Published in final edited form as:

Curr Cardiol Rep. 2013 April ; 15(4): 347. doi:10.1007/s11886-013-0347-5.

Functional Impairment in Peripheral Artery Disease and How to Improve It in 2013

Mary McGrae McDermott, MD

Professor of Medicine, Northwestern University Feinberg School of Medicine, 750 N. Lake Shore Drive, Chicago, IL 60611, Telephone: 312-503-6419, Fax: 312-503-2777
mdm608@northwestern.edu

Abstract

Lower extremity peripheral artery disease (PAD) affects eight million men and women in the United States and will be increasingly common as the U.S. population lives longer with chronic disease. People with PAD have poorer walking endurance, slower walking velocity, and poorer balance, compared to individuals without PAD. People with PAD may reduce their walking activity to avoid leg symptoms. Thus, clinicians should not equate stabilization or improvement in exertional leg symptoms with stabilization or improvement in walking performance in PAD. Additionally, even asymptomatic PAD patients have greater functional impairment and faster functional decline than individuals without PAD. Of the two FDA-approved medications for treating claudication symptoms, pentoxifylline may not be more efficacious than placebo, while cilostazol confers a modest improvement in treadmill walking performance. Supervised treadmill walking exercise is associated with substantial improvement in walking endurance, but many PAD patients do not have access to supervised exercise programs. Unsupervised walking exercise programs may be beneficial in PAD, but data are mixed.

Keywords

Peripheral artery disease; intermittent claudication; physical functioning; exercise rehabilitation

Introduction

Lower extremity peripheral artery disease (PAD) affects eight million men and women in the United States (1) and is expected to be increasingly prevalent as the U.S. population survives longer with chronic disease. Risk factors for PAD include diabetes mellitus, cigarette smoking, LDL cholesterol, and hypertension (1). Patients with PAD have an increased rate of cardiovascular events, compared to patients without PAD. Even after adjusting for atherosclerotic disease risk factors and cardiovascular disease history, people with PAD have a 1.6 to 2.0 fold increased rate of cardiovascular events and all-cause mortality, compared to individuals without PAD (1-3). Therefore, the clinical care of patients with PAD consists of secondary preventive therapies to prevent cardiovascular events, including LDL-lowering therapy, blood pressure control, and assistance with smoking cessation. For reasons described below, management of patients with PAD should also include interventions to improve functional performance and prevent functional decline.

Compared to the association of PAD with cardiovascular events, the association of PAD with functional impairment and functional decline may be less well appreciated. Only a

small proportion of patients with PAD develop gangrene, require amputation, or undergo surgical revascularization (4-6). In addition, in some surgical series, patients with claudication report that over a five year period their claudication symptoms are unchanged or have even improved (4-6). Thus, the natural history of PAD with regard to lower extremity outcomes has been traditionally considered benign (4-6). However, the phenomenon of stabilization or improvement in claudication symptoms is explained in part by restriction of physical activity to avoid ischemic leg symptoms (7). In addition, even asymptomatic patients have greater functional impairment and faster functional decline than individuals without PAD (7,8). Thus, improvement or stabilization of symptoms should not be equated with improvement or stabilization of functional performance. Assessment of lower extremity outcomes in PAD should include objective measures of functional impairment and decline, to objectively assess changes in functional performance, even among PAD patients without claudication symptoms.

PAD is associated with lower physical activity levels and functional impairment

Among 726 men and women in the Walking and Leg Circulation Study (WALCS) cohort who completed a six-minute walk test, participants with an ABI < 0.50 were nearly 12 times more likely to need to stop and rest during the six-minute walk test, compared to participants with a normal ABI value (9) (Figure 1). Those with ABI 0.50 to <0.70 were nearly seven times more likely to need to stop during the six-minute walk, and those with an ABI of 0.70 to < 0.90 were nearly three times more likely to need to stop during the six-minute walk, compared to participants with a normal ABI (9) (Figure 1). These results demonstrate that people with PAD have poorer walking endurance than individuals without PAD and that more severe PAD, as indicated by a lower ABI value, is associated with greater impairment in walking endurance, compared to individuals without PAD. Similar associations between the ABI and distance achieved during the six-minute walk, walking velocity at usual pace, and walking velocity at fastest pace were also observed in the WALCS cohort (9). For example, participants with ABI values < 0.50, 0.50 to < 0.70, 0.70 to < 0.90, and ABI 0.90 to < 1.10 achieved shorter distances in the six-minute walk of -515 feet, -323 feet, -335 feet, and -102 feet, respectively, compared to participants with an ABI value of 1.10-1.50 (9). ABI values of < 0.50, 0.50 to < 0.70, 0.70 to < 0.90, and ABI 0.90 to < 1.10 were associated with slower walking velocity by magnitudes of -0.21 meters/second, -0.16 meters/second, -0.17 meters/second, and -0.09 meters/second, compared to individuals with an ABI of 1.10-1.50 (9). Even standing balance is impaired among people with lower ABI values. Among individuals in the WALCS cohort, ABI values of < 0.50, 0.50 to < 0.70, and 0.70 to < 0.90 were associated with 0.37, 0.47, and 0.73 lesser odds of being able to hold a tandem stand (i.e. stand with one foot directly in front of the other) for ten full seconds, compared to WALCS participants with a normal ABI (9). Physical activity levels are also substantially lower among individuals with lower ABI values, compared to individuals with normal ABI values (9). In summary, PAD is associated with greater functional impairment than individuals without PAD. More severe PAD is associated with progressively greater functional impairment.

PAD and functional decline over time

Low ABI values are also associated with faster rates of functional decline over time, compared to individuals without PAD (8,10,11). Although patients with PAD decline in many aspects of functional performance, they are particularly limited in walking endurance.

In the WALCS cohort of men and women age 55 and older, individuals with ABI < 0.50 at baseline had an average annual decline in six-minute walk performance of - 73.0 feet per year, those with ABI 0.50 to 0.90 had an average decline of -58.8 feet per year, and those with a normal ABI had an average decline of -12.6 feet per year (8). These rates of

functional decline take into account differences in comorbidities, age, sex, and other characteristics across the three ABI categories. These results demonstrate that at two-year follow-up, people with PAD have faster rates of decline in functional performance than people without PAD. Furthermore, more severe PAD at baseline is associated with faster functional decline.

At five year follow-up in the WALCS cohort, participants with PAD had higher rates of mobility loss, compared to individuals without PAD (10). Lower ABI values, consistent with more severe PAD, were associated with higher rates of mobility loss. Mobility loss is defined as becoming unable to climb a flight of stairs or walk ¼ mile without assistance in people who could previously complete these tasks without assistance. Compared to participants with a baseline ABI value of 1.10 to 1.30, those with a baseline ABI value < 0.50 had a hazard ratio of 4.15 (95% Confidence Interval (CI)=1.58-10.92) for the outcome of mobility loss. Compared to participants with a baseline ABI value of 1.10 to 1.30, those with a baseline ABI value of 0.50 to 0.69 had a hazard ratio of 3.82 (95% CI=1.66-8.81), those with a baseline ABI value of 0.70 to 0.89 had a HR of 3.22 (95% CI=1.43-7.21), those with a baseline ABI value of 0.90 to 0.99 had a HR of 3.07 (95% CI=1.21-7.84) and those with an ABI value of 1.00 to 1.09 had a HR of 2.61 (95% CI=1.08-6.32) for the outcome of mobility loss. Together, these data demonstrate that PAD is associated with an increased rate of mobility loss, compared to individuals without PAD, and that more severe PAD, measured by lower ABI values, is associated with greater mobility loss. Importantly, these results also show that even people with mild PAD, measured by an ABI of 0.90 to 0.99, and those with low normal ABI values, measured by an ABI of 1.00 to 1.09, have higher rates of mobility loss compared to people without PAD.

Assessing change in functional performance over time in patients with PAD—

Clinicians should not be reassured by stabilization or improvement in leg symptoms. Because patients with PAD may slow their walking speed or reduce their walking activity in order to avoid leg symptoms, patients with PAD may describe that their leg symptoms as stable or even improved over time. Patients with PAD who report no exertional leg symptoms frequently will develop leg symptoms during a six-minute walk test (9). These asymptomatic PAD patients have slowed their walking speed or limited their walking activity to avoid exertional leg symptoms. In addition, PAD patients who report no exertional leg symptoms nonetheless experience decline in six-minute walk and other functional outcomes over time (8,11). Thus, clinicians should not equate stabilization or improvement in leg symptoms with lack of functional decline.

In contrast to leg symptoms, an objective test, such as the six-minute walk, can measure walking endurance in patients with PAD and can be used to track change in functional performance over time. The six-minute walk can be performed in a clinician's office. A 100-foot hallway and a stopwatch are required. PAD patients are asked to walk back and forth along the 100-foot hallway for six minutes, with the goal of achieving the greatest distance possible during the six minutes. PAD patients are allowed to stop and rest. However, the stopwatch continues running while the patient rests. The distance walked during the six-minutes is recorded at the end of the time period. This six-minute walk can be repeated over time to track changes in functional performance.

The six-minute walk is a well-validated measure of functional impairment in people with PAD, with excellent test re-test reliability (12-14). Among people with PAD, poorer six-minute walk performance is associated with increased rates of all-cause mortality, cardiovascular mortality, and mobility loss (15,16). In addition, among people with PAD, greater declines in six-minute walk performance during a two-year period are associated with higher subsequent mortality and mobility loss (17). Thus, the six-minute walk is useful

both for tracking decline in functional performance and for assessing prognosis regarding functional decline and mortality in people with PAD.

Asymptomatic PAD and functional impairment or decline—Intermittent claudication is the classic symptom of peripheral artery disease (18). Intermittent claudication is characterized by exertional calf pain that does not begin at rest and resolves within 10 minutes of walking cessation. However, it is now recognized that most patients with PAD do not have these classical symptoms of intermittent claudication (19,20). Many patients with PAD are asymptomatic (i.e. they have no exertional leg symptoms) and others have exertional leg symptoms other than classic intermittent claudication symptoms. The prevalence of classic intermittent claudication symptoms varies from approximately 10% in community dwelling men and women with PAD to 30% in patients with PAD identified from a non-invasive vascular laboratory (19-22). The prevalence of asymptomatic lower extremity atherosclerosis varies from 20% among PAD patients identified from a vascular laboratory setting to 67% among community-dwelling elderly with an ABI < 0.90 (19-24). Even PAD patients who are asymptomatic have greater functional impairment and faster functional decline than individuals without PAD (21). For example, in an analysis of community-dwelling women age 65 and older who reported no exertional leg symptoms, women with low ABI values were more likely to report inability to walk ¼ mile or climb a flight of stairs without assistance, compared to women with normal ABI values (21). Among WALCS study participants, those with asymptomatic PAD at baseline had an average annual decline in six-minute walk performance of -76.8 feet per year at two-year follow-up, compared to -8.7 feet per year among WALCS participants without PAD at baseline. Finally, among WALCS study participants who had asymptomatic PAD at baseline and did not develop leg symptoms during the six-minute walk, the hazard ratio for mobility loss at five-year follow-up was 2.94 (95% CI= 1.39-6.19), relative to WALCS participants without PAD at baseline (11).

Therapeutic Strategies for Functional Impairment and Functional Decline in PAD

A summary of therapeutic strategies for functional impairment in PAD is shown in Table 1. Only two medications are FDA-approved for treatment of functional impairment in individuals with PAD. Pentoxifylline was FDA-approved in 1984 and cilostazol was approved in 1999 for treatment of walking impairment due to intermittent claudication symptoms. Pentoxifylline is a methylxanthine derivative that was originally believed to improve walking performance in PAD by reducing blood viscosity. However, recent evidence suggests that pentoxifylline is not much better than placebo for improving treadmill walking performance in patients with PAD (25). Side effects of pentoxifylline include abdominal bloating, diarrhea, flushing, and palpitations. Pentoxifylline is dosed three times daily. Cilostazol is a phosphodiesterase 3 inhibitor that confers a 40 to 50% improvement in treadmill walking performance (26). This is a modest gain in walking performance, compared to supervised treadmill exercise (27). Cilostazol is also associated with improvements in patient quality of life (28). Side effects of cilostazol include diarrhea, headache, and palpitations. Although asymptomatic PAD is associated with functional impairment and decline, no medications have been approved specifically for treatment of asymptomatic PAD.

Supervised Treadmill Walking Exercise for PAD

Supervised treadmill walking exercise is a highly effective therapy for improving walking performance in patients with PAD. A Cochrane Collaboration meta-analysis of randomized controlled clinical trials published in 2008 demonstrated that supervised treadmill walking exercise increases maximal treadmill walking time by five minutes and maximal treadmill walking distance by 82.2 meters as compared to usual care (27). The most effective

supervised treadmill exercise interventions consist of treadmill exercise sessions conducted at least three times weekly and including at least 30 minutes of walking exercise per session. Supervised sessions include an exercise physiologist or person of similar skill who monitors the PAD patient, establishes goals, and encourages the PAD patient throughout their walking exercise. The most effective supervised exercise programs are those in which the patient pushes themselves to develop ischemic leg pain during walking exercise (30). Improvement in ischemic walking symptoms typically occurs 4 to 8 weeks after the start of a supervised treadmill exercise program and continues for as long as the participant continues in the supervised walking exercise program (30,31). If the participant stops exercise, improvements in walking exercise are typically lost over time (30). Although most clinical trials have been conducted in PAD patients who have intermittent claudication symptoms, a recent trial included PAD participants who were asymptomatic or had atypical exertional leg symptoms other than intermittent claudication (32). This trial demonstrated significant improvements in walking endurance and quality of life in response to supervised treadmill exercise even among PAD patients who were asymptomatic or who had atypical exertional leg symptoms other than intermittent claudication (32). While supervised treadmill walking exercise is associated with significant improvements in walking performance among people with PAD, medical insurance typically does not pay for this exercise intervention. Many PAD patients do not participate in supervised treadmill walking exercise (33,34). A successful response to a supervised treadmill exercise intervention requires that the PAD patient be committed to attending sessions three times weekly and that they continue with the exercise program over the long-term.

Unsupervised walking exercise for patients with peripheral artery disease

Unsupervised walking exercise programs are attractive for patients with PAD in part because many PAD patients may not have access to supervised walking exercise programs. However, a Cochrane Collaboration meta-analysis that summarized evidence from randomized clinical trials comparing supervised and unsupervised walking exercise programs concluded that unsupervised walking exercise programs are less effective than supervised walking exercise programs for patients with PAD and intermittent claudication (35). However, this meta-analysis conclusion was based on five clinical trials that involved a total of 85 participants (35). Two more recent trials of unsupervised walking exercise in PAD patients included 119 and 145 participants, respectively (36,37). A study by Gardner et al randomized 119 participants with PAD and intermittent claudication to supervised treadmill exercise, unsupervised treadmill exercise, or a control group. PAD participants in the supervised treadmill exercise arm exercised three times weekly for 40 minutes. PAD participants in the unsupervised treadmill exercise arm exercised three times weekly for 45 minutes and were provided with pedometers and walking logs. Participants in the unsupervised exercise group had contact with the study team twice weekly during which the study team provided feedback on their walking progress. At six-month follow-up, participants in each of the exercise arms had significantly increased their maximum treadmill walking time and their pain-free treadmill walking time, compared to the control group (36). The degree of improvement in maximum and pain-free walking time was greater in the supervised treadmill exercise group than in the unsupervised walking exercise group, but the difference was not statistically significant (36). A separate study by Collins et al randomized 145 patients with intermittent claudication and diabetes mellitus to a home-based exercise program or an attention control group. Participants in the home-based walking exercise program attended weekly walking exercise sessions at an exercise center and were asked to walk an additional three days per week at home. Participants had bi-weekly contact with study staff, during which their walking exercise progress was monitored and feedback was provided (37). At follow-up, there was no significant difference in maximum or pain-free treadmill walking distance between the intervention and control

groups (37). In summary, evidence regarding the ability of a home-based exercise program to improve walking endurance in patients with PAD remains unclear.

Upper and Lower Extremity Ergometry Exercise in PAD

Although supervised treadmill walking exercise is the most well studied exercise intervention for patients with PAD, recent evidence supports upper and lower extremity ergometric exercise for patients with PAD (38). These exercise interventions entail arm or leg ergometry cycling at a rate of 50 revolutions per minute. Two-minute bouts of exercise are alternated with two minutes of rest until a total of 20 minutes of exercise has been achieved. In one representative study that included an arm-ergometry group, a leg ergometry group, and a control group, maximal walking distance increased by 29% in the upper arm aerobic exercise group and by 31% in the lower arm aerobic exercise group at 24-week follow-up. Time to onset of claudication pain increased by 51% in the upper extremity ergometry group and by 57% in the lower extremity ergometry group. There were no changes in maximal walking distance or time to onset of claudication pain in the control group. In summary, available data suggest that arm and leg ergometry exercise are each effective for improving walking endurance in patients with PAD.

Lower extremity endovascular revascularization to improve functional performance in PAD

Rates of lower extremity endovascular procedures are increasing. A better understanding of the relative benefits of lower extremity endovascular revascularization interventions for improving walking performance in patients with PAD is needed. A recent meta-analysis of eight clinical trials that compared lower extremity endovascular revascularization interventions to exercise interventions in PAD patients with aorto-iliac or femoropopliteal disease concluded that neither therapy was clearly superior. However, the combination of endovascular revascularization with exercise was better than either therapy alone (39). When counseling patients about endovascular and exercise therapy, it is important to advise them that endovascular therapy typically results in immediate improvement in walking performance, while supervised walking exercise interventions typically require weeks before substantial improvement in walking performance is realized. In addition, sustaining the benefits of supervised exercise requires that patients continue exercise over the long-term. However, endovascular procedures are associated with greater risks, peri-procedurally, than supervised walking exercise. In addition, endovascular procedures are associated with risk of re-stenosis, which increases with length of time after the procedure.

The CLEVER trial randomized 111 PAD participants with aorto-iliac atherosclerosis to one of three groups: optimal medical care, optimal medical care plus supervised exercise, or optimal medical care plus stent revascularization (40). At six-month follow-up, participants randomized to optimal medical care plus supervised treadmill exercise therapy achieved significantly greater improvement in treadmill walking performance than the group that received optimal medical care plus stent revascularization. However, more consistent improvement in quality of life outcomes was observed in the group that underwent stent revascularization, compared to the exercise group (40). Thus, the CLEVER study demonstrates that supervised treadmill exercise is superior to stent revascularization for the primary study outcome of maximal treadmill walking time.

Mechanisms of functional impairment and functional decline in PAD are not well understood

Although the association of PAD with functional impairment and functional decline is well documented, mechanisms of these associations are unclear. PAD is characterized by obstructions in lower extremity blood flow. Yet obstruction to lower extremity blood flow does not appear to be the only determinant of functional impairment in PAD. First, reversal

of lower extremity arterial obstruction with revascularization does not reverse functional impairment comparably to the degree of improvement in lower extremity blood flow (29). Secondly, observational study shows that functional decline in patients with PAD occurs to a greater degree than ultrasound-measured progression of lower extremity atherosclerosis (41). Third, supervised treadmill exercise improves functional performance, but is not typically associated with improvement of lower extremity arterial obstruction (27). These phenomena suggest that factors other than lower extremity arterial obstruction contribute to functional impairment in PAD. In addition, there is evidence for an ischemia-related myopathy in calf skeletal muscle that consists of calf muscle atrophy and increased infiltration of calf muscle with fat tissue, a finding that is independent of differences in physical activity levels between individuals with vs. without PAD (42). Preliminary evidence also suggests that PAD is associated with mitochondrial dysfunction, and that this association is not fully reversible with lower extremity revascularization (43,44). Larger and more numerous collateral vessels may be associated with better functional performance in PAD, but further study is needed to better characterize these associations (45). An improved understanding of mechanisms of functional impairment and decline in PAD is needed in order to identify new therapies to improve functional performance in PAD.

Conclusion

PAD is common and will be increasingly prevalent as the U.S. population survives longer with chronic disease. Patients with PAD have greater functional impairment and faster functional decline than individuals without PAD. Functional impairment and functional decline is observed even among PAD patients who are asymptomatic. Therapeutic options available to improve functional performance in PAD have limitations. Although supervised treadmill exercise effectively improves PAD-related walking performance, Medicare and most medical insurance companies do not pay for this therapy, limiting access to this therapy. Consequently, most patients with PAD do not participate in supervised treadmill exercise. Lower extremity endovascular revascularization has limited durability and functional improvements from the FDA-approved medications for PAD-related functional impairment have limited efficacy. Further research is needed to improve our understanding of the mechanisms of functional impairment and functional decline in people with PAD. This information will help identify new therapies to improve outcomes and quality of life in people with PAD.

Acknowledgments

Disclosure

Conflicts of interest: M.M. McDermott: has received grant support from the NIH (funded by R01-HL107510 and R01-HL109244); and has been involved with the Foundation for Informed Medical Decision Making.

References

1. Roger VL, Go AS, Lloyd-Jones DM, Benjamin EJ, Berry JD, Borden WB, Bravata DM, Dai S, Ford ES, Fox CS, Fullerton HJ, Gillespie C, Hailpern SM, Heit JA, Howard VJ, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Makuc DM, Marcus GM, Marelli A, Matchar DB, Moy CS, Mozaffarian D, Mussolino ME, Nichol G, Paynter NP, Soliman EZ, Sorlie PD, Sotoodehnia N, Turan TN, Virani SS, Wong ND, Woo D, Turner MB. American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Executive summary: heart disease and stroke statistics--2012 update: a report from the American Heart Association. *Circulation*. 2012 Jan 3; 125(1):188–97. [PubMed: 22215894]
2. Fowkes FG, Murray GD, Butcher I, Heald CL, Lee RJ, Chambless LE, Folsom AR, Hirsch AT, Dramaix M, deBacker G, Wautrecht JC, Kornitzer M, Newman AB, Cushman M, Sutton-Tyrrell K,

Fowkes FG, Lee AJ, Price JF, d'Agostino RB, Murabito JM, Norman PE, Jamrozik K, Curb JD, Masaki KH, Rodríguez BL, Dekker JM, Bouter LM, Heine RJ, Nijpels G, Stehouwer CD, Ferrucci L, McDermott MM, Stoffers HE, Hooi JD, Knottnerus JA, Ogren M, Hedblad B, Witteman JC, Breteler MM, Hunink MG, Hofman A, Criqui MH, Langer RD, Fronck A, Hiatt WR, Hamman R, Resnick HE, Guralnik J, McDermott MM. Ankle Brachial Index Collaboration. Ankle brachial index combined with Framingham Risk Score to predict cardiovascular events and mortality: a meta-analysis. *JAMA*. 2008 Jul 9; 300(2):197–208. [PubMed: 18612117]

3. Heald CL, Fowkes FG, Murray GD, Price JF. Ankle Brachial Index Collaboration. Risk of mortality and cardiovascular disease associated with the ankle-brachial index: Systematic review. *Atherosclerosis*. 2006 Nov; 189(1):61–9. [PubMed: 16620828]
4. Imparato AM, Kim GE, Davidson T, et al. Intermittent claudication: Its natural course. *Surgery*. 1975; 78:795–799. [PubMed: 1188622]
5. McAllister FF. The fate of patients with intermittent claudication managed non-operatively. *Am J Surg*. 1976; 132:593–595. [PubMed: 984302]
6. Boyd AM. The natural course of arteriosclerosis of the lower extremities. *Proc R Soc Med*. 1962; 55:591–3. [PubMed: 13872137]
7. 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. [PubMed: 11585483]
8. 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. [PubMed: 15280343]
9. 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 as a measure of leg functioning and physical activity in peripheral arterial disease: the walking and leg circulation study. *Ann Intern Med*. 2002; 136:873–883. [PubMed: 12069561]
10. McDermott MM, Guralnik JM, Tian L, Liu K, Ferrucci L, Liao Y, Sharma L, Criqui MH. Associations of borderline and low normal ankle-brachial index values with functional decline at 5-year follow-up: the WALCS (Walking and Leg Circulation Study). *J Am Coll Cardiol*. 2009; 53:1056–62. This manuscript summarizes five-year follow-up data from the Walking and Leg Circulation Study (WALCS) cohort and demonstrates that even borderline ankle brachial index values are associated with functional decline. The manuscript includes objective and subjective outcome measures and represents a prospective study design of a well characterized cohort. [PubMed: 19298919]
11. 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 Jul; 58(7):1256–62. This manuscript summarizes associations of specific types of leg symptom categories in the WALCS cohort with functional decline and mobility loss among participants with PAD at five-year follow-up. The study design is prospective and the cohort is well characterized. [PubMed: 20550604]
12. Peeters P, Mets T. The six-minute walk as an appropriate exercise test in elderly patients with chronic heart failure. *J Gerontol Med Sci*. 1996; 51A:M147–M151.
13. McDermott MM, Ades PA, Dyer A, Ferrucci L, Guralnik JM, Pearce WH, Lloyd-Jones D, 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. [PubMed: 18829215]
14. Montgomery PS, Gardner AW. The clinical utility of a six-minute walk test in peripheral arterial occlusive disease patients. *J Am Geriatr Soc*. 1998; 46:706–711. [PubMed: 9625185]
15. 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. [PubMed: 17765125]

16. McDermott MM, Guralnik JM, Tian L, Ferrucci L, Liu K, Liao Y, Criqui MH. Prognostic value of functional performance for mortality in patients with peripheral artery disease. *J Am Coll Cardiol*. 2008; 51:1482–1489. [PubMed: 18402904]
17. 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 Feb; 2257(8):962–70. [PubMed: 21329843]
18. Rose GA. The diagnosis of ischaemic heart pain and intermittent claudication in field surveys. *Bull World Health Organ*. 1962; 27:645–58. [PubMed: 13974778]
19. Hirsch AT, Criqui MH, Treat-Jacobson D, Regensteiner JG, Creager MA, Olin JW, Krook SH, Hunninghake DB, Comerota AJ, Walsh ME, McDermott MM, Hiatt WR. Peripheral arterial disease detection, awareness, and treatment in primary care. *JAMA*. 2001 Sep 19; 286(11):1317–24. [PubMed: 11560536]
20. 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 May 13; 117(19):2484–91. [PubMed: 18458172]
21. 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 Mar 7; 101(9):1007–12. [PubMed: 10704168]
22. Criqui MH, Fronek A, Klauber MR, Barrett-Connor E, Gabriel S. The sensitivity, specificity, and predictive value of traditional clinical evaluation of peripheral arterial disease: results from noninvasive testing in a defined population. *Circulation*. 1985 Mar; 71(3):516–22. [PubMed: 3156007]
23. Criqui MH, Fronek A, Barrett-Connor E, Klauber MR, Gabriel S, Goodman D. The prevalence of peripheral arterial disease in a defined population. *Circulation*. 1985 Mar; 71(3):510–5. [PubMed: 3156006]
24. Criqui MH, Denenberg JO, Bird CE, Fronek A, Klauber MR, Langer RD. The correlation between symptoms and non-invasive test results in patients referred for peripheral arterial disease testing. *Vasc Med*. 1996; 1(1):65–71. [PubMed: 9546918]
25. Girolami B, Bernardi E, Prins MH, Ten Cate JW, Hettiarachchi R, Prandoni P, Girolami A, Buller HR. Treatment of intermittent claudication with physical training, smoking cessation, pentoxifylline, or nafronyl: A meta-analysis. *Arch Intern Med*. 1999; 159:337–345. [PubMed: 10030306]
26. Dawson DL, Cutler BS, Meissner MH, Strandness DEJ. Cilostazol has beneficial effects in treatment of intermittent claudication: Results from a multi-center, randomized, prospective, double-blind trial. *Circulation*. 1998; 98:678–686. [PubMed: 9715861]
27. Watson L, Ellis B, Leng GC. Exercise for intermittent claudication. *Cochrane Database Syst Rev*. 2008 CD000990.
28. 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 Dec; 50(12):1939–46. [PubMed: 12473004]
29. Regensteiner JG, Hargarten ME, Rutherford RB, Hiatt WR. Functional benefits of peripheral vascular bypass surgery for patients with intermittent claudication. *Angiology*. 1993; 44:1–10. [PubMed: 8424578]
30. Gardner AW, Poehlman ET. Exercise rehabilitation programs for the treatment of claudication pain. A meta-analysis. *JAMA*. 1995; 274:975–980. [PubMed: 7674529]
31. Gardner AW, Montgomery PS, Parker DR. Optimal exercise program length for intermittent claudication. *J Vasc Surg*. 2012; 55:1346–1354. [PubMed: 22459748]
- 32•. 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(2):165–174. This

randomized controlled clinical trial of exercise in participants with PAD is the first to include PAD participants both with and without symptoms of classical intermittent claudication. Most participants do not have classical symptoms of intermittent claudication. The manuscript also includes a resistance training intervention. [PubMed: 19141764]

33. Falcone RA, Hirsch AT, Regensteiner JG, Treat-Jacobson D, Williams MA, Hiatt WR, Stewart KJ. Peripheral arterial disease rehabilitation: A review. *J Cardiopulm Rehabil.* 2003; 23:170–175. [PubMed: 12782899]
34. Regensteiner JG. Exercise rehabilitation for the patient with intermittent claudication: a highly effective yet underutilized treatment. 2004; 4:233–239.
35. Bendermacher BL, Willigendael EM, Teijink JA, Prins MH. Supervised exercise therapy versus non-supervised exercise therapy for intermittent claudication. *Cochrane Database Syst Rev.* 2006 Apr 19.(27) CD005263.
- 36••. Gardner AW, Parker DE, Montgomery PS, et al. Efficacy of quantified home-based exercise and supervised exercise in patients with intermittent claudication. A randomized controlled trial. *Circulation.* 2011; 123:491–498. This is the first randomized controlled clinical trial to demonstrate that a home-based walking exercise program is associated with significantly greater improvement in treadmill walking performance than a control group. The study included three parallel arms: supervised treadmill exercise, home-based walking exercise, and a control group. The supervised treadmill exercise group achieved greater gains in treadmill walking performance than the home-based group, but these differences were not statistically significant. [PubMed: 21262997]
- 37••. Collins TC, Lunos S, Carlson T, et al. Effects of a home-based walking intervention on mobility and quality of life in people with diabetes and peripheral arterial disease. *Diabetes Care.* 2011; 34:2174–2179. This randomized controlled trial of participants with diabetes and PAD compared a home-based walking exercise program to a control group. There were no differences in treadmill walking performance at follow-up between the exercise and the control group. Thus, findings contrast with those reported by Gardner AW. [PubMed: 21873560]
38. Zwierska I, Walker R, Choksy SA, Male JS, Pckley 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; 42:1122–30. [PubMed: 16376202]
- 39••. Frans FA, Bipat S, Reekers JA, Legemate DA, Koelemay MG. Systematic review of exercise training or percutaneous transluminal angioplasty for claudication. *British Journal of Surgery.* 2012; 99:16–28. This systematic review summarizes eight randomized controlled trials, published as of 2011, that compare exercise vs. percutaneous transluminal angioplasty for patients with intermittent claudication. It is a current summary of randomized trial evidence, although it was published just prior to release of the CLEVER trial results. [PubMed: 21928409]
- 40••. Murphy TP, Hirsch AT, Cutlip DE, Regensteiner JG, Comerota AJ, Mohler E, Cohen DJ, Massaro J. CLEVER Investigators. Claudication: exercise vs endoluminal revascularization (CLEVER) study update. *J Vasc Surg.* 2009 Oct; 50(4):942–945. e2. This is the largest multi-centered randomized controlled clinical trial in the U.S. to evaluate the ability of a supervised treadmill exercise program and angioplasty +stenting to improve walking performance in PAD patients with aortoiliac disease. The randomized trial included three parallel arms: optimal medical care + supervised treadmill exercise, optimal medical care + angioplasty and stenting, and optimal medical care alone. At six-month follow-up, the optimal medical care + supervised treadmill exercise group achieved greater improvement in treadmill walking performance compared to the optimal medical care + stenting group. However, the optimal medical care + stenting group achieved greater gains in quality of life measures than the optimal medical care + supervised exercise group. [PubMed: 19660897]
41. Gardner AW, Montgomery PS, Killewich LA. Natural history of physical function in older men with intermittent claudication. *J Vasc Surg.* 2004; 40:73–78. [PubMed: 15218465]
42. 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 Jul 15; 41(2):262–9. [PubMed: 16814106]

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 Oct; 38(4):827–32. [PubMed: 14560237]
44. McDermott MM, Hoff F, Ferrucci L, Pearce WH, Guralnik JM, Tian L, Liu K, Schneider JR, Sharma L, Tan J, Criqui MH. Lower extremity ischemia, calf skeletal muscle characteristics, and functional impairment in peripheral arterial disease. *J Am Geriatr Soc.* 2007; 55:400–406. [PubMed: 17341243]
45. McDermott MM, Carroll T, Kibbe M, et al. Proximal superficial femoral artery occlusion, collateral vessels, and walking performance in peripheral artery disease. *J Am Coll Cardiol Imaging.* In Press.

Figure 1.

Association of the ankle brachial index with the ability to walk for six minutes continuously without rest. From 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 as a measure of leg functioning and physical activity in peripheral arterial disease: the walking and leg circulation study. (With permission from: 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 as a measure of leg functioning and physical activity in peripheral arterial disease: the walking and leg circulation study. *Ann Intern Med* 2002;136:873-883) [9].

Table 1

Summary of Interventions for Improving Functioning in Patients with Peripheral Artery Disease

Intervention	Magnitude of Benefit for improvement in maximal treadmill walking distance	Adverse Effects	Additional Considerations
<i>FDA approved medications for intermittent claudication</i>			
Pentoxifylline	Improvement in walking performance is comparable to placebo.	Abdominal bloating, diarrhea, flushing, palpitations.	Dosed three times daily.
Cilostazol	Improvement of 40% to 50%	Diarrhea, palpitations, headache.	Dosed twice daily. There is a black box warning advising against use in patients with heart failure.
<i>Exercise Interventions</i>			
Supervised treadmill exercise	Increase in treadmill walking distance of approximately 120% or five minutes.	Musculoskeletal discomfort.	Risk of cardiac events is low. However, an exercise stress test is recommended before PAD patients begin a new exercise program. Medical insurance typically does not pay for supervised exercise for PAD patients.
Home-based walking exercise	Less effective than supervised treadmill exercise. Efficacy data are mixed as compared to usual care. One study reported a 30% increase in treadmill walking time while another reported no improvement in treadmill walking after a home-based walking exercise program.	Musculoskeletal discomfort. Risk of falling.	Requires a motivated patient who can adhere to a home-based program without the benefit of an exercise physiologist to encourage walking activity. A pedometer may help the PAD patient monitor their progress more effectively.
Arm or leg ergometry	Improvement of approximately 30% as compared to a control group that does not exercise.	Musculoskeletal side effects.	Many patients may not have access to arm ergometry equipment. Further study is needed to
<i>Endovascular Revascularization</i>			
Angioplasty and stent	Results are variable, but typically the patient experiences immediate improvement in walking-related leg symptoms. In the CLEVER trial of patients with aorto-iliac disease, supervised treadmill exercise was superior to stenting for improving treadmill walking performance. However, in general, quality of life improved to a greater degree in the stenting group than in the exercise group.	Bleeding, infection, or acute vessel closure related to the procedure.	The combination of supervised treadmill exercise + stenting is better than either therapy alone.