

## Exercise Rehabilitation in Peripheral Artery Disease Functional Impact and Mechanisms of Benefits

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In the United States, 8 million adults have peripheral artery disease (PAD), a number that is likely to escalate as the population ages.<sup>1–3</sup> Lower-extremity PAD is a component of systemic atherosclerosis and confers a markedly heightened risk of cardiovascular morbidity and mortality.<sup>4–7</sup> It is now established that PAD accelerates functional decline leading to physical disability.<sup>8,9</sup> Exercise therapy combined with comprehensive secondary prevention has the potential to benefit patients with PAD by preserving or improving functional capacity and reducing cardiovascular events. Accordingly, this review will address the relation between exercise intolerance and outcomes in patients with PAD; the effects of exercise training in PAD and the many possible mechanisms of benefit; and the potential role of comprehensive secondary prevention programs in these patients.

### PAD as a Marker of Cardiovascular Risk

Traditionally, PAD has been viewed as a disease of the lower extremities typified by intermittent claudication. Studies now have demonstrated the malignant cardiovascular course of PAD even in the absence of claudication. The presence of PAD can be readily identified by the ankle-brachial index (ABI), a simple test comparing systolic blood pressure measured in the arm and in the ankle by Doppler.<sup>10–12</sup> Among patients with a low ABI (defined as  $\leq 0.90$ ) detected in both population-based and high-risk primary care cohorts, only 10% to 15% have intermittent claudication.<sup>13–15</sup> The international ABI Collaboration patient-level meta-analysis of >48 000 individuals found that a low ABI predicted a doubling of 10-year risk of mortality, cardiovascular mortality, and major coronary events at all levels of Framingham Risk Score.<sup>4</sup> Importantly, the German Epidemiological Study on Ankle Brachial Index recently reported that asymptomatic individuals with PAD identified in a primary care screening program had similarly elevated 5-year risk of morbidity and mortality compared with symptomatic PAD patients.<sup>16</sup> As has been reviewed elsewhere, the use of ABI testing to detect PAD in asymptomatic patients remains controversial<sup>17,18</sup>; however, an ABI screening strategy to identify individuals at risk for cardiovascular events and functional decline would allow institution of secondary prevention measures including exercise therapy. Thus, the clinical significance of PAD

derives not only from limb symptoms and functional impairment but as a marker of cardiovascular risk.

### Functional Disability in PAD

Several lines of evidence support the presence of pervasive functional alterations in PAD (Figure). In the past, reduced walking capacity was identified as a consequence of intermittent claudication, the hallmark symptom of PAD. Although a minority of patients with PAD experience classic claudication, up to 50% describe atypical leg symptoms that interfere with mobility.<sup>13,14</sup> Importantly, PAD limits exercise capacity and hastens physical decline, even in the absence of reported leg symptoms.<sup>19–21</sup> Asymptomatic patients and patients with atypical symptoms who have PAD experience progressive functional impairment and an increased risk of becoming unable to walk for 6 minutes compared with individuals without PAD.<sup>9,22</sup> The physical limitations in asymptomatic patients may reflect self-imposed activity restriction to prevent the occurrence of symptoms.

Impaired walking ability has several important clinical implications. Patients with PAD have markedly reduced health-related quality of life and a higher prevalence of depression, which is largely related to leg symptoms.<sup>23,24</sup> Diminished physical activity in daily life predicts higher overall mortality in PAD.<sup>25,26</sup> Functional measures including the 6-minute walk test and treadmill walking time have been associated with increased mortality and risk of cardiovascular events in PAD.<sup>27–31</sup> Together, these findings suggest that interventions that augment exercise performance in PAD may have wide-ranging health benefits.

### Effects of Exercise Training on Functional Status in PAD

Supervised exercise programs have been recommended as first-line therapy for treatment of claudication.<sup>32–34</sup> Recent evidence demonstrates benefits of exercise training even among those patients with PAD who do not have claudication.<sup>35</sup> Exercise programs combined with risk factor modification offer the possibility of altering the clinical trajectory of PAD. The goals of comprehensive prevention strategies, including exercise, are 3-fold: (1) to reduce limb symptoms; (2) to improve exercise capacity and prevent or lessen

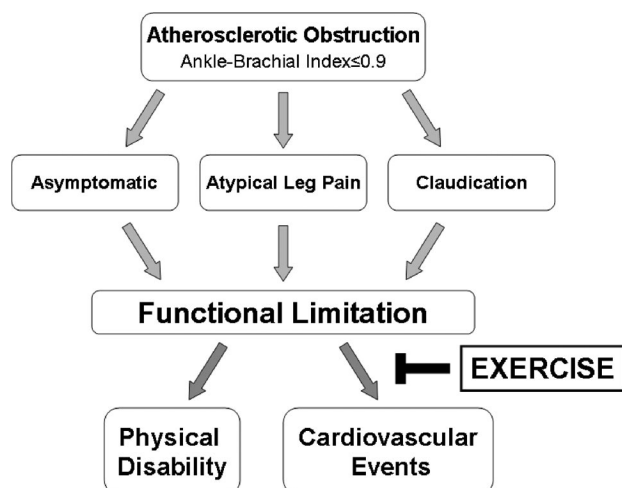
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**Figure.** Functional consequences of PAD. PAD is characterized by atherosclerotic lesions that limit blood flow manifest as reduced ABI. Patients with PAD have diminished functional capacity across the spectrum of leg symptoms. Functional impairment has clinical impact including progression to disability and increasing cardiovascular risk. Exercise training has the potential to interrupt functional decline. Further studies are needed to evaluate the impact of exercise training on long-term cardiovascular events in PAD patients.

physical disability; and (3) to decrease the occurrence of cardiovascular events.

Exercise training markedly improves walking ability in PAD patients with intermittent claudication. A meta-analysis performed in 1995 that included uncontrolled trials suggested clinical efficacy of exercise in ameliorating claudication symptoms, indicating that supervised exercise increased pain-free walking distance by 180%.<sup>36</sup> A rigorous systematic review including only controlled clinical trials encompassing 22 studies with >1200 participants conducted by the Cochrane group in 2008 compared supervised exercise programs with usual care in the treatment of claudication.<sup>37</sup> Exercise produced clinically relevant increases in walking time (5 minutes) and walking distance (>100 m). Although all studies show exercise-related improvements in treadmill-based measures, the degree of benefit varies across studies and individuals. Differences in exercise intensity as well as adherence to exercise programs may account for the observed variability in treatment effect. The magnitude of functional benefit derived from exercise training exceeds that observed in drug therapy trials with both pentoxifylline and cilostazol<sup>38</sup>; however, data that directly compare the 2 treatment modalities are limited. Improvements in treadmill performance appear to translate to improved physical activity and quality of life. In randomized trials of exercise rehabilitation in patients with claudication, exercise has been shown to increase daily activity levels measured by accelerometer<sup>39</sup> and patient-perceived health-related quality of life.<sup>40,41</sup> Increased physical activity may translate to slower functional decline and potentially to reduced cardiovascular risk.<sup>25,42,43</sup>

Limited controlled data are available comparing revascularization with exercise training for intermittent claudication. In a single randomized trial, both exercise training and lower-limb bypass surgery improved maximal walking dis-

tance to a similar degree at 1 year.<sup>44</sup> A second study indicated greater walking distance at 1 year in a combined surgical and endovascular revascularization group compared with an exercise-trained group; however, the compliance with exercise training was poor, with fewer than two thirds of assigned patients completing the exercise program.<sup>45</sup> In a study performed >20 years ago, exercise training induced a greater increase in walking distance compared with angioplasty, particularly in patients with superficial femoral artery lesions.<sup>46</sup> However, a more contemporary trial showed greater benefit of endovascular therapy compared with supervised exercise training at 6 months but no difference at 1 year.<sup>47</sup> The Claudication: Exercise versus Endoluminal Revascularization (CLEVER) study is an ongoing National Institutes of Health-funded multicenter randomized trial comparing medical therapy, stenting, and exercise training in patients with claudication and aortoiliac obstructive disease.<sup>48,49</sup> The results from this important study in which contemporary endovascular and exercise training techniques were used are anticipated to provide additional information that may guide choices about optimal therapy to improve functional outcomes in PAD patients.

Exercise training has been incorporated into current guidelines for the management of PAD. Multiple societal guidelines including *American College of Cardiology/American Heart Association 2005 Practice Guidelines for the Management of Patients With Peripheral Arterial Disease*, *American Association of Cardiovascular and Pulmonary Rehabilitation 2004 Guidelines for Cardiac Rehabilitation and Secondary Prevention Programs*, *Intersociety Consensus for the Management of PAD (TASC II)*, and *American College of Sports Medicine 2010 Guidelines for Exercise Testing and Prescription* all recommend supervised exercise training in the treatment of claudication symptoms in PAD.<sup>33,34,50,51</sup>

A recent seminal study extends the therapeutic impact of exercise training to the larger population of PAD patients without classic claudication symptoms. McDermott and colleagues<sup>35</sup> conducted a randomized trial of supervised treadmill exercise compared with strength training and usual care in 156 PAD patients. The symptom pattern corresponded to the observed distribution in clinical practice: 18% had claudication, and 82% had atypical symptoms or were asymptomatic. At 6 months, patients in the treadmill exercise group increased exercise performance as evidenced by a longer 6-minute walk distance (+20.9 m) compared with a decline in the control group (−15 m). Lower-extremity resistance training improved leg strength as well as maximum treadmill walking time without an increase in 6-minute walk distance. Both treadmill and resistance exercise training improved physical functioning–associated quality of life measures. However, increases in exercise tolerance in both training groups were not associated with a change in daily physical activity as measured by accelerometer. Perhaps additional behavioral interventions are needed to attain such increases. Thus, the findings support (1) recommending supervised exercise programs for all patients with PAD regardless of symptom status and (2) the notion that exercise training can interrupt functional deterioration in PAD.

**Table 1. Potential Mechanisms of Functional Impairment and Benefits of Exercise in PAD**

Pathophysiological Process	Functional Consequence	Effect of Exercise
Arterial obstruction	Reduced blood flow	Minimal increase in collateral flow
Endothelial dysfunction	Decreased vasodilator function	Improved nitric oxide-dependent vasodilation
	Increased arterial stiffness	
	Impaired hyperemic response	
	Impaired arterial remodeling	
	Increased inflammatory activation	
Mitochondrial dysfunction	Impaired energy production	Improved mitochondrial energetics
	Impaired oxygen utilization	Increase in mitochondrial biogenesis in animal models
	Increased reactive oxygen species	
	Reduced skeletal muscle content	
Inflammatory activation	Adverse skeletal muscle remodeling	Decreased markers of systemic inflammation
	Increased atherosclerotic progression	

### Mechanisms of Functional Impairment and Benefits of Exercise in PAD

Multiple mechanisms contribute to reduced exercise capacity in PAD. Atherosclerotic disease exists in the presence of pathophysiological processes that together may contribute to impaired walking ability. Similarly, the functional benefits of exercise are likely attributable to amelioration of diverse maladaptive responses. Potential mechanisms are outlined in Table 1, and the available evidence supporting the role of arterial obstruction, endothelial dysfunction, altered skeletal muscle phenotype including mitochondrial dysfunction, and inflammatory activation in limiting exercise ability in PAD is discussed in this section. Exercise has the potential to reverse these pathological events and thereby interrupt the clinical course toward disability.

### Arterial Obstruction and Blood Flow Limitation

Functional limitation in PAD traditionally has been ascribed to diminished blood flow induced by arterial obstruction from atherosclerotic stenoses. Typical intermittent claudication could theoretically be attributed to ischemia induced by an oxygen demand and supply imbalance. Certainly, fixed atherosclerotic lesions reflected in a diminished ABI are the precipitating event that leads to functional abnormalities in PAD. However, multiple findings indicate that the pathophysiology of functional decline in PAD and the improvement with exercise are more complex.

The association between the severity of arterial obstruction and functional status in PAD is inconsistent. Compared with individuals with normal ABI, patients with PAD have reduced self-reported and measured walking ability.<sup>8,52</sup> Select studies have demonstrated a moderate association between ABI and walking distance among PAD patients,<sup>53–56</sup> whereas others have reported no association of ABI with functional measures.<sup>57,58</sup> Similarly, calf blood flow measured with a magnetic resonance–based technique was shown to be only modestly associated with walking distance (unadjusted  $r=0.3$ ,  $P<0.01$ ).<sup>59</sup> In contrast, calf blood flow assessed by plethysmography did not correlate with baseline treadmill walking time or the subsequent 3-month change in walking time in an intervention study.<sup>57</sup> In an observational, longitudinal study of 676 individuals with and without PAD, the presence of an abnormal ABI predicted a greater decline in walking measured at 2 years, thus confirming the clinical relevance of PAD to functional outcomes.<sup>9</sup> However, the relation between severity of ABI reduction and functional decline in PAD patients remains ill defined. Overall, the lack of consistency in the prior studies suggests that additional factors beyond anatomic disease contribute to development of functional impairment in PAD.

Theoretically, enhanced distal blood flow due to vascular adaptations could underlie the benefits of exercise therapy in PAD. In animal models of arterial insufficiency, available evidence indicates that exercise training augments peripheral arterial supply.<sup>60–63</sup> Restoration of blood flow after arterial occlusion involves multiple complex processes that produce vascular growth.<sup>64</sup> Tissue ischemia in the underperfused muscle induces growth factors, including vascular endothelial growth factor and hypoxia inducible factor-1 $\alpha$ , leading to angiogenesis.<sup>65,66</sup> Recent studies demonstrate that exercise stimulates gains in collateral blood flow after femoral occlusion in rodent models through collateral enlargement.<sup>60,67,68</sup> Collateral growth induced by exercise reflects vascular structural remodeling, a process that depends on both growth factor activity and increased nitric oxide bioavailability via shear stress stimulation of endothelial nitric oxide synthase.<sup>60,67,69</sup>

In contrast, studies in patients with PAD have not convincingly demonstrated that exercise training produces clinically relevant gains in peripheral blood flow. Maximal hyperemic blood flow increased in some<sup>39,70,71</sup> but not all exercise training studies.<sup>72,73</sup> In addition, an association between the increase in blood flow and walking time has not been shown.<sup>70</sup> In a trial comparing surgical revascularization with exercise training, the change in maximal calf blood flow after exercise at 13-month follow-up was not associated with the change in walking distance.<sup>44</sup> In a study of angioplasty compared with exercise, angioplasty produced an immediate increase in ABI, whereas exercise training improved walking time after a longer time period with more sustained efficacy.<sup>46</sup> The results of this study indicate a divergence between improvements in arterial flow and functional parameters with exercise intervention. Several factors may explain the apparent contradiction between the animal and human studies. Patients with PAD typically have multilevel disease of the vascular tree that may impede sufficient collateral growth.

Concomitant endothelial dysfunction may inhibit shear stress-mediated vascular remodeling in PAD patients.<sup>74,75</sup> Finally, it remains possible that more sophisticated measures of collateral flow are required to detect exercise-mediated changes in humans. However, a recent meta-analysis of 7 exercise training studies demonstrated no change in the resting ABI, a cumulative measure of blood supply to the lower extremity.<sup>37</sup> Taken together, the studies in PAD patients indicate that an anatomic model of increased blood supply does not appear to account for the functional benefits of exercise.

### Disruption of Endothelial Function

Functional limitations in PAD likely reflect an integration of abnormal vascular function with severity of arterial obstruction. Normal vascular function depends on a healthy endothelium that elaborates vasoprotective factors, including nitric oxide to regulate arterial flow.<sup>76</sup> Reduced nitric oxide bioavailability in the skeletal muscle microcirculation diminishes the hyperemic flow response to ischemia and may impede augmentation of blood flow during exercise in PAD.<sup>77,78</sup> As has been observed in coronary arteries, endothelial dysfunction could also lead to peripheral arterial vasoconstriction and limit vasodilator responses to flow, which would tend to exacerbate blood flow limitation during exercise.<sup>79–81</sup>

Consistent with these potential links between vascular function and functional status, a number of studies have demonstrated impaired endothelial vasodilator responses in PAD. Patients with PAD have attenuated flow-mediated dilation of the brachial artery as well as reduced acetylcholine-induced vasodilation, both consistent with the loss of nitric oxide activity.<sup>82–85</sup> In a cross-sectional study, greater physical activity during daily life was associated with greater brachial artery flow-mediated dilation in 111 patients with PAD, supporting a relation between functional status and vascular function.<sup>86</sup> Importantly, vascular dysfunction has been observed in the brachial artery of PAD patients, indicating the presence of systemic endothelial abnormalities induced by cardiovascular risk factors and inflammation.<sup>87,88</sup> Vascular stiffness measures, including pulse pressure and augmentation index that depend in part on nitric oxide bioavailability, have also been associated with walking time.<sup>89</sup> The question of whether endothelial dysfunction contributes to functional decline over time in PAD has not been evaluated.

Two studies have demonstrated an improvement in endothelial function with exercise training in PAD. A supervised exercise program increased endothelium-dependent flow-mediated dilation of the brachial artery by 65% in 19 elderly patients with intermittent claudication.<sup>90</sup> In this small study, no correlation was observed between gains in walking time and vasomotor function. In the aforementioned randomized trial comparing treadmill exercise with lower-extremity strength training and with usual care in PAD, McDermott and colleagues<sup>35</sup> evaluated the effect of each exercise regimen on flow-mediated dilation of the brachial artery. Treadmill exercise but not lower-extremity strength training augmented flow-mediated dilation, consistent with improvement in en-

dothelial health. The lack of improvement in endothelial function with resistance training contrasts with a recent randomized trial in patients after myocardial infarction and suggests that further study is needed to clarify the impact of strength training on endothelial function.<sup>91</sup> The ability of exercise to reverse endothelial dysfunction may reflect sustained increases in shear stress that stimulate nitric oxide bioactivity.<sup>92</sup> A study in patients with coronary disease showed that exercise rehabilitation induced favorable effects on coronary endothelial function associated with increased endothelial nitric oxide synthase expression and activation.<sup>93</sup> Because impaired endothelial function predicts higher risk for cardiovascular events among patients with PAD,<sup>75,94</sup> the exercise-induced improvement in vasodilator function may have the potential to reduce cardiovascular risk.

### Altered Skeletal Muscle Phenotype and Mitochondrial Dysfunction

It is increasingly clear that vascular obstruction has adverse consequences on the distal skeletal muscle tissue in PAD. Metabolic dysfunction at the skeletal muscle level superimposed on compromised blood flow has the potential to magnify physical limitation. Episodic ischemia in concert with chronically low physical activity levels alters skeletal muscle phenotype in PAD patients.<sup>95</sup> Imaging studies demonstrate gross structural changes in calf muscle tissue including reduced overall area, decreased muscle density, and increased fat content.<sup>20,96</sup> At the cellular level, there is evidence of increased muscle apoptosis, reduced type I fibers, and reduced capillary density.<sup>97,98</sup>

Altered skeletal muscle energetics in PAD has been linked to mitochondrial dysfunction. Intermediate metabolites of substrate oxidation, including acylcarnitines, accumulate in the blood and muscle of PAD patients and are consistent with impaired metabolism at the mitochondrial level.<sup>99</sup> Whereas muscle mitochondrial content is higher, aberrant mitochondrial function impedes energy production and favors reactive oxygen species generation.<sup>100–103</sup> Abnormal mitochondrial function may interfere with skeletal muscle oxygen utilization and accelerate endothelial damage.<sup>104,105</sup> Further studies are needed to elucidate the contribution of mitochondrial abnormalities to vascular dysfunction in PAD.

Growing evidence relates adverse skeletal muscle changes, including mitochondrial dysfunction, to functional impairment in PAD.<sup>106</sup> Decreased calf muscle area and lower type I fiber content are associated with impairments in functional performance measures.<sup>96,98</sup> Abnormal mitochondrial function, evidenced by delayed phosphocreatine recovery on magnetic resonance spectroscopy, has been shown to be associated with treadmill exercise time but not with 6-minute walk distance.<sup>59</sup> The level of muscle acylcarnitine accumulation appears to be related to exercise intolerance.<sup>99</sup> In a prospective study, PAD patients with adverse calf muscle characteristics, including higher calf muscle fat and lower calf muscle density, had a heightened risk of functional decline over 2 years.<sup>107</sup>

Exercise training has the potential to enhance skeletal muscle metabolism and mitochondrial function. In experimental models of ischemia, peroxisome proliferator-acti-



vated receptor-gamma coactivator-1 $\alpha$ , a key regulator of mitochondrial biogenesis, is critical to blood vessel recovery.<sup>108</sup> Interestingly, exercise-induced capillary growth in skeletal muscle also depends on peroxisome proliferator-activated receptor-gamma coactivator-1 $\alpha$ , suggesting a connection between mitochondrial function and exercise adaptations relevant to PAD.<sup>109</sup> Higher levels of physical activity in daily life are related to more favorable calf muscle traits, an association that is likely bidirectional.<sup>110</sup> In PAD patients, exercise training has been shown to restore carnitine metabolism in association with improved treadmill walking.<sup>70,102</sup> Whether exercise training improves mitochondrial energy production or calf muscle characteristics in PAD remains to be evaluated.

### Inflammatory Activation

Chronic inflammation participates in the atherosclerotic process. Systemic markers of inflammation including C-reactive protein and soluble intercellular adhesion molecule-1 increase the risk of developing PAD.<sup>111,112</sup> Higher levels of inflammation are associated with disease progression and with adverse cardiac and lower-extremity outcomes.<sup>113–115</sup> Inflammation may accelerate functional impairment in PAD by favoring plaque growth and inducing skeletal muscle injury. In addition, endothelial inflammatory activation reduces nitric oxide bioavailability and may impede vasodilatory function during exercise.<sup>116</sup>

A number of studies have assessed associations of functional measures and inflammation in PAD. Higher levels of inflammatory markers including C-reactive protein, interleukin-6, and soluble vascular cell adhesion molecule-1 are related to poorer walking ability in PAD patients.<sup>117,118</sup> Systemic inflammation may also impair functional status through adverse skeletal muscle remodeling. Multiple inflammatory markers were associated with lower calf muscle area and higher calf muscle fat content in a computed tomography study.<sup>119</sup> In longitudinal follow-up, both higher levels of inflammatory markers and an increase in C-reactive protein have been shown to predict functional decline among individuals with PAD.<sup>120</sup>

Physical activity may have favorable effects in PAD by suppressing inflammatory activation. Extensive epidemiological data demonstrate lower inflammatory marker levels in individuals who participate in regular physical activity compared with those who are sedentary.<sup>121</sup> Similarly in PAD, physical activity has an inverse association with C-reactive protein, interleukin-6, fibrinogen, soluble intercellular adhesion molecule-1, and soluble vascular cell adhesion molecule-1.<sup>122</sup> Whereas brief bouts of exercise increase inflammatory markers in claudicants, long-term exercise training appears to curb inflammation.<sup>123</sup> A 3-month exercise program ameliorated neutrophil activation after treadmill exercise in 46 PAD patients with claudication.<sup>124</sup> Whether reduced inflammation produced by long-term exercise training underlies increased walking ability and translates to decreased events remains to be determined.

### Exercise Rehabilitation Programs for PAD

Clinical studies have defined the optimal methods for implementing exercise training in PAD. Supervised exercise pro-

grams appear to deliver a greater improvement in functional measures compared with unsupervised training. A Cochrane review in 2006 of 8 small randomized trials with a total of 319 participants concluded that supervised exercise training was superior to unsupervised exercise and yielded a 150-m greater improvement in walking time.<sup>125</sup> The *American College of Cardiology/American Heart Association 2005 Practice Guidelines for the Management of Patients With Peripheral Arterial Disease* provide a class I recommendation for supervised exercise training but only a class IIb recommendation for unsupervised training. They note that there is limited supporting symptom-based evidence for simply advising patients to walk more independently,<sup>33</sup> although increased daily physical activity may have other health benefits.<sup>126</sup> The differences between supervised and unsupervised training may be related to better patient adherence and greater intensity of treadmill exercise compared with normal walking. Results from the ongoing National Institute on Aging randomized controlled trial of home-based versus supervised exercise for people with claudication promise to provide further information on this important area.<sup>127</sup>

Supervised exercise programs commence with a baseline assessment of functional status. The American Heart Association and the American College of Cardiology, the American College of Sports Medicine, and the American Association of Cardiovascular and Pulmonary Rehabilitation all recommend an exercise treadmill test before exercise training to evaluate walking capacity and to assess the degree of exercise limitation (class I; level of evidence B).<sup>33,50,51</sup> However, some patients may have symptoms that are so limiting as to preclude the performance of an exercise test. Because PAD patients frequently have coexistent coronary artery disease, exercise testing may identify potential cardiovascular complications including exercise-related ischemia and arrhythmias. It should be noted that exercise stress testing may have reduced sensitivity for ischemic chest pain or arrhythmias in PAD patients because the leg symptoms may limit the ability to achieve an adequate cardiac workload.<sup>128</sup> Exercise testing protocols, including individualized ramp protocols that begin at low work rates and have low work rate increments per stage, may be useful among patients with severe claudication symptoms. Treadmill testing serves as a guide to tailor initial exercise intensity levels. Although the data are sparse, adverse event rates are low but not absent during exercise training.<sup>35</sup> As patients walk farther and at higher intensity levels, cardiac signs and symptoms may be unmasked.

Exercise training with the use of treadmill walking has been used most frequently in clinical trials.<sup>125</sup> The treadmill walking exercise prescription for patients with PAD and symptoms of intermittent claudication is outlined in Table 2.<sup>48</sup> Patients with leg symptoms are instructed to exercise to mild to moderate pain (3 to 4 of 5 on the claudication scale) and then stop. When claudication has resolved, the patient begins walking on the treadmill again.<sup>48</sup> PAD patients without intermittent claudication should follow the exercise prescription for patients with cardiovascular disease as outlined in Table 3, in which exercise intensity is guided by an exercise tolerance test with the use of heart rate reserve or oxygen uptake reserve.<sup>50,51</sup> In all patients with PAD, treadmill

**Table 2. Exercise Prescription for Supervised Endurance Training in PAD Patients With Intermittent Claudication**

Frequency	3–5 d/wk
Modality	Treadmill walking
Intensity	Exercise at a given work rate at which the patient experiences the onset of claudication; continue walking until the patient has an ischemic leg pain symptom score of mild to moderate (3–4 of maximum 5 points); then stop until pain completely subsides; resume exercise again at similar intensity; repeat rest/exercise bouts. Progress to a higher work rate when the patient is able to walk for 8-minute bouts without the need to stop for leg symptoms
Duration	Total exercise time (including rest periods) should equal 50 min/d

Adapted From Reference 48.

walking exercise is the preferred modality, but supplemental exercise with the use of other exercise modalities, including resistance training as recommended for patients with cardiovascular disease (Table 3), may be of additional benefit.<sup>50,129</sup>

Several studies have investigated alternate exercise training approaches. Arm ergometry exercise increases walking performance in patients with claudication and may be an appropriate exercise modality, especially in patients with difficulty in performing treadmill walking, including patients with prior leg amputation.<sup>130–132</sup> Polestriding has also been shown to have efficacy in increasing walking performance in claudicants.<sup>133,134</sup> Low-intensity exercise and pain-free walking have both been shown to increase walking time in small studies.<sup>135–137</sup>

Patients can be gradually transitioned to independent, unsupervised exercise over time if independent exercise is deemed safe by the program staff and if the patient understands the basic principles of self-monitoring, as outlined in detail elsewhere.<sup>50,51</sup> At the completion of the supervised training program, patients should be given a home exercise prescription to maintain activity levels because it is expected that exercise training should be continued as a life-long activity. However, as yet, the benefits of home exercise in patients with PAD remain unproven. Patients should be encouraged to contact the exercise program staff or their physician for any questions or concerns that they may have and to periodically update the exercise prescription.

### Barriers to Exercise Training in PAD

Although a number of barriers restrict or prevent patients with PAD from participation in supervised exercise programs, a major impediment is the lack of coverage for such programs by medical insurance. In 2001, the proven clinical efficacy of exercise in the treatment of claudication resulted in the creation of a Current Procedural Terminology Code (CPT 93.668) for PAD rehabilitation. However, both Medicare and most private insurers still do not provide exercise training for PAD as a covered benefit. It is important to note that the lack of insurance coverage is incongruent with the clear clinical efficacy of exercise training in PAD. At this time, many patient and professional groups continue to advocate for expanded coverage to include PAD as a primary

**Table 3. Exercise Prescription for Endurance and Resistance Training for Patients With Cardiovascular Disease**

Endurance training	
Frequency	3–5 d/wk
Modality	(For patients with intermittent claudication symptoms, see Table 2) Treadmill walking Stairclimber Stationary cycle Arm cycle ergometry Rowing Swimming
Intensity	40% to <60% heart rate reserve+resting heart rate or 40% to <60% $\dot{V}O_2$ reserve+resting $\dot{V}O_2$
Duration	30–60 min/d
Resistance training	
Frequency	$\geq 2$ –3 d/wk
Intensity	1–3 sets of 8–15 RM for each muscle group
All major muscle groups	
Arms/shoulders	Biceps curl Triceps extension Overhead press Lateral raises
Chest/back	Bench press Lateral pull-down/pull-ups Bent-over/seated row
Legs	Leg extensions, curls, press Adductor/abductor

Modalities listed above are not all-inclusive. Heart rate reserve indicates peak—resting heart rate; RM, maximum number of times a load can be lifted before fatigue;  $\dot{V}O_2$ , measured oxygen uptake; and  $\dot{V}O_2$  reserve, peak  $\dot{V}O_2$ —resting  $\dot{V}O_2$ . Adapted from References 50 and 129.

qualifying diagnosis. Patients who have a concurrent eligible cardiac condition may qualify for exercise rehabilitation on this basis. Additional patient- and physician-related factors may limit the use of supervised exercise, including physician referral, patient willingness to participate, availability of programs, time constraints and logistical issues, and medical comorbidities. Patients with foot ulcers or rest pain or those who are planning to undergo revascularization should defer exercise training until their condition has been treated and stabilized.

### Comprehensive Vascular Rehabilitation and Secondary Prevention Programs in PAD

Comprehensive cardiovascular rehabilitation that includes exercise training is a model for expanded delivery of secondary prevention in PAD.<sup>43,129</sup> Prevention strategies have potential to improve cardiovascular health for patients with PAD, and the medical therapy of PAD has been reviewed elsewhere.<sup>38,138</sup> We have included a brief discussion of secondary prevention therapies here to emphasize the potential benefit of a multifaceted exercise-based intervention to improve risk profile in PAD patients. As outlined in Table 4,

**Table 4. Secondary Prevention to Reduce Cardiovascular Events in PAD**

Lipid-lowering therapy	Treatment with statin for all PAD patients to target LDL cholesterol <100 mg/dL Target LDL cholesterol <70 mg/dL for high-risk patients
Hypertension treatment	Treat to target blood pressure <140/90 mm Hg (<130/80 mm Hg for patients with diabetes mellitus or chronic kidney disease) Consider ACE inhibitor in hypertensive patients Use of $\beta$ -blockers is not contraindicated in PAD
Smoking cessation	Provide comprehensive smoking intervention program Consider pharmacotherapy to support smoking cessation
Antiplatelet therapy	Treat with aspirin 75–325 mg or clopidogrel 75 mg Treat with aspirin+thienopyridine in patients with acute coronary syndrome or coronary or peripheral stent

LDL indicates low-density lipoprotein; ACE, angiotensin-converting enzyme. Adapted from Reference 33.

multiple interventions to reduce cardiovascular risk have proven efficacy in PAD.<sup>38,138</sup> Even among patients with clinically identified PAD, utilization of guideline-based risk factor interventions remains low in comparison to patients with coronary artery disease.<sup>33,34,139,140</sup> In a meta-analysis of >30 000 PAD patients described in studies between 1999 and 2008, there was low penetration of optimal therapies, including only 63% of patients on antiplatelet agents and 45% on lipid-lowering medications.<sup>141</sup> Among PAD patients undergoing vascular surgery, only 41% achieved guideline-based medication therapy, although the use of recommended therapies was associated with reduced 3-year mortality.<sup>142</sup> Implementation of secondary prevention in PAD is vital to mitigating the high cardiovascular risk in this population. Accordingly, patients with PAD may derive additional favorable effects from exercise training combined with comprehensive risk reduction interventions. Cardiac rehabilitation programs serve as a coordinating center for the implementation of secondary prevention therapies in patients with coronary artery disease and could readily assimilate patients with PAD. *The American Heart Association/American Association of Cardiovascular and Pulmonary Rehabilitation Core Components of Cardiac Rehabilitation/Secondary Prevention Programs* outline the comprehensive nature of such programs with the ultimate goal of reducing physical disability and cardiovascular risk while restoring optimal physical, psychological, and social functioning. Such programs integrate exercise into the overall treatment plan that includes lipid management, blood pressure control, smoking cessation, nutrition education and weight reduction, diabetes mellitus treatment, and psychosocial intervention.<sup>129</sup> With the use of this multifaceted approach, cardiac rehabilitation/secondary prevention programs have been associated with up to a 56% improvement in survival among patients after myocardial infarction and a 28% reduction in risk of recurrent myocardial infarction.<sup>143</sup> Such benefits are seen despite age, gender, and ethnic background.<sup>144</sup> Furthermore, the benefits of such programs appear to be dose related in that patients who attend

36 sessions have a 14%, 22%, and 47% lower risk of mortality than those who attended 24 sessions, 12 sessions, and 1 session, respectively.<sup>145</sup> However, no study has yet been conducted to evaluate the effect of exercise rehabilitation in PAD patients on mortality. Nonetheless, given the elevated cardiovascular risk and the proven benefit of multiple secondary prevention measures in PAD patients, it is reasonable to anticipate analogous reductions in risk among those who actively participate in comprehensive rehabilitation.

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## Disclosures

None.

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