

## **A Primary Care Approach to the Diagnosis and Management of Peripheral Arterial Disease**

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### **Objectives:**

- Be able to recognize characteristic symptoms of intermittent claudication
- Diagnose PAD on the basis of history, physical exam, and simple limb blood pressure measurements
- Recognize the significance of peripheral artery disease as a marker for coronary or cerebrovascular atherosclerosis
- Provide appropriate medical management of atherosclerosis risk factors—including use of antiplatelet therapy to reduce risk of myocardial infarction, stroke and death
- Manage symptoms of intermittent claudication with program of smoking cessation, exercise, and medication

The diagnosis of intermittent claudication secondary to peripheral artery disease (PAD) can often be made on the basis of history and physical examination. Additional evaluation of PAD is multi-modal and the techniques used will vary depending on the nature and severity of the patient's presenting problem. Most patients can be appropriately managed without referral for specialized diagnostic services or interventions.

### **Claudication**

The incidence and prevalence of PAD increases with age. Claudication is the most common symptom of lower extremity PAD with an estimated prevalence of >350,000 in the US. About only 5% of patients with claudication will ever develop critical (limb threatening) ischemia.

Claudication is pain, aching or muscle fatigue occurring after the onset of exercise (walking) and relieved by rest. The history is characteristic and reproducible, and the history alone is enough for diagnosis in most cases. A complete physical examination is indicated, however, to evaluate potentially important contributing factors that may impact clinical management. Pulse palpation should be correlated with symptom severity and location. Auscultation of bruits may be helpful, as well.

Claudication is a marker for atherosclerotic cardiovascular disease. The 20-25% five-year mortality of patients with claudication is significantly higher than comparable populations without claudication. Patients with claudication frequently have significant coronary or cerebrovascular disease, with a correlative incidence of myocardial infarction or stroke. Patients with claudication should be evaluated for risk factors for atherosclerosis, including hypertension, lipid abnormalities, and diabetes mellitus. The following blood tests should be performed in all new patients presenting with PAD:

- Complete blood count
- Platelet count
- Fasting blood glucose or hemoglobin A<sub>1c</sub>
- Creatinine
- Fasting lipid profile
- Urinalysis (for glycosuria/proteinuria)

In addition, for patients with and early age of onset, personal or family history of thrombotic events, or a lack of common risk factors for atherosclerosis, the following laboratory investigations are indicated:

- Hypercoagulability screen
- Homocysteine levels

Unless contraindicated, patients with atherosclerotic disease should be on aspirin, or other antiplatelet therapy. Management guidelines for PAD patients are summarized in the accompanying table.

### **Ankle/Brachial Index**

Objective findings can help confirm the diagnosis of hemodynamically significant peripheral artery disease. Because of its simplicity, the ankle brachial index (measured with continuous wave Doppler and pneumatic cuffs) remains a mainstay of screening for PAD. The ankle/brachial index (ABI) is defined as:

$$\text{Ankle/Brachial Index (ABI)} = \frac{\text{ankle pressure (higher of the tibial artery pressures)}}{\text{brachial pressure (higher of the two arm pressures)}}$$

The ABI should be measured in both legs of all new patients with intermittent claudication. The ABI is considered abnormal if it is  $\leq 0.90$ , but a normal individual will typically have an ABI of 1.0 to 1.10. (Though the normal mean blood pressure at the ankle is equal to mean brachial pressure, the pressure waveforms are different. The normal ankle systolic blood pressure—measured with the patient supine—is slightly higher than the brachial artery systolic pressure.) Patients with moderately severe intermittent claudication typically have an ABI in the range of 0.70 to 0.90. The lower the ABI, the more severe the disease. Patients with critical ischemia often have an ABI  $< 0.35$ .

### **Treadmill Exercise Testing**

Treadmill testing is sometimes useful in the evaluation of patients with claudication. Treadmill tests can be conducted in a variety of ways, but usually the speed is kept constant, for example, 2 mi/h (3.2 km/h). Either a fixed incline can be used, or a graded intensity test profile can be selected.

The time or distance walked until the onset of claudication symptoms should be recorded. This is the "pain free walking distance" (PFD) or the "initial claudication distance" (ICD). When claudication symptoms stop the patient from walking any farther, the patient has reached the "maximum walking distance" (MWD) or "absolute claudication distance" (ICD). Pain is subjective and results for some patients may be markedly different from others with similar severity of occlusive disease. Also, a variability of  $\pm 20\%$  is not uncommon if the tests are repeated for a single patient on different days.

Treadmill walking distances can be compared before and after therapy to evaluate the efficacy of the intervention.

Treadmill walking tests are also useful for objectively documenting the severity of, or confirming a diagnosis of claudication. A post-exercise drop in the ankle pressure of  $\cdot 20$  mm Hg is to be expected when patient's symptoms are truly from vasculogenic claudication. A greater pressure drop, and a longer recovery time, indicates more severe disease.

Some patients may have both mild to moderate PAD and musculoskeletal or neurospinal conditions. If they develop symptoms that stop their walking early, but they do not have an associated drop in ankle pressure; it is unlikely that vascular disease is the exercise-limiting condition.

Treadmill tests can also be useful to document mild to moderate proximal occlusive disease that only becomes hemodynamically significant under conditions of exercise. Some patients with aortoiliac disease may have intact pulses and near normal resting segmental pressures. However, after exercising on the treadmill a drop in the limb pressures will be detectable.

## **Peripheral Arterial Duplex Scanning**

If it is desirable to localize and gauge the severity of the PAD in order to assist with the planning of an intervention, duplex scanning or magnetic resonance arteriography can be used as a preliminary, noninvasive examination before arteriography. Arteriography is only indicated when a decision has already been made to intervene, should a suitable lesion or pattern of disease be identified.

An experienced vascular sonographer can image the lower extremity arterial tree from the diaphragm to the feet. While some studies can be limited by abnormal or distorted anatomy (obesity, bowel gas, open wounds, etc.), most patients can be successfully studied with ultrasound. Complete arterial mapping can take two hours or more, though. Ultrasound B-mode imaging reliably demonstrates aneurysms, pseudoaneurysms, and other morphologic features. Color flow imaging facilitates vessel identification (especially useful when scanning small or deeply situated vessels). Color flow imaging and pulsed Doppler can demonstrate patency, focal stenosis, and can characterize segmental hemodynamics, but overall accuracy is better for larger, proximal segments.<sup>1</sup> Further, the ability to specifically characterize degree of arterial narrowing with duplex scanning is limited when there is significant proximal disease and when the segment of interest has diffuse, rather than focal narrowing. Severe stenoses are generally characterized by focal increases in velocity, but this may not be seen if the stenosis is not well localized.

## **Office-based management of PAD**

Claudication can significantly effect the quality of life of affected individuals. The first line of therapy is a program of regular exercise and smoking cessation. Pharmacologic treatment options include pentoxifylline (Trental®) or cilostazol

(Pletal®), but in a prospective, blinded comparison trial, cilostazol improved walking ability more than either pentoxifylline or placebo. For patients with lifestyle limiting symptoms that are not adequately managed with these means, surgical or endovascular revascularization could be considered.

**Additional Reading:**

Dormandy J, Rutherford R. Management of peripheral arterial disease (PAD). TASC Working Group. *J Vasc Surg.* 2000;31:S1-S296.

## Medical Management Guidelines for Peripheral Arterial Disease (PAD) Patients\*

Goals	Therapy	Comments
Antiplatelet therapy	Aspirin (ASA) Clopidogrel (Plavix®)	↓ risk of MI <sup>†</sup> , stroke, vascular death <sup>2, 3</sup>  ASA may reduce need for surgery for PAD <sup>4</sup>  Clopidogrel may be more effective for risk reduction for PAD patients <sup>5</sup>
<b>Management of specific atherosclerosis risk factors:</b>		
Cigarette smoking	Behavioral programs Nicotine replacement Bupropion (Wellbutrin®)	↓ risk of PAD progression, MI, stroke, death <sup>6, 7</sup>  ↓ risk of critical ischemia and limb loss <sup>8</sup>
Obesity	Dietary modification ↑physical activity	
Diabetes mellitus	Dietary therapy Oral hypoglycemics; Metformin (Glucophage®) and others  Insulin	Intensive glycemic control may improve outcomes, including ↓ risk of MI and death <sup>9-11</sup>  Recommend fasting blood glucose 80 to 120 mg/dL; postprandial glucose <180 mg/dL; hemoglobin A <sub>1c</sub> <7.0%

\* Adapted from the recommendations of the TransAtlantic Inter-society Consensus<sup>1</sup>

<sup>†</sup> MI: myocardial infarction

Hyperlipidemia	<p>Screen all PAD patients</p> <p>Dietary modification</p> <p>Medications if LDL-cholesterol <math>\geq 100</math> mg/dL</p> <p>Consider niacin for low HDL-cholesterol</p> <p>Consider fibrates for low HDL-cholesterol and high triglycerides</p>	<p>Lp(a) in an independent risk factor for PAD<sup>12</sup></p> <p>PAD may stabilize or regress with therapy<sup>13-17</sup></p> <p>↓ risk of PAD progression<sup>18</sup></p> <p>↓ risk of MI and cardiovascular death<sup>19-21</sup></p>
Hypertension	<p>Manage according to guidelines from Joint National Committee (VI), National Heart, Lung, and Blood Institute</p>	<p>Correlation to PAD progression not established</p> <p>Marked ↓ in systolic pressure may slightly worsen claudication symptoms<sup>22</sup></p> <p>No contraindication to <math>\beta</math>-blocker use<sup>23</sup></p> <p>ACE<sup>†</sup> inhibitor (ramipril, Altace®) may ↓ risk of MI or death in PAD patients<sup>24</sup></p>
Hypercoagulable states	<p>Warfarin (Coumadin®)</p>	
Hyperhomocysteinemia	<p>Folic acid</p> <p>Vitamin B12</p> <p>Vitamin B6</p>	<p>Elevated plasma homocysteine is important PAD risk factor in patients &lt;50 years<sup>25</sup></p> <p>Treatment ↓ risks of cardiovascular events and death<sup>26, 27</sup></p>
Post-menopausal state	<p>Hormone replacement therapy (estrogen and progesterone)</p>	<p>May ↓ risk of cardiovascular events in women<sup>28</sup></p>

<sup>†</sup> ACE: angiotensin converting enzyme



## References for Table

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## **Pharmacotherapy for Symptoms of Intermittent Claudication<sup>§</sup>**

### **FDA<sup>®</sup>-approved drugs (recommended options)**

Cilostazol  
Pentoxifylline

### **Other established drugs with some or potential benefit for claudication**

Buflomedil  
Naftidrofuryl

### **Therapies with minimal or no benefit (not recommended for clinical use)**

Antiplatelet drugs  
Aminophylline  
Anticoagulation  
Cinnarizine  
Defibrotide  
Dextran  
Ginkgo biloba  
Isosuprine  
Isovolemic hemodilution  
Ketanserin  
Nicotinic acid derivatives  
Vasodilators  
Verapamil (and other calcium channel blockers)  
Vitamin E

### **Incompletely studied drugs with potential benefit (not yet FDA-approved)**

Beraprost sodium  
Carnitine  
L-arginine  
Propionyl-L-carnitine  
Prostaglandins and prostanoids  
Protein kinase C inhibitors  
Vascular endothelial growth factor (VEGF)

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<sup>§</sup> Adapted from recommendations of the TransAtlantic Inter-Society Consensus, reported by Dormandy J, Rutherford R. Management of peripheral arterial disease (PAD). TASC Working Group. *J Vasc Surg.* 2000;31:S1-S296.

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\*\* FDA: United States Food and Drug Administration

# Treatment Algorithm for Patients with Peripheral Artery Disease

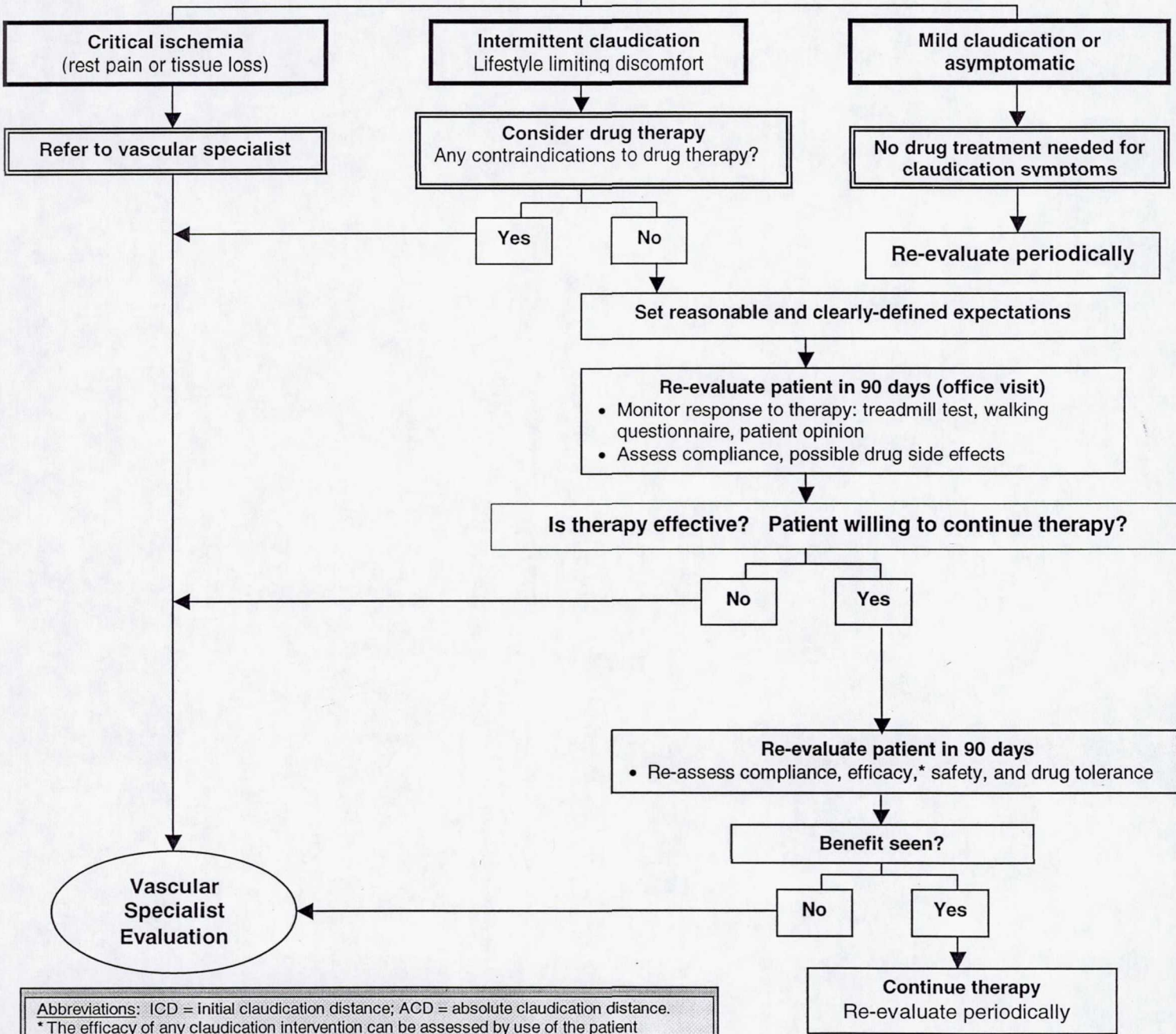
**Initial Diagnostic Assessment**

- Patient history: "Do you have pain, aching, or fatigue in your leg muscles when you walk that disappears when you rest?"
- Physical examination: Include pulse evaluation & ankle-brachial index (ABI)
- Optional assessments: Treadmill test, Walking Impairment Questionnaire

**PAD-Specific Lifestyle Modifications (See table)**

- Begin lifelong antiplatelet therapy
- Control other atherosclerosis risk factors
- Walking exercise program, supervised whenever possible

modified from Dawson DL, Chow MSS, Regensteiner JG, Vogt MT, Hegg C, Lee S, Treat-Jacobson D, Hirsch AT: Treating intermittent claudication secondary to peripheral arterial disease. *Pharm Therap* Dec 1999; 24(12): 616-622.



**Abbreviations:** ICD = initial claudication distance; ACD = absolute claudication distance.  
 \*The efficacy of any claudication intervention can be assessed by use of the patient history, or more formal use of walking impairment questionnaires, treadmill tests, or objective quality of life evaluations.