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Medical Management of Functional Impairment in Peripheral Artery Disease: A Review

Mary M. McDermott, MD [Professor of Medicine]

Northwestern University Feinberg School of Medicine

Abstract

Lower extremity peripheral artery disease (PAD) now affects 200 million people worldwide and is a major cause of disability. Cilostazol is the only Federal Drug Administration approved medication for PAD-related ischemic symptoms that is recommended by clinical practice guidelines. Supervised treadmill exercise significantly improves treadmill walking performance in PAD. Recent evidence shows that home-based exercise interventions that include occasional medical center visits and incorporate behavioral change techniques also significantly improve walking endurance in PAD. Upper and lower extremity ergometry (cycling) also improve walking ability in PAD. A recent decision by the Center for Medicaid and Medicare Services to cover supervised exercise for people with symptomatic PAD will increase access to exercise for the large number of people disabled by PAD.

Keywords

Peripheral artery disease; claudication; exercise; physical functioning

Lower extremity peripheral artery disease (PAD) is a major cause of disability and mobility loss in older men and women. PAD now affects more than eight million men and women in the United States and more than 200 million people worldwide (1,2). The prevalence of PAD is likely to increase as the population lives to older ages and as the obesity epidemic increases the prevalence of diabetes mellitus. Older age, diabetes, and cigarette smoking are major risk factors for PAD.

PAD can be diagnosed and quantified with the ankle brachial index (ABI), a ratio of Doppler recorded systolic pressures measured at the ankle (dorsalis pedis and posterior tibial arteries) divided by the ratio of Doppler recorded systolic pressures in the upper extremity (brachial) arteries (3). In the absence of lower extremity atherosclerosis, systolic pressures increase with greater distance from the heart. Therefore, arterial pressures at the ankle are normally higher than the brachial artery pressures and a normal ABI ranges from 1.10 to 1.30. An

Corresponding author information: Mary M. McDermott, MD, 750 North Lake Shore Drive, Chicago, IL 60611, Telephone: 312-503-6419, Fax: 312-503-2777, mdm608@northwestern.edu.

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ABI < 0.90 is approximately 72% sensitive and 99% specific for PAD (4). Lower ABI values are indicative of more severe PAD.

Compared to people without PAD, people with PAD have increased rates of cardiovascular (CV) morbidity and mortality, faster rates of functional decline, and increased rates of mobility loss (5-10). For example, adjusting for atherosclerotic risk factors, people with an ankle brachial index (ABI) < 0.90 have a 2-fold increased rate of cardiovascular mortality compared to people with a normal ABI (5,6). The association of PAD with increased CV mortality is observed in men and women, respectively, and in people with asymptomatic and symptomatic PAD (5,6). Treatment goals for people with PAD consist of reducing CV event rates, improving functional performance, and preventing functional decline and mobility loss (11). This review focuses on evidence regarding medical therapies that improve functional performance and prevent functional decline and mobility loss in PAD.

Magnitude of Functional Impairment and Decline in PAD

Few people with PAD develop critical limb ischemia or require limb amputation (11,12). For example, over a five year period, fewer than five percent of people with PAD will develop critical limb ischemia or require amputation. However, people with PAD have higher rates of mobility loss, significantly greater functional limitations, and poorer quality of life than people without PAD (5-10). Compared to people without PAD, those with PAD have lower physical activity (PA) levels, slower walking speed over short distances, poorer walking endurance, faster declines in walking endurance, and higher rates of mobility loss (7-10,12). These associations are independent of differences in age, sex, race, and comorbidities between people with and without PAD (7-10). For example, in cross-sectional analyses of 726 men and women age 55 and older in the Walking and Leg Circulation Study (WALCS), including 460 participants with PAD, more than 60% of those with an ABI < 0.40 were unable to walk for six-minutes without stopping to rest, compared to fewer than five percent of those with ABI 1.00 to 1.50 (7). In prospective, longitudinal analyses, at five-year follow-up, participants with severe PAD in the WALCS cohort were 4.2 times more likely to become unable to walk ¼ mile or walk up one flight of stairs without assistance compared to people without PAD, independently of age, comorbidities, and other confounders (9). Those with mild PAD were 3.2 times more likely to become unable to walk ¼ mile or walk up one flight of stairs without assistance, compared to people without PAD (9). Therefore, compared to people without PAD, those with PAD have significant functional impairment and the natural history of lower extremity outcomes in people with PAD consists of functional decline and mobility loss (5-10,12-13). Table 1 summarizes the spectrum of functional limitations and functional decline observed in PAD.

Leg Symptoms, Asymptomatic PAD, and Functional Decline in PAD

Intermittent claudication is considered the most classical symptom of PAD and is characterized by exertional calf pain that resolves within 10 minutes of resting and that does not begin at rest (15,16). However, most people who have symptomatic PAD report ischemic exertional leg symptoms that are not typical for intermittent claudication and in community-based populations, most people with PAD report no exertional leg symptoms and therefore

are considered asymptomatic (12,14,16,17). Many people with PAD restrict their activity or slow their walking speed in daily life to avoid exertional ischemic leg symptoms and many report no symptoms (7). Among 1,566 community-dwelling people age 70-89 in the LIFE Study, 220 (14%) had an ABI < 0.90, consistent with PAD (14). Of these, 66% reported no exertional leg symptoms (14). Similarly, among 933 older women in the Women's Health and Aging Study with an ABI < 0.90 consistent with PAD, 63% were asymptomatic (12). Therefore, PAD is commonly asymptomatic or associated with atypical leg symptoms other than intermittent claudication.

Functional impairment and functional decline are observed even in people with PAD who report no exertional leg symptoms (7-10,12-14). Among men and women in the LIFE study who reported no leg symptoms, those with PAD had significantly slower 400 meter walk time and slower walking velocity over four meters, compared to those without PAD (14). In the longitudinal WALCS cohort, people with PAD who reported at baseline that they had no exertional leg symptoms, even during the 6-minute walk test, were approximately three times more likely to develop mobility loss compared to people with PAD who had classical claudication symptoms (HR=2.94, 95% CI=1.39-6.19) (10).

Overview of Therapy for Functional Impairment in PAD

Because of the substantial burden of functional impairment and functional decline in PAD, improving functional performance and preventing functional decline and mobility loss are major therapeutic goals for people with PAD (11,18). While endovascular and lower extremity revascularization procedures significantly improve walking performance in people with PAD (19-21), revascularization procedures are not therapeutic options for many people with PAD, either due to the presence of comorbid diseases or because the location and type of atherosclerotic disease in the lower extremities is not amenable to revascularization (18). Revascularization is invasive, costly, and associated with risks. For these reasons, clinicians should be familiar with medical therapies to improve lower extremity functioning in PAD that are effective, accessible, and well tolerated for people with PAD.

Medications to Improve Ischemic Leg Symptoms in PAD

Currently only two medications are Federal Drug Administration (FDA) approved for improving walking performance in people with PAD: Pentoxifylline was approved by the FDA in 1984 and cilostazol was approved by the FDA in 1999 for treatment of intermittent claudication symptoms. No new drugs have been approved by the FDA for treatment of intermittent claudication since 1999. Furthermore, in recent studies of people with PAD, pentoxifylline has not significantly improved intermittent claudication symptoms or maximal walking distance more than placebo (11,18). Recently published clinical practice guidelines recommend against prescription of pentoxifylline for intermittent claudication symptoms, due to lack of benefit (11).

Cilostazol is a phosphodiesterase inhibitor that provides approximately 25% to 40% improvement in treadmill walking performance in people with symptomatic PAD. Cilostazol is a vasodilator, but the mechanism by which it improves walking ability in people with PAD

remains unclear. A recent systematic review that included 15 randomized clinical trials and 3,718 participants with PAD and intermittent claudication concluded that cilostazol was associated with significant benefit in improving treadmill walking performance in PAD (22). In a meta-analysis of eight randomized trials, cilostazol 100 mgs twice daily was associated with a 43 meter improvement in maximal treadmill walking distance and 50 mgs twice daily was associated with a 32 meter improvement. For distance to onset of claudication pain on the treadmill, cilostazol 100 mgs twice daily was associated with a 31 meter improvement, and 50 mgs twice daily was associated with a 20 meter improvement (22). There was no association of cilostazol with all cause or CV mortality (22). Side effects of cilostazol include headache, diarrhea, palpitations, and lightheadedness. In one study, 20% of patients treated with cilostazol discontinued the drug due to side effects (23). Clinical practice guidelines recommend cilostazol for improving walking performance in people with PAD (Class I, level of evidence A, indicating that multiple randomized trials show benefit and that this therapy should be prescribed for people with symptomatic PAD). There is a black box warning against prescribing cilostazol to people with history of heart failure.

Overview of exercise interventions for people with PAD

Exercise interventions for PAD have been studied for more than 30 years. At least 33 randomized trials of exercise including more than 2,000 participants with PAD have been published (24,25). The most common form of exercise studied for patients with PAD is supervised treadmill exercise (24,25). Multiple randomized clinical trials have consistently demonstrated that supervised treadmill exercise significantly improves treadmill walking performance in people with PAD (24,25). More recently, randomized trials have demonstrated that home based walking exercise interventions that incorporate behavioral change techniques improve walking performance in people with PAD and have a greater effect on improving six-minute walk distance than supervised treadmill exercise (26-28). Randomized trial data show that arm and leg ergometry improve walking endurance in people with PAD (29-31), while data on resistance training for PAD are mixed (32-35).

In general, exercise and general PA improves walking performance in people with PAD. A recent Cochrane Collaboration meta-analysis and systematic review of exercise therapy for people with PAD summarized results of 32 randomized trials and included 1,835 with PAD stable leg pain who were randomized to either exercise therapy or a non-exercise group (24). Most of the randomized trials studied supervised treadmill exercise, but the meta-analysis also included randomized trials of strength training, polestriding, and upper and lower extremity ergometry. Among the 32 trials, supervised exercise sessions were typically held at least twice per week. In a meta-analysis of ten randomized trials including 500 participants with PAD and stable intermittent claudication, exercise therapy was associated with a 120 meter increase in maximal treadmill walking distance (95% Confidence Interval-50.8 to 189.9 meters). In meta-analysis of nine trials of 391 participants with PAD and stable claudication, exercise therapy was associated with an 82 meter improvement in pain-free walking distance (95% Confidence interval of 72 to 92 meters) (24). The Cochrane meta-analysis did not compare efficacy of different exercise modalities for PAD (i.e. supervised treadmill exercise, strength training, or ergometry). Collectively, the exercise interventions significantly improved treadmill walking performance, but did not improve the

ABI or mortality (24). Exercise was associated with improved quality of life, measured by the Short-Form 36 physical summary score, mental summary score, and physical function score (24). Exercise was not associated with improvements in other domains of the SF-36 such as bodily pain, vitality, role physical, or social functioning (24). There was insufficient evidence regarding the benefits of exercise on amputation or CV event rates.

Supervised Walking Exercise for PAD

Clinical practice guidelines recommend supervised treadmill exercise as first line therapy for walking impairment in PAD (Class IA recommendation, indicating that supervised treadmill exercise is recommended or should be performed, based on high quality evidence from more than one randomized clinical trial). Fakhry et al. completed a meta-analysis of supervised walking therapy for people with PAD that included 25 randomized trials and 1054 PAD patients with intermittent claudication (25). The meta-analysis included randomized trials of supervised walking therapy interventions that included treadmill walking performance outcomes at baseline and follow-up and a control group that did not receive exercise. Twenty-five studies published between 1996 and 2012 were included, ranging from four to 104 weeks in duration. The authors included one study of supervised pole-striding exercise. In this meta-analysis, supervised exercise was associated with a 180 meter greater gain in maximal treadmill walking distance and a 128 meter greater gain in pain-free treadmill walking distance, compared to the control group (25). In meta-regression analyses, there was no statistically significant difference in the degree of improvement in treadmill walking performance according to whether the exercise interventions instructed participants to walk to the onset of ischemic leg pain or to maximal ischemic leg pain vs. instructing them to exercise pain free (i.e. at a slower walking pace). Three trials in which participants engaged in 'pain free' supervised walking therapy achieved a 257 meter gain in maximal treadmill walking distance, compared to the control group, while 10 trials in which participants exercised to maximum ischemic leg pain achieved a 177 meter gain in maximal treadmill walking distance. Six supervised exercise programs that did not use a treadmill for exercise training achieved shorter gains in maximal treadmill walking distance (100 meters vs. 200 meters) and shorter gains in pain-free walking distances (57 meters vs. 128 meters) compared to exercise programs using a treadmill. However, these differences were not statistically significant and the suggestion of greater benefit for programs that used treadmill exercise training may be due to the fact that treadmill exercise trains people to become more comfortable with and walk better on a treadmill (36). In general, supervised walking exercise programs that include at least three sessions per week for at least 30 minutes per session and that last 12 to 26 weeks in duration are beneficial for patients with PAD.

Center for Medicare and Medicaid Services (CMS) Coverage for Supervised Exercise

Despite multiple randomized trials demonstrating benefits of supervised walking exercise for people with PAD, many patients with PAD have not had access to supervised exercise in part because of lack of medical insurance coverage for this therapy. In May of 2017, the CMS announced a decision to provide coverage for supervised treadmill exercise for people

with PAD (37). In their decision, the CMS indicated that evidence was sufficient to cover supervised exercise therapy for treatment of symptomatic PAD and that 36 sessions of supervised exercise over a 12 week period would be covered, provided that certain conditions were met (see Table 2). CMS will cover supervised exercise programs for PAD that consist of 30-60 minute sessions of exercise training, that are held in a hospital outpatient setting or at a physician's office, that are delivered by qualified personnel with training in exercise therapy for PAD, and that are under the direct supervision of a physician, physician assistant, or nurse practitioner/clinical nurse specialist trained in basic and advanced life support techniques (37). CMS requires that patients with PAD have a face-to-face meeting with their physician prior to initiating supervised exercise therapy. During this face-to-face meeting, the physician must provide information about CV disease risk and risk factor reduction. After the 12 weeks of supervised exercise are completed, CMS has the discretion to cover an additional 36 sessions over an extended period of time. A second physician referral is required for these additional sessions. This new coverage by CMS is expected to increase access to supervised exercise therapy for millions of people in the United States who are disabled by PAD.

Implementing Supervised Exercise Therapy for Symptomatic PAD

Supervised treadmill exercise should be provided three times per week for people with PAD. Exercise should be tailored for each individual patient. Typically, PAD patients starting an exercise program for the first time should engage in 10-15 minutes of walking exercise per session. Successful randomized trials of supervised exercise have pushed patients with PAD to walk at a speed that elicits significant leg ischemia symptoms within ten minutes (34,38). Patients should stop and rest when ischemic leg symptoms are moderate to severe. Once leg pain subsides, the PAD patient should resume walking exercise and PA. If the PAD patient can walk for more than 10 minutes without resting, then the intensity should be increased, by increasing the treadmill speed or the treadmill grade. The duration of exercise time should be increased by five minutes per week, until 45 to 50 minutes of walking exercise per session is reached (excluding rest periods). However, there are substantial differences in ability between patients with PAD and some more severely disabled patients may not be capable of increasing their walking exercise to more than about 30 minutes per session. Maximal improvement in treadmill walking performance is typically experienced after about twelve weeks of supervised treadmill exercise training and continued exercise serves to maintain the gains in treadmill walking performance (39).

Educating Patients with PAD about the Benefits of Supervised Exercise Therapy

As described above, CMS requires a face-to-face meeting between the treating physician and the patient with PAD prior to covering supervised exercise. During this meeting, the physician should address cardiovascular risk factor reduction with the patient. In addition, PAD patients are often not knowledgeable about the association between PAD and their walking difficulty and are likely to benefit from education about what to expect regarding exercise activity and general PA. Patients should be educated that ischemia-related leg pain

is not harmful and that benefits from walking exercise activity are not immediate. Patients should be advised that weeks of regular walking exercise activity may be required before ischemic leg symptoms substantially improve. Patients with PAD should also be advised that their walking exercise sessions will consist of walking episodes to moderate ischemic pain, with intermittent rest periods between bouts of walking exercise.

Home-Based Walking Exercise for PAD

Travelling to an exercise center three times weekly for supervised exercise training can be burdensome and many people with PAD decline participation in supervised exercise programs (40,41). A recent systematic review demonstrated that even when supervised exercise was available in a research setting without cost to the patient with PAD, approximately 2/3 of people with PAD declined participation due to inconvenience, the presence of significant comorbidities, or lack of interest in supervised exercise (40). Home-based exercise programs are important for people with PAD who are unable or unwilling to take part in supervised exercise programs and may help patients with PAD maintain walking gains when supervised exercise therapy is completed. Clinical practice guidelines provide a Class IIA recommendation for home-based walking exercise in people with PAD, indicating that treatment with home-based walking exercise is reasonable based on high quality evidence from more than one randomized clinical trial (11).

Evidence for home-based walking exercise in PAD

Three randomized clinical trials demonstrated that walking exercise predominately conducted at home significantly improves walking performance in people with PAD (26-28). All of these trials included periodic visits to the medical center and behavioral change techniques, including goal setting, self-monitoring, and a coach who monitored their progress and provided feedback (26-28).

In the Group Oriented Arterial Leg Study (GOALS) clinical trial of home-based exercise, 192 participants with PAD were randomized to one of two groups: a home-based exercise group vs. an attention control group (27). The GOALS intervention consisted of a Group Mediated Cognitive Behavioral (GMCB) intervention designed to help patients with PAD adhere to a home-based walking exercise program, thereby improving their walking ability (27). During the first six months of GOALS, PAD participants in the intervention group met weekly at the medical center with other PAD patients in the intervention and a facilitator, who led discussions regarding behavioral techniques to help participants adhere to home exercise, including goal setting, self-monitoring, and overcoming obstacles to exercise adherence. PAD participants in the intervention were asked to set exercise goals each week, record their actual walking PA, and evaluate their goals and actual exercise activity in person with the coach during the weekly on-site visits. At six-month follow-up, participants in the GMCB home-based exercise intervention group significantly improved their six-minute walk performance (primary outcome measure), pain-free treadmill walking time, and maximum treadmill walking time relative to the control group. The home-based exercise intervention group had a 53.5 meter greater increase in six-minute walk performance, a 1.01 minute greater increase in maximal treadmill walking time, and a 1.02 minute greater

increase in pain-free treadmill walking time than the control group. The GMCB home-based exercise intervention also significantly improved PA levels and the Walking Impairment Questionnaire (WIQ) distance score, compared to the control group. After the six-month primary and secondary outcomes were measured, participants in the GOALS intervention received telephone calls from the coach facilitator between months 7-12. At 12-month follow-up, those in the intervention group continued to have significantly greater six-minute walk distance compared to the control group, six months after the final on-site study intervention (42). Participants in the GOALS trial consisted of people with objective evidence of PAD, both with and without classical symptoms of intermittent claudication, indicating that home-based walking exercise improves walking ability even in PAD patients without classical claudication symptoms.

In a separate clinical trial, Gardner et al randomized 180 participants with PAD and intermittent claudication to one of three groups for 12 weeks: home-based walking exercise, traditional supervised treadmill exercise, or a control group that engaged in light resistance training (26). Participants randomized to home exercise were asked to walk for exercise in an unsupervised setting at a self-selected pace, three days weekly, working up to 45 minutes per session. They received an activity monitor to track their home walking exercise activity, and they returned to the medical center at one-week, four-week, eight-week, and twelve-week follow-up. During these on-site sessions, a study investigator reviewed the activity monitor data, provided individualized feedback and helped the participant develop home walking exercise goals for the next four weeks. Participants randomized to supervised exercise were asked to walk for exercise on the treadmill three days per week in a standard supervised exercise intervention, working up to 40 minutes per session. Participants randomized to the attention control group participated in upper extremity resistance training. At 12-week follow-up, the home-based walking exercise group increased their maximal treadmill walking time by 110 seconds, the supervised exercise group increased their maximal treadmill walking time by 192 seconds, and the control group increased their walking time by 22 seconds (26). Furthermore, the home-based exercise group increased their six-minute walk distance by 45 meters, the supervised treadmill exercise group increased six-minute walk distance by 15 meters, and the attention control group increased six minute walk distance by four meters. Improvement in six-minute walk distance was significantly greater in the home-exercise group than in the supervised exercise group. Together, this trial and the GOALS randomized trial showed that the six-minute walk distance improved to a greater degree after a home based exercise program (45 to 53 meters) than after a supervised treadmill exercise program (approximately 30-35 meters) (26,27,34,38). This is likely related to the phenomenon in which supervised treadmill exercise helps patients become more comfortable with treadmill walking, while home based exercise helps patients better navigate over ground walking, such as the corridor walking performed in a six-minute walk test.

How to Implement a Home-Based Exercise Intervention for People with PAD

Home-based walking exercise should be recommended for patients with PAD who are unable or unwilling to participate in supervised treadmill exercise or who have completed a supervised treadmill exercise program. Advantages of home-based walking exercise include

that it does not require three times weekly visits to a medical center and that it can be carried out in the neighborhood or home environment of patients with PAD. However, the successful home-based walking exercise interventions have all included periodic visits to the medical center to receive feedback from a coach (26-28). A randomized trial of 200 participants with PAD randomized to a home-exercise intervention that included a wearable PA monitor, social media, and telephone calls from a coach, but no regular visits to the medical center did not achieve improvement in six-minute walk distance compared to usual care (43). To achieve benefit, home-based exercise programs should require patients with PAD to write down walking exercise goals and record their actual walking exercise activity each week (26,27). This information should be reviewed periodically in person with a 'coach' to whom the patient feels accountable. Table 3 compares characteristics of components of successful home-based and supervised walking exercise programs in PAD.

Upper and Lower Extremity Ergometry Exercise Interventions for PAD

In several randomized trials, both upper and lower limb ergometry significantly improved walking performance in people with PAD and intermittent claudication (29-31). Ergometry exercise typically consists of repeated bouts of upper or lower extremity cycling exercise. The mechanism by which ergometry improves walking performance in people with PAD is unclear. However, both upper and lower extremity ergometry improved oxygen consumption and walking endurance in one randomized trial (29). An example of an effective ergometry exercise intervention for PAD consists of two exercise sessions per week, in which the PAD patient performs arm (or leg) cycling for 10 sets of two minute exercise bouts. Each bout of two minutes of exercise is followed by two minutes of rest. Upper and lower extremity ergometry have each been shown to improve corridor walking by approximately 30%. Zwierska et al randomized 104 participants with PAD to arm ergometry, leg ergometry (cycling), or a non-exercise control group for six months (30). The maximal corridor walking distance increased by 29% in the upper limb ergometry group and by 31% in the lower limb ergometry group, while there was no change in the control group at six-month follow-up. Patients with PAD who find walking exercise particularly uncomfortable or difficult may find ergometry exercise more acceptable than treadmill exercise.

Resistance Training Exercise for PAD

People with PAD have impaired lower extremity strength compared to people without PAD and more adverse lower extremity muscle characteristics (17,44). Poorer leg strength and more adverse calf muscle characteristics are associated with greater functional impairment, faster functional decline, and increased rates of mobility loss (17,45,46). Several clinical trials have studied whether lower extremity resistance training improves walking ability in people with PAD, but results have been mixed (32-36). In one clinical trial of 20 patients with PAD who were randomized to lower extremity resistance training (3 times/week) or a control group for six months, gastrocnemius muscle biopsies showed increases in Type 1 and Type 2 muscle fiber area and increased capillary density in the resistance trained group, compared to control (32). In a second clinical trial, 22 patients with PAD were randomized to low intensity resistance training, high intensity resistance training, or a control group that engaged in unsupervised walking for six months (35). High intensity progressive resistance

training improved the six-minute walk distance by 63 meters, while those in low intensity progressive resistance training declined by 48 meters and those in the control group declined by 10 meters at six-month follow-up. In the largest trial of strength training for PAD, McDermott et al randomized 156 participants with PAD to supervised treadmill exercise, supervised resistance training, or a control group for 6-months. At six-month follow-up, supervised treadmill exercise, but not lower extremity resistance training, significantly improved the six-minute walk distance (primary outcome) (+ 35.9 meters in the supervised treadmill exercise group vs attention control and +12.4 meters in the supervised lower extremity resistance trained group vs. attention control, respectively). Maximal treadmill walking distance improved significantly in both the supervised treadmill exercise group (+3.44 minutes, 95% CI= 2.05 to 4.84 minutes) and in the supervised resistance trained group (+1.90 minutes, 95% CI=0.49 to 3.31 minutes), compared to the attention control group. Collectively, these data suggest that resistance training may provide a small benefit for patients with PAD, but the benefit appears less substantial than benefit from walking exercise. No sufficiently powered randomized trials have tested whether the combination of strength training combined with walking exercise significantly improves walking performance in PAD. Table 4 compares characteristics of different types of exercise programs for people with PAD.

Exercise and Preventing CV Morbidity and Mortality

Walking exercise training has had variable effects on CV disease risk factors (47-49). A clinical trial randomized 42 male patients with intermittent claudication to walking exercise vs. a control group that engaged in stretching exercises (49). At 12- week follow-up, the walking exercise decreased systolic blood pressure by a mean of 10 mm and mean blood pressure by 5 mm. A separate 6-month observational study followed 34 patients with PAD who were engaged in exercise rehabilitation and 14 controls with PAD who were not exercising. Exercise rehabilitation lowered total cholesterol by 5%, LDL cholesterol by 8%, and systolic blood pressure by 6%. However, there were no changes in diastolic blood pressure, fasting glucose, the ABI, or body mass index. There is currently no evidence that exercise interventions reduce CV event rates or total mortality in people with PAD (24).

Conclusions

PAD now affects 200 million people worldwide and is a major cause of disability. Cilostazol improves walking ability modestly and is the only FDA approved medication for PAD-related ischemic symptoms that is recommended by clinical practice guidelines. Supervised treadmill exercise therapy significantly improves treadmill walking performance in PAD. Home-based exercise interventions that include occasional medical center visits and incorporate behavioral change techniques significantly improve walking endurance in PAD and have an even greater effect on improvement in six-minute walk distance than supervised treadmill exercise. Upper and lower extremity ergometry (cycling) also improve walking ability in PAD, but data are mixed regarding resistance training. A recent decision by the CMS to cover supervised exercise for people with symptomatic PAD will increase access to exercise for the large number of people disabled by PAD.

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Alphabetical list of abbreviations

ABI	Ankle brachial index
CMS	Center for Medicare and Medicaid Services

CV	Cardiovascular
FDA	Federal Drug Administration
GOALS	Group Oriented Arterial Leg Study
GMCB	Group Medicated Cognitive Behavioral
LIFE	Lifestyle interventions and independence for elders
PA	Physical activity
PAD	Peripheral artery disease
WIQ	Walking Impairment Questionnaire

Table 1
Characteristics of functional Impairment in Peripheral Artery Disease

• Compared to people without PAD, those with PAD have poorer physical activity levels, slower walking speed over short distances, poorer balance, and poorer walking endurance (7).
• People with PAD have faster rates of annual decline in six-minute walk performance than those without PAD (8).
• People with PAD report higher rates of mobility loss than people without PAD (10).
• Many people with PAD reduce their physical activity or slow walking speed to avoid exertional leg symptoms (7,51)
• Functional impairment and functional decline are observed even in people with PAD who report no exertional leg symptoms or who have exertional leg symptoms other than intermittent claudication (12-14).
• More adverse calf skeletal muscle characteristics in PAD are associated with greater functional impairment and increased rates of functional decline and mobility loss (46,51).

Table 2
Elements of supervised exercise required for coverage by the Center for Medicaid and Medicare Services*

- Exercise must be prescribed by a physician after a face-to-face meeting with the patient that includes counseling on cardiovascular disease prevention.
- Prescribed exercise must consist of 12 weeks of exercise sessions occurring three times weekly.
- After completing 12 weeks of supervised exercise, an additional 36 sessions may be prescribed, with written justification, after the first 12 weeks are completed and may take place over a longer period of time.
- The exercise sessions must take place in a physician's office or outpatient hospital-affiliated setting.
- Exercise must be delivered by qualified personnel with training in basic and advance life support and exercise therapy for PAD.
- Exercise must be supervised by a physician, physician's assistant, or nurse practitioner/clinical nurse specialist.

* Table derived from Reference #50.

Table 3
Summary of effective supervised and home-based walking exercise programs for PAD

	Supervised walking exercise	Home based walking exercise
Definitions	Walking exercise at a medical facility or health club under supervision by an exercise physiologist or registered nurse with training in PAD rehabilitation.	Walking exercise carried out near home or in another unstructured setting without supervision.
Frequency	3 times/week	3-5 times/week
Duration	Start with 15 minutes and work up to 40 to 50 minutes/session	Start with 15 minutes/session and work up to 45 to 50 minutes/session.
Intensity	Typically successful programs consist of walking to moderate to severe leg ischemia.	Effective programs have asked participants to walk at a comfortable pace or walk to maximal ischemic discomfort.
Additional characteristics	Requires travel to exercise session three times weekly. Many PAD patients may find this cumbersome.	Requires occasional visits to the medical center for meeting with a coach. Behavioral methods such as goal setting, monitoring progress, and a coach who provide feedback are necessary.

Table 4
Methods of exercise therapy for PAD

	Supervised walking exercise	Home-based walking exercise	Upper and lower extremity ergometry	Resistance training
Session frequency and duration and characteristics	3 x/weekly for 50 minutes/session.	3-5 times/weekly for 45 to 50 minutes/session	2 times weekly for 20 minutes of exercise per session (2 minutes of exercise followed by 2 minutes rest)	2-3 times weekly for 2-3 sets of 8-10 repetitions of strength training. Weights are increased as the patient improves.
Equipment and other resources required	Treadmills that begin at 0.5 miles per hour. Trained staff.	No equipment required. A coach should meet with the patient every one to four weeks.	Ergometer for lower extremities or upper extremities. All randomized trials in PAD have included supervision by trained staff.	Resistance training equipment and trained staff for supervision.
Benefits of exercise	Improves maximal treadmill walking distance by 180 meters and maximal treadmill walking time by 3.44 minutes. Improves pain-free walking distance by 128 meters (25). Improves the six-minute walk by 30-35 meters (34,38).	Improves maximal treadmill walking time by 1-1.5 minutes. Improves six-minute walk by 45-53 meters (26,27).	Upper and lower extremity cycling each improve treadmill walking distance by approximately 75-85 meters (29)	Improves maximal treadmill walking time by 1.9 minutes. Improves six-minute walk by 12.5 to 63 meters, relative to control (34,35)