knee occlusive disease to surgical revascularization, surgical revascularization with subsequent physical training, and physical training

Table 4. Exercise Prescription for Supervised Exercise Treadmill Training in Patients With Claudication

Modality	Supervised Treadmill Walking
Intensity	40%–60% maximal workload based on baseline treadmill test or workload that brings on claudication within 3–5 min during a 6-MWT
Session duration	30–50 min of intermittent exercise; goal is to accumulate at least 30 min of walking exercise
Claudication intensity	Moderate to moderate/severe claudication as tolerated
Work-to-rest ratio	Walking duration should be within 5–10 min to reach moderate to moderately severe claudication followed by rest until pain has dissipated (2–5 min)
Frequency	3 times per week supervised
Program duration	At least 12 wk
Progression	Every 1–2 wk: increase duration of training session to achieve 50 min. As individuals can walk beyond 10 min without reaching prescribed claudication level, manipulate grade or speed of exercise prescription to keep the walking bouts within 5–10 min
Maintenance	Lifelong maintenance at least 2 times per week

Based on currently available evidence. Exercise prescription should be individualized to each patient as tolerated. 6-MWT indicates 6-minute walk test.

alone. Walking performance on a treadmill (COD and PWD) was improved in all 3 groups, with the best effects seen in patients who underwent surgical revascularization and physical training followed by those who had surgery as their only treatment and then by the group with physical training only.

Mazari et al[149] compared the effects of angioplasty, SET, and angioplasty plus SET on PWD and HRQOL (SF-36 and VascuQoL) in patients with claudication caused by femoropopliteal disease. The early results of the study at the 1- and 3-month follow-up were reported in 2010 and showed improved COD and HRQOL in all treatment groups. Intergroup analysis indicated that angioplasty plus SET led to greater improvement in PWD than angioplasty or SET alone, without significant improvement in HRQOL.[149] The final 12-month follow-up data were published in 2012 and confirmed the previous evidence of improved PWD and HRQOL in all groups. However, the effects of angioplasty and SET on clinical outcomes were not durable. Notably, angioplasty plus SET was associated with more sustained improvement in PWD without significant improvement in HRQOL.[150]

SET Versus Revascularization

Creasy et al[144] compared the effects of angioplasty and SET on resting COD and PWD on a treadmill in 56 patients with arterial occlusive disease. These parameters were evaluated every 3 months for 15 months. After angioplasty, PWD had significantly increased at 3 months but did not improve thereafter. In contrast, in the exercise group, PWD was significantly increased at 6, 9, 12, and 15 months. Thirty-seven of the participants in the Creasy et al study underwent re-evaluation to assess their long-term outcomes. At the 70-month follow-up, there was a small, nonsignificant increase in PWD in both groups, with no differences noted between angioplasty and SET.[145]

Gelin et al[146] randomized 264 unselected patients with claudication to SET, revascularization (open surgical or endovascular procedures), or observation to compare the effects of these treatments on treadmill walking capacity (treadmill walking power, expressed in Watts, and PWD). At the 1-year follow up, a significant increase in treadmill walking power and PWD was observed in the invasively treated group but not in the SET or control group.

More recently, Spronk et al[152] compared the clinical effectiveness of primary endovascular revascularization with hospital-based SET as the initial treatment for patients with claudication (Rutherford category 1, 2, or 3). Clinical effectiveness included clinical success (improvement in at least 1 category in the Rutherford scale above pretreatment level, measured after treadmill walking), functional capacity (COD and PWD), and HRQOL (SF-36 and VascuQoL). At 6 months, significantly fewer patients in the revascularization group than in the SET group had symptoms of ipsilateral claudication, but this difference was not observed at 12 months. COD and PWD were improved at 6 and 12 months in both treatment groups. After adjustment for the baseline variables, functional capacity was similar between the 2 groups at the 6- and 12-month follow-up. Both SET and revascularization improved HRQOL scores without significant differences between the 2 groups at 6 or 12 months after adjustment for baseline variables.[152]

SET Versus SET Plus Revascularization

At least 3 studies compared SET alone and SET plus revascularization. Greenhalgh et al[147] enrolled patients with mild to moderate claudication in 2 trials (femoropopliteal, 93 patients; and aortoiliac, 34 patients) and randomized them to angioplasty with SET and best medical therapy or to SET and best medical therapy alone. The SET program consisted of 30 minutes of continuous exercise to maximal pain once a week for 6 months. The primary outcomes included COD and PWD on a treadmill. Secondary outcomes included ABI measurement and HRQOL as measured by the SF-36. In the femoropopliteal trial, at the 24-month follow-up, COD and PWD were significantly higher in the angioplasty group compared with the SET and best medical therapy alone groups. Similar, but not statistically significant, results were observed in the aortoiliac trial. At 24 months, the ABI was significantly higher in the

Table 5. Supervised Exercise Therapy Versus Peripheral Revascularization in Patients With PAD

Author, Year	Inclusion Criteria	Stenosis Location	Supervised Exercise		Revascularization		SET+Revascularization		Follow-Up	Outcomes
			n	Exercise Program	25	Type	n	Type	Duration, mo	Walking Distance
Lundgren et al,[143] 1989	Moderate to severe claudication PWD ≤600 m	Above knee	25	30 min 3 times per week for ≥26 wk	15 15	Surgical revascularization	25	Combination of individual treatments	13	COD: SET=+120 ±47 m; Revascularization= +320 ± 78 m; Revascularization+SET=+489±81 m PWD: SET=+276±66 m; Revascularization=361±73 m; Revascularization+SET=474 ±81 m
Creasy et al,[144] 1990	Unilateral claudication Maximum COD <350 m	Iliac, iliac+SFA, SFA	13 13	30 min 2 times a week for 24 wk	15 15	Balloon angioplasty		NA	3, 6, 9, 12, 15	PWD: SET significantly increased at 6, 9, 12, 15 mo Revascularization: significantly increased at 3 mo but no improvement thereafter
Perkins et al,[145] 1996	Unilateral claudication Maximum COD <350 m	Iliac, iliac+SFA, SFA	13 13	30 min 2 times a week for 24 wk	15 15	Balloon angioplasty		NA	70 (range, 45–83)	PWD: small, nonsignificant increase in both groups; no differences between groups
Gelin et al,[146] 2001	Stable claudication ABI <0.6Calf blood flow <25 mL·m^{-1}·100 g^{-1}	Not specified	88	30 min 3 times a week for months 1–6 and 2 times a week for months 7–12	87	Endovascular or surgical revascularization		NA	12	SET: no improvements in PWD or maximum exercise power (Watts); values not provided Revascularization: maximal exercise power and PWD were improved; values not provided
Greenhalgh et al,[147] 2008	Claudication	Aortoiliac Femoropopliteal	15 45	30 min ≥1 times a week for 26 wk		NA	19 48	Balloon angioplasty, occasional stent	24	Aortoiliac trial: COD: Attaining 200 m without symptoms: SET=25%; Revascularization+SET=61% PWD: SET=+168 m; Revascularization+SET=+354 m Femoropopliteal trial: COD: Attaining 200 m without symptoms: SET=22%; Revascularization+SET=63% PWD: SET=+155 m; Revascularization+SET=+245 m
Spronk et al,[152] 2009	Claudication maximum COD <350 m	Iliac and femoropopliteal	75	30 min 2 times a week for 24 wk	60	Balloon angioplasty with/without stent		NA	6, 12	At 6 mo: COD: SET=+899 m; Revascularization=+679 m PWD: SET=+1138 m; Revascularization=+755 m; At 12 mo: COD: SET=+943 m; Revascularization=+806 m; PWD: SET=+1034 m; Revascularization=+826 m Both SET and revascularization improved QOL No significant differences between groups at 6 or 12 mo
Mazari et al,[149] 2010	Unilateral claudication	Femoropopliteal	51	24–48 min 3 times a week for 12 wk	60	Balloon angioplasty	49	Balloon angioplasty	3	COD: SET=+28 m; Revascularization=+22 m; SET+revascularization=+58 m PWD: SET=+47 m; Revascularization=+35 m; Revascularization+SET=+144 m No significant differences between groups in HRQOL

(Continued)

Table 5.   Continued

Author, Year	Inclusion Criteria	Stenosis Location	Supervised Exercise		Revascularization		SET+Revascularization		Follow-Up	Outcomes
			n	Exercise Program	25	Type	n	Type	Duration, mo	Walking Distance
Mazari et al,[150] 2012	Unilateral claudication	Femoropopliteal	51	24–48 min 3 times a week for 12 wk	46	Balloon angioplasty	49	Balloon angioplasty	12	Improved PRWD and HRQOL in all treatment groups Revascularization+SET was associated with more sustained improvement in PRWD without significant advantage in HRQOL
Murphy et al,[77] 2012	Moderate to severe claudication	Aortoiliac	38	60 min 3 times a week for 26 wk	41	Stent		NA	6	COT: SET=+3.0 min; Revascularization=+3.6 min PWT: SET=+5.8 min; Revascularization=+3.7 min HRQOL improved in both groups; greater in revascularization than SET
Murphy et al,[136] 2015	Moderate to severe claudication	Aortoiliac	34	60 min 3 times a week for 26 wk		Stent		NA	18	COT: SET=+3.4 min; Revascularization=+3.0 min PWT: SET=+5 min; Revascularization=+3.2 min Improvements in HRQOL persisted at 18 mo and were greater for revascularization vs SET
Fakhry et al,[151] 2015	Claudication PWD 100–500 m	Aortoiliac Femoropopliteal	10 6	30–45 min 2–3 times a week for months 1–3, 1 time a week for months 4–6, and 1 time a month for months 7–12		NA	106	Balloon angioplasty, stenting if unsuccessful	12	COD: SET=+577 m; Revascularization+SET=+1003 m PWD: SET=+670 m; Revascularization+SET=+973 m HRQOL significantly improved in both groups; greater in the combination therapy than SET alone.

ABI indicates ankle-brachial index; COD, claudication onset distance; COT, claudication onset time; HRQOL, health-related quality of life; NA, not available; PAD, peripheral artery disease; PRWD, patient-reported walking distance; PWD, peak walking distance; PWT, peak walking time; QOL, quality of life; SET, supervised exercise therapy; and SFA, superficial femoral artery.

angioplasty group in both trials, whereas no overall differences were noted between groups in HRQOL.[147]

Fakhry et al[151] randomly allocated 212 patients to either revascularization plus SET (combination therapy) or SET alone. The primary end point was the difference in PWD on the treadmill at 12 months; secondary end points included treadmill COD, VascuQoL score, and SF-36 scores. At 12 months, the improvement in PWD, COD, VascuQoL score, and SF-36 physical functioning score was significantly greater in the group receiving combination therapy than in the SET alone group. However, the scores of the SF-36 domains of physical role functioning, bodily pain, and general health perceptions did not differ between groups.[151]

SET Versus Revascularization Versus Optimal Medical Therapy (CLEVER)

In the CLEVER study, Murphy et al[77] randomized 111 patients with aortoiliac PAD to optimal medical care, optimal medical care plus SET, or optimal medical care plus stenting. The primary end point was the change in PWT on a graded treadmill test at 6 months compared with baseline. Secondary end points included free-living step activity; HRQOL with the WIQ, PAQ, and SF-12; and cardiovascular risk factors. At the 6-month follow-up, SET led to the largest change in PWT followed by stenting and finally optimal medical care. Compared with optimal medical care, SET and stenting significantly improved HRQOL. Of note, for most scales, the extent of improvement was greater with stenting than with SET.[77] Of the initial 111 patients, 79 completed the 18-month clinical and treadmill follow-up assessment, and their results were published in a subsequent article.[136] At the 18-month follow-up, the improvement in PWT from baseline was similar between the SET and stenting groups, and it was significantly higher for both groups than for the optimal medical care group. Compared with the optimal medical care group, the increase in COT was larger in the SET group but not in the stent recipients. The improvements in the HRQOL scales noted at 6 months were also observed at 18 months, some of which were greater for stenting compared with SET or optical medical care.

Taken together, the results of these studies suggest that both SET and revascularization improve functional outcomes in patients with aortoiliac and femoropopliteal arterial occlusive disease and claudication and that their effects appear to be additive.

EFFICACY OF EXERCISE THERAPY IN ASYMPTOMATIC PAD

The prevalence of asymptomatic PAD ranges from 20% among patients with PAD identified in a noninvasive vascular laboratory to >60% in populations of older community-dwelling men and women.[153–156] Although people with asymptomatic PAD report no exertional leg symptoms, they have significantly greater functional impairment, faster rates of functional decline, and higher rates of mobility loss compared with people without PAD.[15,22,80,156,157] Some patients with asymptomatic PAD limit their physical activity to avoid leg symptoms, and others appear to slow their walking speed to avoid leg symptoms.[22,157] Many people with PAD who report no exertional leg symptoms develop leg symptoms when they begin an exercise program that requires greater walking activity or walking speed than they are accustomed to.

No adequately powered randomized clinical trials have been conducted to specifically address whether exercise interventions improve walking performance in people with asymptomatic PAD. However, at least 5 randomized trials of exercise in PAD (3 of SET and 2 of home-based exercise) included people with PAD who did not have classic symptoms of claudication, including individuals who were asymptomatic.[64–66,158] In these 5 trials, the proportions of participants without classic claudication symptoms ranged from 64% to 100%. Four of the 5 trials, composed predominantly of participants with PAD without claudication, demonstrated that walking exercise significantly improved walking performance in the overall study populations. The SILC randomized trial (Study to Improve Leg Circulation) of supervised treadmill exercise in participants with PAD included those with classic claudication, asymptomatic PAD, or PAD associated with atypical symptoms. Although the study did not have sufficient statistical power to definitively compare outcomes between participants with PAD according to specific leg symptoms, the study did not demonstrate significant differences in response to exercise according to leg symptoms at baseline. In summary, although no adequately powered trials have been conducted, evidence suggests that exercise programs significantly improve walking endurance in patients with PAD who are asymptomatic.

DESCRIPTION OF STRUCTURED HOME-BASED EXERCISE PROGRAMS FOR PAD AND THEIR EFFICACY

Effective structured H-BEx interventions have the potential to be more accessible and acceptable to patients with PAD than SET. SET programs, which typically require travel to the exercise center 3 times per week,

can be burdensome and costly if medical insurance does not pay. A systematic review of recruitment for randomized trials of SET for PAD concluded that 69% of 1541 eligible participants with PAD refused participation, and many refused because of the burdensome requirements of SET programs.[159] For the large number of people who find the demands of SET too difficult, structured H-BEx, which is carried out around the home or in the home, may be a reasonable alternative.

Early studies of H-BEx for patients with symptomatic PAD reported no benefit from unsupervised exercise.[121,123,160] However, these early trials often included only general advice to patients to go home and exercise and did not incorporate behavioral change techniques, which may be essential to help ensure adherence to home-based exercise programs in patients with PAD. Since 2011, 3 randomized trials have demonstrated significant benefit from structured H-BEx in patients with PAD.

Gardner et al[67] randomized 180 participants with PAD and claudication to 1 of 3 groups for 12 weeks: treadmill-based SET, structured H-BEx, or a light resistance training (control) group for 12 weeks. Participants randomized to structured H-BEx walked for exercise in an unsupervised setting 3 days weekly, working up to 45 minutes per session. Participants returned to meet with a study investigator 4 times at 1- to 4-week intervals during the 12-week study. At 12-week follow-up, the supervised exercise group increased their PWT time by 192 seconds, the structured H-BEx group increased their PWT by 110 seconds, and the control group increased their PWT by 22 seconds.[67] The SET group increased their 6-MWT distance by 15 m compared with 45 m in the home-based exercise group and 4 m in the control group. Improvement in the 6-MWT was significantly greater in the home-based exercise group than in the SET group.

The GOALS trial (Group Oriented Arterial Leg Study) tested the ability of a group-mediated cognitive behavioral intervention to help participants with PAD adhere to structured H-BEx, thereby improving their walking performance.[65] One hundred ninety-two participants with PAD were randomized to either a group-mediated cognitive behavioral intervention or an attention control group for 6 months.[65] The intervention consisted of group meetings of participants with PAD and a facilitator once weekly for 6 months. During group meetings, the facilitator led group discussions about effective behavior change methods and adhering to H-BEx, including goal setting, self-monitoring, exercising in cold weather, managing leg pain during exercise, and overcoming other obstacles to exercise adherence. At the 6-month follow-up, the intervention group achieved a 53.5-m greater increase in 6-MWT performance, a 1.01-minute greater increase in PWT, and a 1.02-minute greater increase in COT compared with the control

group. The structured H-BEx intervention also significantly improved physical activity and the WIQ distance score compared with the control group. Six months after the final on-site study intervention, the intervention group continued to have better 6-MWT performance than the control group.[161]

In contrast to these studies, Collins et al[162] randomized 145 participants with PAD and diabetes mellitus to a behavioral intervention versus an attention control group for 6 months. The behavioral intervention consisted of an individualized counseling session at baseline, followed by 1 walking session per week with an instructor at an exercise center and 3 days of walking at home for up to 50 minutes of exercise per session. Participants in the intervention group also received biweekly telephone calls during which an instructor reviewed their readiness to progress their exercise prescription. Tailored, scripted feedback based on their readiness was provided. The attention control group received biweekly calls from a study investigator during which the participant and study investigator discussed risk factor management. At the 6-month follow-up, there were no differences in PWT or COT (primary outcome) between the home-based intervention and the control group. However, participants in the intervention group had improved walking speed and HRQOL (secondary outcomes) compared with the attention control group.

Finally, a recent randomized trial of structured H-BEx that tested the ability of telephone calls by a coach combined with a wearable activity monitor showed no improvement in the 6-MWT at the 9-month follow-up.[163] Home-based exercise interventions that have been successful have included occasional visits to the medical center to meet with a coach.

Based on the 3 randomized trials that demonstrated benefits of home-based exercise, AHA/ACC clinical practice guidelines for PAD recommend home-based exercise for patients with PAD, giving it a Class IIa, Level of Evidence A designation and indicating that this is a reasonable intervention for patients with PAD.[6] Advantages of H-BEx include that it is less burdensome and more convenient for people with PAD to walk in their neighborhood or even within their home environment than to travel to a supervised exercise center.[65,161] In addition, H-BEx preferentially improves over-ground walking, which is more practical for navigating walking activity in daily life.[57,60]

Practical Aspects of Implementing a Home-Based Exercise Program for Patients With PAD

Successful programs of structured H-BEx have advised patients with PAD to walk for exercise 3 to 5 times per week. Two trials advised patients to walk at a self-selected pace, whereas the GOALS trial advised participants

to walk to maximal ischemic leg pain.[65,67,126] Effective H-BEx programs for patients with PAD have asked patients to set goals for walking exercise and used exercise logs to facilitate self-monitoring.[65,67,126] Some have used activity monitors.[67,126] All have included a "coach" to whom the patient is accountable. Therefore, patients with PAD who are advised to engage in home-based exercise should be instructed to write down walking exercise goals and to record their walking exercise activity each week. Walking exercise goals should be as specific as possible. This information should be reviewed periodically by a coach or clinician, and feedback should be provided regularly to the patient. H-BEx programs should be individualized, starting with as little as 10 minutes of walking exercise per session and increasing walking exercise per session by ≈5 minutes per week until the patient is walking for exercise 45 to 50 minutes per session (excluding rest periods).

ALTERNATIVE EXERCISE STRATEGIES FOR PATIENTS WITH PAD

Whereas treadmill walking into ischemic pain is the most recommended form of exercise therapy for patients with claudication, other modes of exercise have also been studied and shown to have some efficacy in improving walking outcomes in patients with PAD.

Pain-Free Walking Exercise Training

Several randomized trials have investigated the efficacy of supervised pain-free treadmill training in patients with claudication.[164–167] All were conducted by the same investigative team. In contrast to the requirement that patients walk to moderate to moderately severe ischemic pain, these programs instructed participants to stop at the very beginning of claudication symptoms. Three randomized controlled studies[164–166] compared a total of 196 subjects who participated in either 3 months of treadmill walking until the onset of claudication or a usual care control group who did not change their activity habits. The results from these studies were consistent, showing an average increase in COD of 110% (217 m) and in PWD of 52% (247 m).

A fourth study[167] is the only study to directly compare treadmill training whereby participants walk to moderate claudication with pain-free treadmill training. Fifty-two randomized subjects completed a 12-week program consisting of either moderate or pain-free training. Both groups had significant improvement in COD and PWD over time, and there were no significant differences between groups. The moderate training group had a 120% (125 m) increase in COD and a 100% (393 m) increase in PWD. The pain-free training group had a 93% (141 m) increase in COD and a 98% (465 m) increase in PWD.

These studies provide evidence that pain-free treadmill training improves walking ability in patients with claudication and that this improvement was similar to that seen with training that requires patients to walk to moderate claudication pain. Pain-free treadmill exercise might be more palatable to some patients for whom walking to pain is less well tolerated, which could result in greater compliance with a walking program and better patient outcomes. Larger randomized controlled trials are needed to confirm the results in additional patient populations.

Leg Cycling Exercise Training

Few studies have evaluated the efficacy of lower-extremity cycling to improve claudication in patients with PAD.[168–170] Sanderson et al[168] randomized 41 individuals with symptomatic PAD to treadmill walking, leg cycling, or control and found significantly less improvement in participants who performed 6 weeks of lower-extremity cycling versus those who performed 6 weeks of treadmill walking. The exercise intervention consisted of ten 2-minute bouts of exercise, each separated by 2 minutes of rest, for a total of 20 minutes of exercise per session. PWD improved by 43 m in the leg-cycling group versus 215 m in the treadmill group, whereas the control group decreased by 16 m. COD increased only 16 m in the leg-cycling group versus 174 m in the treadmill group and 49 m in the control group. In contrast, both Walker et al[169] and Zwierska et al[170] found significant increases in both COD (93% and 57%, respectively) and PWD (50% and 31%, respectively) during a shuttle walk test in lower-extremity cycling groups versus control participants. The shuttle walk test requires participants to walk back and forth between 2 cones placed 10 m apart. Walking speed is controlled by audio signals recorded at steadily decreasing intervals. The test ends when a participant cannot reach the opposite cone before the audio signal sounds. Total distance walked is recorded.[171] Sanderson et al[168] reported that although overall the treadmill group had greater improvement in walking distance, 8 of the 15 participants in the cycling group had a positive response to training. It should be noted that the duration (6 weeks) and the amount of exercise per session (20 minutes) are less than current guideline recommendations.[6]

Aerobic Arm Exercise Training

A series of studies have been conducted comparing arm ergometry (arm cranking or arm cycling) with leg cycling and control[169,170] or control only[172] in a total of 212 participants. Exercise training consisted of 2 times per week for 40-minute sessions (20 minutes of exercise per session), and the program duration was 12 to 24 weeks. Those participating in the arm cycling groups

showed an average of 50% improvement in COD and 30% in PWD. The Exercise Training for Claudication study[125,173] randomized 41 participants to 12 weeks of 3 times per week supervised treadmill training or arm cycling alone or in combination versus usual care in patients with claudication. Arm-cycling participants had a 133-m (82%) improvement in COD versus a 9-m improvement (54%) in the treadmill group, whereas the control group improved by 4 m (3%). PWD improved by 182 m (53%) in the arm-cycling group versus 295 m (69%) in the treadmill group, whereas the control group improved by 45 m (12%).[125] This evidence suggests that upper-extremity aerobic exercise also significantly improves walking ability in people with PAD. Although the mechanism of this response has not been definitively proven, it is hypothesized that it could be related to improvement in systemic endothelial or cardiorespiratory function, which are well-established benefits of aerobic exercise.[125,133,172]

Resistance Training

Several investigators have evaluated the effects of resistance training on changes in walking ability in patients with claudication with somewhat mixed results. One small study[51] found that treadmill exercise was superior to resistance training, whereas 2 studies[66,174] found no difference between the 2 interventions. None of the trials was designed with sufficient statistical power to detect a difference between exercise and strength training. A fourth study[175] found that high-intensity resistance training was superior to low-intensity resistance training in improving walking distance in individuals with PAD (Table 6). Both resistance training groups performed 3 sets of 8 repetitions of exercises for 7 different muscle groups. The high-intensity group began at 50% of the 1-repetition maximum and then progressed over 4 sessions to 80% of 1-repetition maximum. The 1-repetition maximum is the amount of weight a person can lift in 1 repetition. The low-intensity group began at 20% of the 1-repetition maximum and progressed over 4 sessions to 30% of the 1-repetition maximum. In the interpretation of the results of these studies, it is important to consider the exercise regimen of different forms of exercise, the duration of the exercise intervention, and the characteristics of the populations studied.

VARIABILITY OF RESPONSE

Although randomized trials consistently show that treadmill-based SET improves treadmill walking performance in people with PAD, there is some degree of variability in the magnitude of improvement between randomized trials. In the 15 treadmill-based exercise studies[51,66,120–132] included in the meta-analysis by Parmenter and col-

Table 6. Efficacy of Resistance Training on Treadmill Walking Ability in Patients With PAD

Author, Year	Sample Size, n	Program Duration, wk	Change With Resistance Training, m (%)	Change With Treadmill Walking Group, m (%)	Change With Control Group, m (%)
Hiatt et al,[51] 1994	29	12	PWD: +107 (30) COD: +1.6	PWD: +273 (74) COD: +182 (103)	PWD: −5 (−1) COD: −38 (−19)
McDermott et al,[66] 2009	156	26	6-MWT: −3 (−0.6) PWD: +129 (34) COD: +102 (60)	6MWT: 20.9 (6.4) PWD: +212 (51) COD: +156 (110)	6-MWT: −15 (−4.7) PWD: 27 (7.8) COD: 67 (50)
Ritti-Dias et al,[174] 2010	30	12	PWD: +157 (25) COD: +146 (42) Change With High-Intensity Resistance Training	PWD: +149 (26) COD: +127 (37) Change With Low-Intensity Resistance Training	NA
Parmenter et al,[175] 2013	22	26	6-MWT (peak): +60 (19) 6-MWT (onset): +77 (77)	6-MWT (peak): −9 (−12) 6-MWT (onset): −3 (−2)	6-MWT (peak): −10 (−2) 6-MWT (onset): −45 (−20)

COD indicates claudication onset distance on a graded treadmill test; COT, claudication onset time; NA, not available; PAD, peripheral artery disease; PWD, peak walking distance on a graded treadmill test; and 6-MWT, 6-minute walk test.

leagues,[133] graded treadmill testing resulted in a mean improvement in COD ranging from 92 to 243 m among the studies that had 12-week interventions. The change in PWD ranged from 191 to 402 m. In the meta-analysis by Fakhry et al,[56] of 24 walking-based trials (both treadmill-based and nontreadmill walking) included in the meta-analysis for PWT, 9 (37.5%) showed no benefit of SET compared with control, and of 20 trials included in the meta-analysis for COT, 7 (35%) showed no benefit of SET compared with control.[56] Of the 21 trials that reported absolute data for change in PWD, 15 (71%) reported >50% improvement and 5 (21%) reported >100% improvement in PWD.[56]

These studies were conducted over a span of >20 years and had a wide range of variability in terms of participant characteristics and exercise training protocols. Thus, some of the variability in outcomes may be related to the specific characteristics of the intervention because variability existed in program length, use of treadmill walking exercise (versus nontreadmill walking exercise), frequency and duration of exercise, and exercise intensity.[56] For example, in the meta-analysis by Fakhry et al,[56] trials that did not use treadmill walking in the intervention did not demonstrate significant improvement in treadmill walking performance. However, in meta-regression, only the duration of the exercise program was associated significantly with the presence of improvement in treadmill walking performance after SET.[56] Programs with a duration of 12 to 26 weeks achieved greater benefit than programs with a duration of <12 or >26 weeks.[56] In summary, although variability exists, SET programs are generally consistent overall in demonstrating improvement in treadmill walking performance.

Few studies have reported variability in response to walking exercise programs within individual trials of patients with PAD. However, available evidence suggests that there are no clinical characteristics that consistently identify people who will not benefit from walking exercise interventions. For example, post hoc analyses of the GOALS trial[65] demonstrated that significant benefit occurred regardless of baseline participant characteristics, including age, 6-MWT performance, ABI value, sex, black race, and presence versus absence of diabetes mellitus. Similarly, in the SILC trial, there were no meaningful differences in results according to the presence versus absence of exertional leg symptoms or ac-

Table 7. Research Priorities for Exercise Interventions in Patients With PAD

Research to identify the biological pathways by which exercise improves walking performance
Further study of sex-specific outcomes to help determine whether there are differences in response to exercise between men and women
Research to understand better the variability in response and nonresponse to different exercise therapies to enhance the clinician's ability to tailor the therapy for different patient abilities and preferences
Studies that directly compare different exercise training modalities, duration, intensity, session frequency, work-to-rest ratios, and amount of supervision; should be conducted with standardized testing methods and reporting of outcomes to allow comparison across studies
Identification of the optimal form of exercise for individual patients that incorporates personalized selection of exercise to maximize adherence to exercise and functioning (home based, treadmill, cycling, resistance training) for individuals with PAD
Inclusion of functional and quality-of-life outcomes in all intervention studies for claudication to provide broader understanding of the effect of exercise therapies on patients' lives
Studies that evaluate long-term functional and cardiovascular risk outcomes of participation in exercise programs
Clinical implementation studies with the transition from randomized controlled clinical trials to a real-world clinical population
Identification of optimal methods to increase participation of patients with PAD in exercise therapy
Optimal strategies to transition patients from supervised, hospital-based settings to community-based settings to increase the likelihood of life-long behavior change

PAD indicates peripheral artery disease.

cording to the presence versus absence of claudication symptoms.[66] In a post hoc analysis of 48 participants in a randomized trial of SET, men and women significantly and meaningfully improved their PWT (effect size, 1.13 for men and 0.88 for women), but the absolute change in PWT was significantly greater for men than for women.[176] These results are not consistent with results from the GOALS trial, in which there was no significant difference in responsiveness to the exercise intervention in women compared with men.[65] In a separate post hoc analysis of 80 participants with PAD randomized to either home-based or SET interventions (follow-up rate, 75%) that studied associations of diabetes mellitus and sex on response to exercise, women with diabetes mellitus had lower rates of improvements in COT and PWT than men with or without diabetes mellitus and women without diabetes mellitus.[177] The post hoc nature of analyses and the small sample size of women with diabetes mellitus (n=16) limit the ability to draw definitive conclusions from these analyses.[177] A separate post hoc analysis of 53 participants with PAD and claudication reported a statistically significant interaction of obesity on change in the 6-MWT after a center-based walking program in which participants with PAD and obesity had greater benefit from exercise.[93] However, this greater benefit in obese participants appeared to be primarily the result of the finding that obese participants randomized to the control group had a greater decline in walking ability during follow-up than nonobese participants randomized to the control group.

Finally, patients with more severe claudication who are very limited in their walking ability may show less improvement after treadmill-based SET. There is some evidence that the increased ischemia-induced inflammation in these patients may cause harm. In a small pilot study, van Schaardenburgh et al[178] found that in patients with claudication, positive response to an exercise program was related to increased mitochondrial function, whereas negative responders had decreases in mitochondrial function. Greater disease severity was associated with negative response to ischemia-inducing exercise training and a decrease in mitochondrial function. This finding needs to be confirmed in a larger clinical trial but supports the need for alternative exercise strategies.

In summary, limited data identify clinical characteristics that consistently predict poor responsiveness to exercise programs. Given the overall benefit achieved, all patients with PAD should have access to exercise programs to improve walking performance.

AREAS IN NEED OF FUTURE RESEARCH

Additional research is needed in several areas to further determine the optimal exercise training methods for patients with PAD. Further identification of biological mechanisms that underlie improvement in response to

exercise training has the potential to advance the field. Further exploration of clinical or demographic characteristics that may influence response to exercise training will facilitate the individualization of exercise prescription to achieve maximal benefits. Strategies to translate SET for patients with PAD from the research laboratory to the clinical setting are greatly needed. Research priorities are summarized in Table 7.

CONCLUSIONS AND SUMMARY

The benefit of exercise therapy for patients with claudication is supported by a large body of evidence gathered over the past 30 years. Supervised treadmill exercise therapy using intermittent bouts of walking exercise to moderate to moderately severe levels of claudication pain is the form of exercise that has been studied most for patients with PAD and claudication. However, more recent evidence shows that modalities other than supervised treadmill exercise, including H-BEx, arm ergometry, leg cycling, and perhaps resistance training, can also improve walking performance and HRQOL in patients with PAD. Future studies should focus on identifying optimal exercise programs for patients with PAD and delineating biological pathways by which exercise improves walking performance in PAD. Given the magnitude of benefits and relative safety of exercise for patients with PAD, efforts should be made to make exercise accessible to all patients with PAD who are able to exercise.

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CLINICAL STATEMENTS AND GUIDELINES

Disclosures

Writing Group Disclosures

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Mary M. McDermott	Northwestern University, Feinberg School of Medicine	ACI Medical (supplied pneumatic compression devices for a pilot study)*; Chromadex (supplied drug for study)†; Hershey's Company (supplied drug for study)†; NHLBI (funding from 4 ongoing research grants)†; NIA†; PCORI†; Regeneron†; Reserveage (supplied drug for study on resveratrol)*; Viromed (supplied drug for study)†	None	None	None	None	None	None
Ulf G. Bronas	University of Illinois at Chicago	Collaborator and co-mentor for Dr Otto Sanchez's AHA Mentored Scientist Award (provide scientific guidance and mentorship regarding exercise testing and interpretation in PAD after an exploratory pharmacological treatment; no salary support)*; principal investigator (internal UIC funding with no salary support investigating exercise training for patients with claudication)*; principal investigator (internal funding with no salary support investigating symptom presentation differences in patients with claudication symptoms)*	None	None	None	None	None	None
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*Modest.

†Significant.

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    †Significant.

REFERENCES

1. Allison MA, Ho E, Denenberg JO, Langer RD, Newman AB, Fabsitz RR, Criqui MH. Ethnic-specific prevalence of peripheral arterial disease in the United States. *Am J Prev Med*. 2007;32:328–333. doi: 10.1016/j.amepre.2006.12.010

2. Hiatt WR, Goldstone J, Smith SC Jr, McDermott M, Moneta G, Oka R, Newman AB, Pearce WH; for Writing Group 1. Atherosclerotic peripheral vascular disease symposium II: nomenclature for vascular diseases. *Circulation*. 2008;118:2826–2829. doi: 10.1161/CIRCULATIONAHA.108.191171

3. Hiatt WR. Medical treatment of peripheral arterial disease and claudication. *N Engl J Med*. 2001;344:1608–1621. doi: 10.1056/NEJM200105243442108

4. Stewart KJ, Hiatt WR, Regensteiner JG, Hirsch AT. Exercise training for claudication. *N Engl J Med*. 2002;347:1941–1951. doi: 10.1056/NEJMra021135

5. Larsen OA, Lassen NA. Effect of daily muscular exercise in patients with intermittent claudication. *Lancet*. 1966;2:1093–1096.

6. Gerhard-Herman MD, Gornik HL, Barrett C, Barshes NR, Corriere MA, Drachman DE, Fleisher LA, Fowkes FG, Hamburg NM, Kinlay S, Lookstein R, Misra S, Mureebe L, Olin JW, Patel RA, Regensteiner JG, Schanzer A, Shishehbor MH, Stewart KJ, Treat-Jacobson D, Walsh ME. 2016 AHA/ACC guideline on the management of patients with lower extremity peripheral artery disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines [published correction appears in *Circulation*. 2017;135:e790]. *Circulation*. 2017;135:e686–e725. doi: 10.1161/CIR.0000000000000470

7. Center for Medicare & Medicaid Services. National Coverage Analysis (NCA) for supervised exercise therapy (SET) for symptomatic peripheral artery disease (PAD). 2017. https://www.cms.gov/medicare-coverage-database/details/nca-details.aspx?NCAId=287&NcaName=Supervised+Exercise+Therapy+(SET)+for+Symptomatic+Peripheral+Artery+Disease+(PAD)&ExpandComments=y&CommentPeriod=0&bc=gCAAAAAACAAAAA%3D%3D&. Accessed October 26, 2018.

8. Aboyans V, Criqui MH, Abraham P, Allison MA, Creager MA, Diehm C, Fowkes FG, Hiatt WR, Jönsson B, Lacroix P, Marin B, McDermott MM, Norgren L, Pande RL, Preux PM, Stoffers HE, Treat-Jacobson D; on behalf of the American Heart Association Council on Peripheral Vascular Disease; Council on Epidemiology and Prevention; Council on Clinical Cardiology; Council on Cardiovascular Nursing; Council on Cardiovascular Radiology and Intervention, and Council on Cardiovascular Surgery and Anesthesia. Measurement and interpretation of the ankle-brachial index: a scientific statement from the American Heart Association [published correction appears in *Circulation*. 2013;127:e264]. *Circulation*. 2012;126:2890–2909. doi: 10.1161/CIR.0b013e318276fbcb

9. Fowkes FG, Rudan D, Rudan I, Aboyans V, Denenberg JO, McDermott MM, Norman PE, Sampson UK, Williams LJ, Mensah GA, Criqui MH. Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: a systematic review and analysis. *Lancet*. 2013;382:1329–1340. doi: 10.1016/S0140-6736(13)61249-0

10. Nehler MR, Duval S, Diao L, Annex BH, Hiatt WR, Rogers K, Zakharyan A, Hirsch AT. Epidemiology of peripheral arterial disease and critical limb ischemia in an insured national population. *J Vasc Surg*. 2014;60:686–695.e2. doi: 10.1016/j.jvs.2014.03.290

11. Bilano V, Gilmour S, Moffiet T, d'Espaignet ET, Stevens GA, Commar A, Tuyl F, Hudson I, Shibuya K. Global trends and projections for tobacco use, 1990-2025: an analysis of smoking indicators from the WHO Comprehensive Information Systems for Tobacco Control. *Lancet*. 2015;385:966–976. doi: 10.1016/S0140-6736(15)60264-1

12. Zimmet PZ, Alberti KG. Epidemiology of diabetes: status of a pandemic and issues around metabolic surgery. *Diabetes Care*. 2016;39:878–883. doi: 10.2337/dc16-0273

13. Dumville JC, Lee AJ, Smith FB, Fowkes FG. The health-related quality of life of people with peripheral arterial disease in the community: the Edinburgh Artery Study. *Br J Gen Pract*. 2004;54:826–831.

14. Regensteiner JG, Hiatt WR, Coll JR, Criqui MH, Treat-Jacobson D, McDermott MM, Hirsch AT. The impact of peripheral arterial disease on health-related quality of life in the Peripheral Arterial Disease Awareness, Risk, and Treatment: New Resources for Survival (PARTNERS) Program. *Vasc Med*. 2008;13:15–24. doi: 10.1177/1358863X07084911

15. McDermott MM, Ferrucci L, Liu K, Guralnik JM, Tian L, Liao Y, Criqui MH. Leg symptom categories and rates of mobility decline in peripheral arterial disease. *J Am Geriatr Soc*. 2010;58:1256–1262. doi: 10.1111/j.1532-5415.2010.02941.x

16. McDermott MM, Applegate WB, Bonds DE, Buford TW, Church T, Espeland MA, Gill TM, Guralnik JM, Haskell W, Lovato LC, Pahor M, Pepine CJ, Reid KF, Newman A. Ankle brachial index values, leg symptoms, and functional performance among community-dwelling older men and women in the Lifestyle Interventions and Independence for Elders study. *J Am Heart Assoc*. 2013;2:e000257. doi: 10.1161/JAHA.113.000257

17. Leidy NK. Functional status and the forward progress of merry-go-rounds: toward a coherent analytical framework. *Nurs Res*. 1994;43:196–202.

18. Wilson IB, Cleary PD. Linking clinical variables with health-related quality of life: a conceptual model of patient outcomes. *JAMA*. 1995;273:59–65.

19. Treat-Jacobson D, Halverson SL, Ratchford A, Regensteiner JG, Lindquist R, Hirsch AT. A patient-derived perspective of health-related quality of life with peripheral arterial disease. *J Nurs Scholarsh*. 2002;34:55–60.

20. Treat-Jacobson D, Lindquist RA, Witt DR, Kirk LN, Schorr EN, Bronas UG, Davey CS, Regensteiner JG. The PADQOL: development and validation of a PAD-specific quality of life questionnaire. *Vasc Med*. 2012;17:405–415. doi: 10.1177/1358863X12466708

21. Bauer TA, Brass EP, Nehler M, Barstow TJ, Hiatt WR. Pulmonary VO2 dynamics during treadmill and arm exercise in peripheral arterial disease. *J Appl Physiol (1985)*. 2004;97:627–634. doi: 10.1152/japplphysiol.00612.2003

22. McDermott MM, Greenland P, Liu K, Guralnik JM, Celic L, Criqui MH, Chan C, Martin GJ, Schneider J, Pearce WH, Taylor LM, Clark E. The ankle brachial index is associated with leg function and physical activity: the Walking and Leg Circulation Study. *Ann Intern Med*. 2002;136:873–883.

23. de Graaff JC, Ubbink DT, Kools EI, Chamuleau SA, Jacobs MJ. The impact of peripheral and coronary artery disease on health-related quality of life. *Ann Vasc Surg*. 2002;16:495–500. doi: 10.1007/s10016-001-0121-9

24. Mays RJ, Casserly IP, Kohrt WM, Ho PM, Hiatt WR, Nehler MR, Regensteiner JG. Assessment of functional status and quality of life in claudication. *J Vasc Surg*. 2011;53:1410–1421. doi: 10.1016/j.jvs.2010.11.092

25. McDermott MM. Lower extremity manifestations of peripheral artery disease: the pathophysiologic and functional implications of leg ischemia. *Circ Res*. 2015;116:1540–1550. doi: 10.1161/CIRCRESAHA.114.303517

26. Sørlie D, Myhre K. Lower leg blood flow in intermittent claudication. *Scand J Clin Lab Invest*. 1978;38:171–179.

27. Bragadeesh T, Sari I, Pascotto M, Micari A, Kaul S, Lindner JR. Detection of peripheral vascular stenosis by assessing skeletal muscle flow reserve. *J Am Coll Cardiol*. 2005;45:780–785. doi: 10.1016/j.jacc.2004.11.045

28. Young DF, Cholvin NR, Kirkeeide RL, Roth AC. Hemodynamics of arterial stenoses at elevated flow rates. *Circ Res*. 1977;41:99–107.

29. Grenon SM, Chong K, Alley H, Nosova E, Gasper W, Hiramoto J, Boscardin WJ, Owens CD. Walking disability in patients with peripheral artery disease is associated with arterial endothelial function. *J Vasc Surg*. 2014;59:1025–1034. doi: 10.1016/j.jvs.2013.10.084

30. Liao JK, Bettmann MA, Sandor T, Tucker JI, Coleman SM, Creager MA. Differential impairment of vasodilator responsiveness of peripheral resistance and conduit vessels in humans with atherosclerosis. *Circ Res*. 1991;68:1027–1034.

31. Mangiafico RA, Malatino LS, Spada RS, Santonocito M, Messina R, Dell'Arte S, Attinà T. Treadmill exercise-induced release of endothelin-1 in patients with peripheral arterial occlusive disease at Fontaine stage IIb. *Int Angiol*. 2000;19:14–17.

32. Cardillo C, Campia U, Bryant MB, Panza JA. Increased activity of endogenous endothelin in patients with type II diabetes mellitus. *Circulation*. 2002;106:1783–1787.

33. Szuba A, Oka RK, Harada R, Cooke JP. Limb hemodynamics are not predictive of functional capacity in patients with PAD. *Vasc Med*. 2006;11:155–163. doi: 10.1177/1358863x06074828

34. McDermott MM, Ferrucci L, Guralnik J, Tian L, Liu K, Hoff F, Liao Y, Criqui MH. Pathophysiological changes in calf muscle predict mobility loss at 2-year follow-up in men and women with peripheral arterial disease. *Circulation*. 2009;120:1048–1055. doi: 10.1161/CIRCULATIONAHA.108.842328

35. Makris KI, Nella AA, Zhu Z, Swanson SA, Casale GP, Gutti TL, Judge AR, Pipinos II. Mitochondriopathy of peripheral arterial disease. *Vascular*. 2007;15:336–343. doi: 10.2310/6670.2007.00054

36. Pipinos II, Judge AR, Selsby JT, Zhu Z, Swanson SA, Nella AA, Dodd SL. The myopathy of peripheral arterial occlusive disease, part 1: functional and histomorphological changes and evidence for mitochondrial dysfunction. *Vasc Endovascular Surg*. 2007;41:481–489. doi: 10.1177/1538574407311106

37. Marbini A, Gemignani F, Scoditti U, Rustichelli P, Bragaglia MM, Govoni E. Abnormal muscle mitochondria in ischemic claudication. *Acta Neurol Belg*. 1986;86:304–310.

38. Pipinos II, Shepard AD, Anagnostopoulos PV, Katsamouris A, Boska MD. Phosphorus 31 nuclear magnetic resonance spectroscopy suggests a mitochondrial defect in claudicating skeletal muscle. *J Vasc Surg*. 2000;31:944–952. doi: 10.1067/mva.2000.106421

39. Pipinos II, Judge AR, Selsby JT, Zhu Z, Swanson SA, Nella AA, Dodd SL. The myopathy of peripheral arterial occlusive disease, part 2: oxidative stress, neuropathy, and shift in muscle fiber type. *Vasc Endovascular Surg*. 2008;42:101–112. doi: 10.1177/1538574408315995

40. Gillani S, Cao J, Suzuki T, Hak DJ. The effect of ischemia reperfusion injury on skeletal muscle. *Injury*. 2012;43:670–675. doi: 10.1016/j.injury.2011.03.008

41. Brevetti G, Giugliano G, Brevetti L, Hiatt WR. Inflammation in peripheral artery disease. *Circulation*. 2010;122:1862–1875. doi: 10.1161/CIRCULATIONAHA.109.918417

42. Signorelli SS, Mazzarino MC, Di Pino L, Malaponte G, Porto C, Pennisi G, Marchese G, Costa MP, Digrandi D, Celotta G, Virgilio V. High circulating levels of cytokines (IL-6 and TNFalpha), adhesion molecules (VCAM-1 and ICAM-1) and selectins in patients with peripheral arterial disease at rest and after a treadmill test. *Vasc Med*. 2003;8:15–19. doi: 10.1191/1358863x03vm466oa

43. Pipinos II, Sharov VG, Shepard AD, Anagnostopoulos PV, Katsamouris A, Todor A, Filis KA, Sabbah HN. Abnormal mitochondrial respiration in skeletal muscle in patients with peripheral arterial disease. *J Vasc Surg*. 2003;38:827–832.

44. Pipinos II, Judge AR, Zhu Z, Selsby JT, Swanson SA, Johanning JM, Baxter BT, Lynch TG, Dodd SL. Mitochondrial defects and oxidative damage in patients with peripheral arterial disease. *Free Radic Biol Med*. 2006;41:262–269. doi: 10.1016/j.freeradbiomed.2006.04.003

45. Brass EP, Hiatt WR, Gardner AW, Hoppel CL. Decreased NADH dehydrogenase and ubiquinol-cytochrome c oxidoreductase in peripheral arterial disease. *Am J Physiol Heart Circ Physiol*. 2001;280:H603–H609. doi: 10.1152/ajpheart.2001.280.2.H603

46. Askew CD, Green S, Walker PJ, Kerr GK, Green AA, Williams AD, Febbraio MA. Skeletal muscle phenotype is associated with exercise tolerance in patients with peripheral arterial disease. *J Vasc Surg*. 2005;41:802–807. doi: 10.1016/j.jvs.2005.01.037

47. Weiss DJ, Casale GP, Koutakis P, Nella AA, Swanson SA, Zhu Z, Miserlis D, Johanning JM, Pipinos II. Oxidative damage and myofiber degeneration in the gastrocnemius of patients with peripheral arterial disease. *J Transl Med*. 2013;11:230. doi: 10.1186/1479-5876-11-230

48. Garg PK, Liu K, Ferrucci L, Guralnik JM, Criqui MH, Tian L, Sufit R, Nishida T, Tao H, Liao Y, McDermott MM. Lower extremity nerve function, calf skeletal muscle characteristics, and functional performance in peripheral arterial disease. *J Am Geriatr Soc*. 2011;59:1855–1863. doi: 10.1111/j.1532-5415.2011.03600.x

49. McDermott MM, Liu K, Tian L, Guralnik JM, Criqui MH, Liao Y, Ferrucci L. Calf muscle characteristics, strength measures, and mortality in peripheral arterial disease: a longitudinal study. *J Am Coll Cardiol*. 2012;59:1159–1167. doi: 10.1016/j.jacc.2011.12.019

50. Olin JW, White CJ, Armstrong EJ, Kadian-Dodov D, Hiatt WR. Peripheral artery disease: evolving role of exercise, medical therapy, and endovascular options. *J Am Coll Cardiol*. 2016;67:1338–1357. doi: 10.1016/j.jacc.2015.12.049

51. Hiatt WR, Wolfel EE, Meier RH, Regensteiner JG. Superiority of treadmill walking exercise versus strength training for patients with peripheral arterial disease: implications for the mechanism of the training response. *Circulation*. 1994;90:1866–1874.

52. Tisi PV, Hulse M, Chulakadabba A, Gosling P, Shearman CP. Exercise training for intermittent claudication: does it adversely affect biochemical markers of the exercise-induced inflammatory response? *Eur J Vasc Endovasc Surg*. 1997;14:344–350.

53. Andreozzi GM, Leone A, Laudani R, Deinite G, Martini R. Acute impairment of the endothelial function by maximal treadmill exercise in patients with intermittent claudication, and its improvement after supervised physical training. *Int Angiol*. 2007;26:12–17.

54. Duscha BD, Robbins JL, Jones WS, Kraus WE, Lye RJ, Sanders JM, Allen JD, Regensteiner JG, Hiatt WR, Annex BH. Angiogenesis in skeletal muscle precede improvements in peak oxygen uptake in peripheral artery disease patients. *Arterioscler Thromb Vasc Biol*. 2011;31:2742–2748. doi: 10.1161/ATVBAHA.111.230441

55. Hiatt WR, Regensteiner JG, Wolfel EE, Carry MR, Brass EP. Effect of exercise training on skeletal muscle histology and metabolism in peripheral arterial disease. *J Appl Physiol (1985)*. 1996;81:780–788. doi: 10.1152/jappl.1996.81.2.780

56. Fakhry F, van de Luijtgaarden KM, Bax L, den Hoed PT, Hunink MG, Rouwet EV, Spronk S. Supervised walking therapy in patients with intermittent claudication. *J Vasc Surg*. 2012;56:1132–1142. doi: 10.1016/j.jvs.2012.04.046.

57. McDermott MM, Guralnik JM, Criqui MH, Liu K, Kibbe MR, Ferrucci L. Six-minute walk is a better outcome measure than treadmill walking tests in therapeutic trials of patients with peripheral artery disease. *Circulation*. 2014;130:61–68. doi: 10.1161/CIRCULATIONAHA.114.007002

58. Hiatt WR, Rogers RK, Brass EP. The treadmill is a better functional test than the 6-minute walk test in therapeutic trials of patients with peripheral artery disease. *Circulation*. 2014;130:69–78. doi: 10.1161/CIRCULATIONAHA.113.007003

59. Leeper NJ, Myers J, Zhou M, Nead KT, Syed A, Kojima Y, Caceres RD, Cooke JP. Exercise capacity is the strongest predictor of mortality in patients with peripheral arterial disease. *J Vasc Surg*. 2013;57:728–733. doi: 10.1016/j.jvs.2012.07.051

60. McDermott MM, Ades PA, Dyer A, Guralnik JM, Kibbe M, Criqui MH. Corridor-based functional performance measures correlate better with physical activity during daily life than treadmill measures in persons with peripheral arterial disease. *J Vasc Surg*. 2008;48:1231–1237, 1237.e1. doi: 10.1016/j.jvs.2008.06.050

61. Swerts PM, Mostert R, Wouters EF. Comparison of corridor and treadmill walking in patients with severe chronic obstructive pulmonary disease. *Phys Ther*. 1990;70:439–442.

62. Peeters P, Mets T. The 6-minute walk as an appropriate exercise test in elderly patients with chronic heart failure. *J Gerontol A Biol Sci Med Sci*. 1996;51:M147–M151.

63. Greig C, Butler F, Skelton D, Mahmud S, Young A. Treadmill walking in old age may not reproduce the real life situation. *J Am Geriatr Soc*. 1993;41:15–18.

64. McDermott MM, Ferrucci L, Tian L, Guralnik JM, Lloyd-Jones D, Kibbe MR, Polonsky TS, Domanchuk K, Stein JH, Zhao L, Taylor D, Skelly C, Pearce W, Perlman H, McCarthy W, Li L, Gao Y, Sufit R, Bloomfield CL, Criqui MH. Effect of granulocyte-macrophage colony-stimulating factor with or without supervised exercise on walking performance in patients with peripheral artery disease: the PROPEL randomized clinical trial. *JAMA*. 2017;318:2089–2098. doi: 10.1001/jama.2017.17437

65. McDermott MM, Liu K, Guralnik JM, Criqui MH, Spring B, Tian L, Domanchuk K, Ferrucci L, Lloyd-Jones D, Kibbe M, Tao H, Zhao L, Liao Y, Rejeski WJ. Home-based walking exercise intervention in peripheral artery disease: a randomized clinical trial. *JAMA*. 2013;310:57–65. doi: 10.1001/jama.2013.7231

66. McDermott MM, Ades P, Guralnik JM, Dyer A, Ferrucci L, Liu K, Nelson M, Lloyd-Jones D, Van Horn L, Garside D, Kibbe M, Domanchuk K, Stein JH, Liao Y, Tao H, Green D, Pearce WH, Schneider JR, McPherson D, Laing ST, McCarthy WJ, Shroff A, Criqui MH. Treadmill exercise and resistance training in patients with peripheral arterial disease with and without intermittent claudication: a randomized controlled trial. *JAMA*. 2009;301:165–174. doi: 10.1001/jama.2008.962

67. Gardner AW, Parker DE, Montgomery PS, Blevins SM. Step-monitored home exercise improves ambulation, vascular function, and inflammation in symptomatic patients with peripheral artery disease: a randomized controlled trial. *J Am Heart Assoc*. 2014;3:e001107. doi: 10.1161/JAHA.114.001107

68. McDermott MM, Liu K, Ferrucci L, Tian L, Guralnik JM, Liao Y, Criqui MH. Decline in functional performance predicts later increased mobility loss and mortality in peripheral arterial disease. *J Am Coll Cardiol*. 2011;57:962–970. doi: 10.1016/j.jacc.2010.09.053

69. Nicolaï SP, Viechtbauer W, Kruidenier LM, Candel MJ, Prins MH, Teijink JA. Reliability of treadmill testing in peripheral arterial disease: a meta-regression analysis. *J Vasc Surg*. 2009;50:322–329. doi: 10.1016/j.jvs.2009.01.042

70. Brass EP, Jiao J, Hiatt W. Optimal assessment of baseline treadmill walking performance in claudication clinical trials. *Vasc Med*. 2007;12:97–103. doi: 10.1177/1358863X07078602

71. Labs KH, Nehler MR, Roessner M, Jaeger KA, Hiatt WR. Reliability of treadmill testing in peripheral arterial disease: a comparison of a constant load with a graded load treadmill protocol. *Vasc Med*. 1999;4:239–246. doi: 10.1177/1358836X9900400406

72. Regensteiner JG, Ware JE Jr, McCarthy WJ, Zhang P, Forbes WP, Heckman J, Hiatt WR. Effect of cilostazol on treadmill walking, community-based walking ability, and health-related quality of life in patients with intermittent claudication due to peripheral arterial disease: meta-analysis of six randomized controlled trials. *J Am Geriatr Soc*. 2002;50:1939–1946.

73. Gardner AW, Skinner JS, Cantwell BW, Smith LK. Progressive vs single-stage treadmill tests for evaluation of claudication. *Med Sci Sports Exerc*. 1991;23:402–408.

74. Hiatt WR, Hirsch AT, Regensteiner JG, Brass EP. Clinical trials for claudication: assessment of exercise performance, functional status, and clinical end points: Vascular Clinical Trialists. *Circulation*. 1995;92:614–621.

75. Creager MA, Olin JW, Belch JJ, Moneta GL, Henry TD, Rajagopalan S, Annex BH, Hiatt WR. Effect of hypoxia-inducible factor-1alpha gene therapy on walking performance in patients with intermittent claudication. *Circulation*. 2011;124:1765–1773. doi: 10.1161/CIRCULATIONAHA.110.009407

76. Hiatt WR, Hirsch AT, Creager MA, Rajagopalan S, Mohler ER, Ballantyne CM, Regensteiner JG, Treat-Jacobson D, Dale RA, Rooke T. Effect of niacin ER/lovastatin on claudication symptoms in patients with peripheral artery disease. *Vasc Med*. 2010;15:171–179. doi: 10.1177/1358863X09360579

77. Murphy TP, Cutlip DE, Regensteiner JG, Mohler ER, Cohen DJ, Reynolds MR, Massaro JM, Lewis BA, Cerezo J, Oldenburg NC, Thum CC, Goldberg S, Jaff MR, Steffes MW, Comerota AJ, Ehrman J, Treat-Jacobson D, Walsh ME, Collins T, Badenhop DT, Bronas U, Hirsch AT; for the CLEVER Study Investigators. Supervised exercise versus primary stenting for claudication resulting from aortoiliac peripheral artery disease: six-month outcomes from the Claudication: Exercise Versus Endoluminal Revascularization (CLEVER) study. *Circulation*. 2012;125:130–139. doi: 10.1161/CIRCULATIONAHA.111.075770

78. McDermott MM, Leeuwenburgh C, Guralnik JM, Tian L, Sufit R, Zhao L, Criqui MH, Kibbe MR, Stein JH, Lloyd-Jones D, Anton SD, Polonsky TS, Gao Y, de Cabo R, Ferrucci L. Effect of resveratrol on walking performance in older people with peripheral artery disease: the RESTORE randomized clinical trial. *JAMA Cardiol*. 2017;2:902–907. doi: 10.1001/jamacardio.2017.0538

79. Chang ST, Hsu JT, Chu CM, Pan KL, Jang SJ, Lin PC, Hsu HC, Huang KC. Using intermittent pneumatic compression therapy to improve quality of life for symptomatic patients with infrapopliteal diffuse peripheral obstructive disease. *Circ J*. 2012;76:971–976.

80. McDermott MM, Liu K, Greenland P, Guralnik JM, Criqui MH, Chan C, Pearce WH, Schneider JR, Ferrucci L, Celic L, Taylor LM, Vonesh E, Martin GJ, Clark E. Functional decline in peripheral arterial disease: associations with the ankle brachial index and leg symptoms. *JAMA*. 2004;292:453–461. doi: 10.1001/jama.292.4.453

81. McDermott MM, Guralnik JM, Tian L, Ferrucci L, Liu K, Liao Y, Criqui MH. Baseline functional performance predicts the rate of mobility loss in persons with peripheral arterial disease. *J Am Coll Cardiol*. 2007;50:974–982. doi: 10.1016/j.jacc.2007.05.030

82. McDermott MM, Greenland P, Tian L, Kibbe MR, Green D, Zhao L, Criqui MH, Guralnik JM, Ferrucci L, Liu K, Wilkins JT, Huffman MD, Shah SJ, Liao Y, Lloyd-Jones DM. Association of 6-minute walk performance and physical activity with incident ischemic heart disease events and stroke in peripheral artery disease. *J Am Heart Assoc*. 2015;4:e001846. doi: 10.1161/JAHA.115.001846

83. Perera S, Mody SH, Woodman RC, Studenski SA. Meaningful change and responsiveness in common physical performance measures in older adults. *J Am Geriatr Soc*. 2006;54:743–749. doi: 10.1111/j.1532-5415.2006.00701.x

84. McDermott MM, Polonsky TS. Home-based exercise: a therapeutic option for peripheral artery disease. *Circulation*. 2016;134:1127–1129. doi: 10.1161/CIRCULATIONAHA.116.023691

85. Normahani P, Kwasnicki R, Bicknell C, Allen L, Jenkins MP, Gibbs R, Cheshire N, Darzi A, Riga C. Wearable Sensor Technology Efficacy in Peripheral Vascular Disease (wSTEP): a randomized controlled trial [published online May 11, 2017]. *Ann Surg*. doi: 10.1097/SLA.0000000000002300. https://insights.ovid.com/pubmed?pmid=28498233.

86. Mays RJ, Hiatt WR, Casserly IP, Rogers RK, Main DS, Kohrt WM, Ho PM, Regensteiner JG. Community-based walking exercise for peripheral artery disease: an exploratory pilot study. *Vasc Med*. 2015;20:339–347. doi: 10.1177/1358863X15572725

87. Garg PK, Tian L, Criqui MH, Liu K, Ferrucci L, Guralnik JM, Tan J, McDermott MM. Physical activity during daily life and mortality in patients with peripheral arterial disease. *Circulation*. 2006;114:242–248. doi: 10.1161/CIRCULATIONAHA.105.605246

88. Garg PK, Liu K, Tian L, Guralnik JM, Ferrucci L, Criqui MH, Tan J, McDermott MM. Physical activity during daily life and functional decline in peripheral arterial disease. *Circulation*. 2009;119:251–260. doi: 10.1161/CIRCULATIONAHA.108.791491

89. Regensteiner J, Steiner JF, Panzer RJ, Hiatt WR. Evaluation of walking impairment by questionnaire in patients with peripheral arterial disease. *J Vasc Med Biol*. 1990;2:142–152.

90. Morgan MB, Crayford T, Murrin B, Fraser SC. Developing the Vascular Quality of Life Questionnaire: a new disease-specific quality of life measure for use in lower limb ischemia. *J Vasc Surg*. 2001;33:679–687. doi: 10.1067/mva.2001.112326

91. Spertus J, Jones P, Poler S, Rocha-Singh K. The Peripheral Artery Questionnaire: a new disease-specific health status measure for patients with peripheral arterial disease. *Am Heart J*. 2004;147:301–308. doi: 10.1016/j.ahj.2003.08.001

92. Regensteiner JG, Steiner JF, Hiatt WR. Exercise training improves functional status in patients with peripheral arterial disease. *J Vasc Surg*. 1996;23:104–115.

93. Addison O, Ryan AS, Prior SJ, Katzel LI, Kundi R, Lal BK, Gardner AW. Changes in function after a 6-month walking intervention in patients with intermittent claudication who are obese or nonobese. *J Geriatr Phys Ther*. 2017;40:190–196. doi: 10.1519/JPT.0000000000000096

94. Schroë H, Holden AH, Goueffic Y, Jansen SJ, Peeters P, Keirse K, Ito W, Vermassen F, Micari A, Blessing E, Jaff MR, Zeller T. Stellarex drug-coated balloon for treatment of femoropopliteal arterial disease: the ILLUMENATE Global Study: 12-month results from a prospective, multicenter, single-arm study. *Catheter Cardiovasc Interv*. 2018;91:497–504. doi: 10.1002/ccd.27348

95. Lindgren H, Qvarfordt P, Åkesson M, Bergman S, Gottsäter A; Swedish Endovascular Claudication Stenting Trialists. Primary stenting of the superficial femoral artery in intermittent claudication improves health related quality of life, ABI and walking distance: 12 month results of a controlled randomised multicentre trial. *Eur J Vasc Endovasc Surg*. 2017;53:686–694. doi: 10.1016/j.ejvs.2017.01.026

96. Nead KT, Zhou M, Diaz Caceres R, Olin JW, Cooke JP, Leeper NJ. Walking impairment questionnaire improves mortality risk prediction models in a high-risk cohort independent of peripheral arterial disease status. *Circ Cardiovasc Qual Outcomes*. 2013;6:255–261. doi: 10.1161/CIRCOUTCOMES.111.000070

97. Larsen ASF, Reiersen AT, Jacobsen MB, Kløw NE, Nordanstig J, Morgan M, Wesche J. Validation of the Vascular Quality of Life Questionnaire - 6 for clinical use in patients with lower limb peripheral arterial disease. *Health Qual Life Outcomes*. 2017;15:184. doi: 10.1186/s12955-017-0760-3

98. Nordanstig J, Pettersson M, Morgan M, Falkenberg M, Kumlien C. Assessment of minimum important difference and substantial clinical benefit with the Vascular Quality of Life Questionnaire-6 when evaluating revascularisation procedures in peripheral arterial disease. *Eur J Vasc Endovasc Surg*. 2017;54:340–347. doi: 10.1016/j.ejvs.2017.06.022

99. Kumlien C, Nordanstig J, Lundström M, Pettersson M. Validity and test retest reliability of the Vascular Quality of Life Questionnaire-6: a short form of a disease-specific health-related quality of life instrument for patients with peripheral arterial disease. *Health Qual Life Outcomes*. 2017;15:187. doi: 10.1186/s12955-017-0762-1

100. Nordanstig J, Wann-Hansson C, Karlsson J, Lundström M, Pettersson M, Morgan MB. Vascular Quality of Life Questionnaire-6 facilitates health-related quality of life assessment in peripheral arterial disease. *J Vasc Surg*. 2014;59:700–707. doi: 10.1016/j.jvs.2013.08.099

101. Corriere MA, Goldman MP, Barnard R, Saldana S, Stafford JM, Easterling D, Ip EH, Burke GL. Cumulative number of treatment interventions predicts health-related quality of life in patients with critical limb ischemia. *Ann Vasc Surg*. 2017;44:41–47. doi: 10.1016/j.avsg.2017.01.029

102. Smolderen KG, Aquarius AE, de Vries J, Smith OR, Hamming JF, Denollet J. Depressive symptoms in peripheral arterial disease: a follow-up study on prevalence, stability, and risk factors. *J Affect Disord*. 2008;110:27–35. doi: 10.1016/j.jad.2007.12.238

103. Smolderen KG, Hoeks SE, Aquarius AE, Scholte op Reimer WJ, Spertus JA, van Urk H, Denollet J, Poldermans D. Further validation of the peripheral artery questionnaire: results from a peripheral vascular surgery survey in the Netherlands. *Eur J Vasc Endovasc Surg*. 2008;36:582–591. doi: 10.1016/j.ejvs.2008.07.015

104. Salisbury DL, Whipple MO, Burt M, Brown RJL, Hirsch A, Foley C, Treat-Jacobson D. Translation of an evidence-based therapeutic exercise program for patients with peripheral artery disease. *J Vasc Nurs*. 2018;36:23–33. doi: 10.1016/j.jvn.2017.09.003

105. Treat-Jacobson D, Bronas UG, Krause BJ, Robinson C, Santilli SM, Leon AS. Aerobic arm exercise to improve outcomes for patients with severe claudication and ischemic rest pain. *J Vasc Med*. 2012;17:204.

106. Ware JE Jr, Sherbourne CD. The MOS 36-Item Short-Form Health Survey (SF-36), I: conceptual framework and item selection. *Med Care*. 1992;30:473–483.

107. Ware J Jr, Kosinski M, Keller SD. A 12-item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. *Med Care*. 1996;34:220–233.

108. Euro QOL Group. EuroQol: a new facility for the measurement of health-related quality of life. *Health Policy*. 1990;16:199–208.

109. Lane R, Harwood A, Watson L, Leng GC. Exercise for intermittent claudication. *Cochrane Database Syst Rev*. 2017;12:CD000990. doi: 10.1002/14651858.CD000990.pub4

110. Brooks R. EuroQol: the current state of play. *Health Policy*. 1996;37:53–72.

111. Spronk S, Bosch JL, den Hoed PT, Veen HF, Pattynama PM, Hunink MG. Cost-effectiveness of endovascular revascularization compared to supervised hospital-based exercise training in patients with intermittent claudication: a randomized controlled trial. *J Vasc Surg*. 2008;48:1472–1480. doi: 10.1016/j.jvs.2008.06.016

112. Mehta T, Venkata Subramaniam A, Chetter I, McCollum P. Assessing the validity and responsiveness of disease-specific quality of life instruments in intermittent claudication. *Eur J Vasc Endovasc Surg*. 2006;31:46–52. doi: 10.1016/j.ejvs.2005.08.028

113. Gardner AW, Poehlman ET. Exercise rehabilitation programs for the treatment of claudication pain: a meta-analysis. *JAMA*. 1995;274:975–980.

114. Leng GC, Fowler B, Ernst E. Exercise for intermittent claudication. *Cochrane Database Syst Rev*. 2000:CD000990.

115. Lane R, Ellis B, Watson L, Leng GC. Exercise for intermittent claudication. *Cochrane Database Syst Rev*. 2014:CD000990.

116. Bulmer AC, Coombes JS. Optimising exercise training in peripheral arterial disease. *Sports Med*. 2004;34:983–1003.

117. Fokkenrood HJ, Bendermacher BL, Lauret GJ, Willigendael EM, Prins MH, Teijink JA. Supervised exercise therapy versus non-supervised exercise therapy for intermittent claudication. *Cochrane Database Syst Rev*. 2013:CD005263.

118. Parmenter BJ, Raymond J, Fiatarone Singh MA. The effect of exercise on fitness and performance-based tests of function in intermittent claudication: a systematic review. *Sports Med*. 2013;43:513–524. doi: 10.1007/s40279-013-0038-9

119. Watson L, Ellis B, Leng G. Exercise for intermittent claudication. *Cochrane Database Syst Rev*. 2008:CD000990.

120. Hiatt WR, Regensteiner JG, Hargarten ME, Wolfel EE, Brass EP. Benefit of exercise conditioning for patients with peripheral arterial disease. *Circulation*. 1990;81:602–609.

121. Savage P, Ricci MA, Lynn M, Gardner A, Knight S, Brochu M, Ades P. Effects of home versus supervised exercise for patients with intermittent claudication. *J Cardiopulm Rehabil*. 2001;21:152–157.

122. Tsai JC, Chan P, Wang CH, Jeng C, Hsieh MH, Kao PF, Chen YJ, Liu JC. The effects of exercise training on walking function and perception of health status in elderly patients with peripheral arterial occlusive disease. *J Intern Med*. 2002;252:448–455.

123. Regensteiner JG, Meyer TJ, Krupski WC, Cranford LS, Hiatt WR. Hospital vs home-based exercise rehabilitation for patients with peripheral arterial occlusive disease. *Angiology*. 1997;48:291–300. doi: 10.1177/000331979704800402

124. Allen JD, Stabler T, Kenjale A, Ham KL, Robbins JL, Duscha BD, Dobrosielski DA, Annex BH. Plasma nitrite flux predicts exercise performance in peripheral arterial disease after 3months of exercise training. *Free Radic Biol Med*. 2010;49:1138–1144. doi: 10.1016/j.freeradbiomed.2010.06.033

125. Treat-Jacobson D, Bronas UG, Leon AS. Efficacy of arm-ergometry versus treadmill exercise training to improve walking distance in patients with claudication. *Vasc Med*. 2009;14:203–213. doi: 10.1177/1358863X08101858

126. Gardner AW, Parker DE, Montgomery PS, Scott KJ, Blevins SM. Efficacy of quantified home-based exercise and supervised exercise in patients with intermittent claudication: a randomized controlled trial. *Circulation*. 2011;123:491–498. doi: 10.1161/CIRCULATIONAHA.110.963066

127. Gardner AW, Katzel LI, Sorkin JD, Bradham DD, Hochberg MC, Flinn WR, Goldberg AP. Exercise rehabilitation improves functional outcomes and peripheral circulation in patients with intermittent claudication: a randomized controlled trial. *J Am Geriatr Soc*. 2001;49:755–762.

128. Nicolaï SP, Teijink JA, Prins MH; Exercise Therapy in Peripheral Arterial Disease Study Group. Multicenter randomized clinical trial of supervised exercise therapy with or without feedback versus walking advice for intermittent claudication. *J Vasc Surg*. 2010;52:348–355. doi: 10.1016/j.jvs.2010.02.022

129. Crowther RG, Spinks WL, Leicht AS, Sangla K, Quigley F, Golledge J. Effects of a long-term exercise program on lower limb mobility, physiological responses, walking performance, and physical activity levels in patients with peripheral arterial disease. *J Vasc Surg*. 2008;47:303–309. doi: 10.1016/j.jvs.2007.10.038

130. Gardner AW, Montgomery PS, Parker DE. Optimal exercise program length for patients with claudication. *J Vasc Surg*. 2012;55:1346–1354. doi: 10.1016/j.jvs.2011.11.123

131. Crowther RG, Leicht AS, Spinks WL, Sangla K, Quigley F, Golledge J. Effects of a 6-month exercise program pilot study on walking economy, peak physiological characteristics, and walking performance in patients with peripheral arterial disease. *Vasc Health Risk Manag*. 2012;8:225–232. doi: 10.2147/VHRM.S30056

132. Hodges LD, Sandercock GR, Das SK, Brodie DA. Randomized controlled trial of supervised exercise to evaluate changes in cardiac function in patients with peripheral atherosclerotic disease. *Clin Physiol Funct Imaging*. 2008;28:32–37. doi: 10.1111/j.1475-097X.2007.00770.x

133. Parmenter BJ, Dieberg G, Smart NA. Exercise training for management of peripheral arterial disease: a systematic review and meta-analysis. *Sports Med*. 2015;45:231–244. doi: 10.1007/s40279-014-0261-z

134. McDermott MM. Exercise training for intermittent claudication. *J Vasc Surg*. 2017;66:1612–1620. doi: 10.1016/j.jvs.2017.05.111

135. Jakubseviciene E, Vasiliauskas D, Velicka L, Kubilius R, Milinaviciene E, Venclovienė J. Effectiveness of a new exercise program after lower limb arterial blood flow surgery in patients with peripheral arterial disease: a

randomized clinical trial. *Int J Environ Res Public Health*. 2014;11:7961–7976. doi: 10.3390/ijerph110807961

136. Murphy TP, Cutlip DE, Regensteiner JG, Mohler ER 3rd, Cohen DJ, Reynolds MR, Massaro JM, Lewis BA, Cerezo J, Oldenburg NC, Thum CC, Jaff MR, Comerota AJ, Steffes MW, Abrahamsen IH, Goldberg S, Hirsch AT. Supervised exercise, stent revascularization, or medical therapy for claudication due to aortoiliac peripheral artery disease: the CLEVER study. *J Am Coll Cardiol*. 2015;65:999–1009. doi: 10.1016/j.jacc.2014.12.043

137. Gardner AW, Montgomery PS, Flinn WR, Katzel LI. The effect of exercise intensity on the response to exercise rehabilitation in patients with intermittent claudication. *J Vasc Surg*. 2005;42:702–709. doi: 10.1016/j.jvs.2005.05.049

138. Gommans LN, Saarloos R, Scheltinga MR, Houterman S, de Bie RA, Fokkenrood HJ, Teijink JA. Editor's choice: the effect of supervision on walking distance in patients with intermittent claudication: a meta-analysis. *Eur J Vasc Endovasc Surg*. 2014;48:169–184. doi: 10.1016/j.ejvs.2014.04.019

139. Parmenter BJ, Raymond J, Dinnen P, Singh MA. A systematic review of randomized controlled trials: walking versus alternative exercise prescription as treatment for intermittent claudication. *Atherosclerosis*. 2011;218:1–12. doi: 10.1016/j.atherosclerosis.2011.04.024

140. American College of Sports Medicine. *ACSM's Guidelines for Exercise Testing and Prescription*. Philadelphia, PA: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2018.

141. Schorr EN, Treat-Jacobson D, Lindquist R. The relationship between peripheral artery disease symptomatology and ischemia. *Nurs Res*. 2017;66:378–387. doi: 10.1097/NNR.0000000000000230

142. Fokkenrood HJ, Lauret GJ, Verhofstad N, Bendermacher BL, Scheltinga MR, Teijink JA. The effect of supervised exercise therapy on physical activity and ambulatory activities in patients with intermittent claudication. *Eur J Vasc Endovasc Surg*. 2015;49:184–191. doi: 10.1016/j.ejvs.2014.11.002

143. Lundgren F, Dahllöf AG, Lundholm K, Scherstén T, Volkmann R. Intermittent claudication–surgical reconstruction or physical training? A prospective randomized trial of treatment efficiency. *Ann Surg*. 1989;209:346–355.

144. Creasy TS, McMillan PJ, Fletcher EW, Collin J, Morris PJ. Is percutaneous transluminal angioplasty better than exercise for claudication? Preliminary results from a prospective randomised trial. *Eur J Vasc Surg*. 1990;4:135–140.

145. Perkins JM, Collin J, Creasy TS, Fletcher EW, Morris PJ. Exercise training versus angioplasty for stable claudication: long and medium term results of a prospective, randomised trial. *Eur J Vasc Endovasc Surg*. 1996;11:409–413.

146. Gelin J, Jivegård L, Taft C, Karlsson J, Sullivan M, Dahllöf AG, Sandström R, Arfvidsson B, Lundholm K. Treatment efficacy of intermittent claudication by surgical intervention, supervised physical exercise training compared to no treatment in unselected randomised patients, I: one year results of functional and physiological improvements. *Eur J Vasc Endovasc Surg*. 2001;22:107–113. doi: 10.1053/ejvs.2001.1413

147. Greenhalgh RM, Belch JJ, Brown LC, Gaines PA, Gao L, Reise JA, Thompson SG; Mimic Trial Participants. The adjuvant benefit of angioplasty in patients with mild to moderate intermittent claudication (MIMIC) managed by supervised exercise, smoking cessation advice and best medical therapy: results from two randomised trials for stenotic femoropopliteal and aortoiliac arterial disease. *Eur J Vasc Endovasc Surg*. 2008;36:680–688. doi: 10.1016/j.ejvs.2008.10.007

148. Spronk S, White JV, Ryjewski C, Rosenblum J, Bosch JL, Hunink MG. Invasive treatment of claudication is indicated for patients unable to adequately ambulate during cardiac rehabilitation. *J Vasc Surg*. 2009;49:1217–1225. doi: 10.1016/j.jvs.2008.11.066

149. Mazari FA, Gulati S, Rahman MN, Lee HL, Mehta TA, McCollum PT, Chetter IC. Early outcomes from a randomized, controlled trial of supervised exercise, angioplasty, and combined therapy in intermittent claudication. *Ann Vasc Surg*. 2010;24:69–79. doi: 10.1016/j.avsg.2009.07.005

150. Mazari FA, Khan JA, Carradice D, Samuel N, Abdul Rahman MN, Gulati S, Lee HL, Mehta TA, McCollum PT, Chetter IC. Randomized clinical trial of percutaneous transluminal angioplasty, supervised exercise and combined treatment for intermittent claudication due to femoropopliteal arterial disease. *Br J Surg*. 2012;99:39–48. doi: 10.1002/bjs.7710

151. Fakhry F, Spronk S, van der Laan L, Wever JJ, Teijink JA, Hoffmann WH, Smits TM, van Brussel JP, Stultiens GN, Derom A, den Hoed PT, Ho GH, van Dijk LC, Verhofstad N, Orsini M, van Petersen A, Woltman K, Hulst I, van Sambeek MR, Rizopoulos D, Rouwet EV, Hunink MG. Endovascular revascularization and supervised exercise for peripheral artery disease and intermittent claudication: a randomized clinical trial. *JAMA*. 2015;314:1936–1944. doi: 10.1001/jama.2015.14851

152. Spronk S, Bosch JL, den Hoed PT, Veen HF, Pattynama PM, Hunink MG. Intermittent claudication: clinical effectiveness of endovascular revascularization versus supervised hospital-based exercise training–randomized controlled trial. *Radiology*. 2009;250:586–595. doi: 10.1148/radiol.2501080607

153. McDermott MM, Greenland P, Liu K, Guralnik JM, Criqui MH, Dolan NC, Chan C, Celic L, Pearce WH, Schneider JR, Sharma L, Clark E, Gibson D, Martin GJ. Leg symptoms in peripheral arterial disease: associated clinical characteristics and functional impairment. *JAMA*. 2001;286:1599–1606.

154. Newman AB, Siscovick DS, Manolio TA, Polak J, Fried LP, Borhani NO, Wolfson SK. Ankle-arm index as a marker of atherosclerosis in the Cardiovascular Health Study: Cardiovascular Heart Study (CHS) Collaborative Research Group. *Circulation*. 1993;88:837–845.

155. Newman AB, Naydeck BL, Sutton-Tyrrell K, Polak JF, Kuller LH; Cardiovascular Health Study Research Group. The role of comorbidity in the assessment of intermittent claudication in older adults. *J Clin Epidemiol*. 2001;54:294–300.

156. McDermott MM, Fried L, Simonsick E, Ling S, Guralnik JM. Asymptomatic peripheral arterial disease is independently associated with impaired lower extremity functioning: the Women's Health and Aging Study. *Circulation*. 2000;101:1007–1012.

157. McDermott MM, Guralnik JM, Ferrucci L, Tian L, Liu K, Liao Y, Green D, Sufit R, Hoff F, Nishida T, Sharma L, Pearce WH, Schneider JR, Criqui MH. Asymptomatic peripheral arterial disease is associated with more adverse lower extremity characteristics than intermittent claudication. *Circulation*. 2008;117:2484–2491. doi: 10.1161/CIRCULATIONAHA.107.736108

158. McDermott MM, Tiukinhoy S, Greenland P, Liu K, Pearce WH, Guralnik JM, Unterreiner S, Gluckman TJ, Criqui MH, Ferrucci L. A pilot exercise intervention to improve lower extremity functioning in peripheral arterial disease unaccompanied by intermittent claudication. *J Cardiopulm Rehabil*. 2004;24:187–196.

159. Harwood AE, Smith GE, Cayton T, Broadbent E, Chetter IC. A systematic review of the uptake and adherence rates to supervised exercise programs in patients with intermittent claudication. *Ann Vasc Surg*. 2016;34:280–289. doi: 10.1016/j.avsg.2016.02.009

160. Menard JR, Smith HE, Riebe D, Braun CM, Blissmer B, Patterson RB. Long-term results of peripheral arterial disease rehabilitation. *J Vasc Surg*. 2004;39:1186–1192. doi: 10.1016/j.jvs.2004.01.034

161. McDermott MM, Guralnik JM, Criqui MH, Ferrucci L, Zhao L, Liu K, Domanchuk K, Spring B, Tian L, Kibbe M, Liao Y, Lloyd Jones D, Rejeski WJ. Home-based walking exercise in peripheral artery disease: 12-month follow-up of the GOALS randomized trial. *J Am Heart Assoc*. 2014;3:e000711. doi: 10.1161/JAHA.113.000711

162. Collins TC, Lunos S, Carlson T, Henderson K, Lightbourne M, Nelson B, Hodges JS. Effects of a home-based walking intervention on mobility and quality of life in people with diabetes and peripheral arterial disease: a randomized controlled trial. *Diabetes Care*. 2011;34:2174–2179. doi: 10.2337/dc10-2399

163. McDermott MM, Spring B, Berger JS, Treat-Jacobson D, Conte MS, Creager MA, Criqui MH, Ferrucci L, Gornik HL, Guralnik JM, Hahn EA, Henke P, Kibbe MR, Kohlman-Trighoff D, Li L, Lloyd-Jones D, McCarthy W, Polonsky TS, Skelly C, Tian L, Zhao L, Zhang D, Rejeski WJ. Effect of a home-based exercise intervention of wearable technology and telephone coaching on walking performance in peripheral artery disease: the HONOR randomized clinical trial. *JAMA*. 2018;319:1665–1676. doi: 10.1001/jama.2018.3275

164. Mika P, Spodaryk K, Cencora A, Unnithan VB, Mika A. Experimental model of pain-free treadmill training in patients with claudication. *Am J Phys Med Rehabil*. 2005;84:756–762.

165. Mika P, Spodaryk K, Cencora A, Mika A. Red blood cell deformability in patients with claudication after pain-free treadmill training. *Clin J Sport Med*. 2006;16:335–340.

166. Mika P, Wilk B, Mika A, Marchewka A, Nizankowski R. The effect of pain-free treadmill training on fibrinogen, haematocrit, and lipid profile in patients with claudication. *Eur J Cardiovasc Prev Rehabil*. 2011;18:754–760. doi: 10.1177/1741826710389421

167. Mika P, Konik A, Januszek R, Petriczek T, Mika A, Nowobilski R, Nizankowski R, Szczeklik A. Comparison of two treadmill training programs on walking ability and endothelial function in intermittent claudication. *Int J Cardiol*. 2013;168:838–842. doi: 10.1016/j.ijcard.2012.10.003

168. Sanderson B, Askew C, Stewart I, Walker P, Gibbs H, Green S. Short-term effects of cycle and treadmill training on exercise tolerance

in peripheral arterial disease. *J Vasc Surg*. 2006;44:119–127. doi: 10.1016/j.jvs.2006.03.037

169. Walker RD, Nawaz S, Wilkinson CH, Saxton JM, Pockley AG, Wood RF. Influence of upper- and lower-limb exercise training on cardiovascular function and walking distances in patients with intermittent claudication. *J Vasc Surg*. 2000;31:662–669. doi: 10.1067/mva.2000.104104

170. Zwierska I, Walker RD, Choksy SA, Male JS, Pockley AG, Saxton JM. Upper- vs lower-limb aerobic exercise rehabilitation in patients with symptomatic peripheral arterial disease: a randomized controlled trial. *J Vasc Surg*. 2005;42:1122–1130. doi: 10.1016/j.jvs.2005.08.021

171. Singh SJ, Morgan MD, Scott S, Walters D, Hardman AE. Development of a shuttle walking test of disability in patients with chronic airways obstruction. *Thorax*. 1992;47:1019–1024.

172. Tew G, Nawaz S, Zwierska I, Saxton JM. Limb-specific and cross-transfer effects of arm-crank exercise training in patients with symptomatic peripheral arterial disease. *Clin Sci (Lond)*. 2009;117:405–413. doi: 10.1042/CS20080688

173. Bronas UG, Treat-Jacobson D, Leon AS. Comparison of the effect of upper body-ergometry aerobic training vs treadmill training on central cardiorespiratory improvement and walking distance in patients with claudication. *J Vasc Surg*. 2011;53:1557–1564. doi: 10.1016/j.jvs.2011.01.077

174. Ritti-Dias RM, Wolosker N, de Moraes Forjaz CL, Carvalho CR, Cucato GG, Leão PP, de Fátima Nunes Marucci M. Strength training increases walking tolerance in intermittent claudication patients: randomized trial. *J Vasc Surg*. 2010;51:89–95. doi: 10.1016/j.jvs.2009.07.118

175. Parmenter BJ, Raymond J, Dinnen P, Lusby RJ, Fiatarone Singh MA. High-intensity progressive resistance training improves flat-ground walking in older adults with symptomatic peripheral arterial disease. *J Am Geriatr Soc*. 2013;61:1964–1970. doi: 10.1111/jgs.12500

176. Gardner AW, Parker DE, Montgomery PS. Predictors of improved walking after a supervised walking exercise program in men and women with peripheral artery disease. *Int J Vasc Med*. 2016;2016:2191350. doi: 10.1155/2016/2191350

177. Gardner AW, Parker DE, Montgomery PS, Blevins SM. Diabetic women are poor responders to exercise rehabilitation in the treatment of claudication. *J Vasc Surg*. 2014;59:1036–1043. doi: 10.1016/j.jvs.2013.10.058

178. van Schaardenburgh M, Wohlwend M, Rognmo Ø, Mattsson EJR. Exercise in claudicants increase or decrease walking ability and the response relates to mitochondrial function. *J Transl Med*. 2017;15:130. doi: 10.1186/s12967-017-1232-6