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New treatments for peripheral artery disease

ABSTRACT

The stenosis or occlusion of extremities defining peripheral artery disease (PAD) is a risk factor for adverse cardiovascular events and adverse limb events including amputation. PAD is common, can occur without symptoms or with claudication, and is easily diagnosed. Proper diagnosis and adherence to guideline-directed therapy can reduce the morbidity and potential mortality associated with PAD.

KEY POINTS

PAD is stenosis or occlusion of the upper or lower extremities caused by atherosclerotic plaque.

PAD is common, often overlooked because it is frequently asymptomatic, but easily diagnosed by obtaining an ankle-brachial index.

Management and medical therapies for PAD include lifestyle measures, optimal blood pressure and cholesterol control, antithrombotic agents to manage the risk of thrombotic events, and claudication therapy.

INTRODUCTION

Peripheral artery disease (PAD) is characterized by stenosis or occlusion of the arteries of the upper or lower limbs due to atherosclerotic plaque in the vessel walls. PAD is common but often overlooked. A public awareness survey found 74% of respondents (N = 2,501) were not aware of PAD. Unfortunately, many physicians also lack awareness of PAD or fail to consider it when evaluating patients.

PAD is easily diagnosed in any office setting by obtaining an ankle-brachial index, which is the ratio calculated by the measured lower extremity (ankle) systolic pressure divided by the brachial artery (arm) systolic pressure. An ankle-brachial index of 0.91 to 1.4 is normal, 0.90 or less is diagnostic for PAD, and less than 0.40 is diagnostic for severe PAD. Patients may experience leg pain (claudication), rest pain, or leg ulcerations. The ankle-brachial index is 95% sensitive and 99% specific for PAD. With greater awareness and screening for PAD, significant patient morbidity can be avoided.

EPIDEMIOLOGY AND PATHOPHYSIOLOGY

Over 200 million people worldwide have PAD and it occurs in men and women equally. The prevalence of PAD increases with age occurring in about 30% of people over 70 and in people 50 to 69 with diabetes or those who smoke. Both mortality and disability from PAD have increased over the last several decades. Patients with PAD are at high risk for major adverse cardiovascular events and major adverse limb events, the most dreaded complication being amputation.

SIGN AND SYMPTOMS

Failure to recognize PAD is largely due to the absence of symptoms. In the ambulatory setting, about 50% of individuals with PAD have no leg symptoms whatsoever. Only about 15% of those with PAD have typical claudication, 30% have atypical limb symptoms, and about 3% have critical limb ischemia.

The 5-year outcome for patients with PAD includes stable claudication in 70% to 80% of patients; 10% to 20% will require lower extremity revascularization,
and about 1% to 2% will go on to have chronic limb ischemias (Table 1). Amputation rates are as high as 25% in patients with chronic limb ischemia. It is important to note that for patients with PAD, 20% will have a myocardial infarction or stroke, and death can occur in 15% to 30% over a 5-year period. As these data make clear, PAD is not a benign condition.

**TABLE 1**
Natural history of peripheral artery disease

| Symptoms at diagnosis in patients with PAD | Patients (%) | 5-Year outcomes |
|-------------------------------------------|--------------|-----------------|
| Asymptomatic                               | 20–50        | Major adverse limb events |
| Atypical leg discomfort                     | 40–50        | Stable claudication: 70%–80% |
| Claudication                               | 10–30        | Lower extremity revascularization: 10%–20% |
| Critical limb ischemia                     | 1–2          | Critical limb ischemia: 1%–2% |
|                                           |              | Major adverse cardiovascular events |
|                                           |              | Myocardial infarction/stroke: 20% |
|                                           |              | Death: 15%–30% |

1-year outcomes

| Critical limb ischemia | 1–2          | Amputation: 25% |

Source: Data from reference 6.

### Medical Therapies and Management

As stated, PAD is routinely underdiagnosed but even with proper diagnosis, patients with PAD are less frequently treated with guideline-directed therapies compared with patients with coronary artery disease. Medical therapies for, and the management of PAD revolve around preventing myocardial infarction, stroke, and death; improving function and quality of life; and protecting the feet to avoid and prevent amputation.

**Diet, exercise, tobacco cessation**

Patients with PAD should be counseled about maintaining a healthy diet, exercise, and complete cessation of tobacco use. Recommended exercise programs for patients with PAD have been established and are covered services for older patients by US Centers for Medicare & Medicaid Services. A 12-week supervised treadmill exercise program consists of 3 weekly sessions that begin at 15 minutes and increase to 45 to 50 minutes a session. A home-based walking exercise program or a supervised ergometry exercise program are also recommended and may be better suited to some patients.

**Medical therapy**

In addition to lifestyle measures, medical therapies for PAD should be employed to:

- Optimize blood pressure preferably using an angiotensin-converting-enzyme inhibitor
- Lower and maintain low-density lipoprotein cholesterol (LDL-C) to less than 70 mg/dL using a statin, ezetimibe, or a proprotein convertase subtilisin-kexin 9 inhibitor or combination.
- Manage risk of thrombotic events with antithrombotic agents such as aspirin, clopidogrel, ticagrelor, vorapaxar, and rivaroxaban
- Treat claudication pain in the extremities with cilostazol if no heart failure.

Several major clinical trials have evaluated antithrombotic agents in patients with PAD, especially symptomatic PAD (Table 2). Among these trials, Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) evaluated cardiovascular outcomes in 27,395 patients including 27% with PAD. Patients received 2.5 mg rivaroxaban twice daily plus 100 mg aspirin, or 5 mg rivaroxaban twice daily, or 100 mg aspirin daily. The cardiovascular outcomes in patients with stable atherosclerotic vascular disease were more favorable in the rivaroxaban-plus-aspirin cohort (hazard ratio = 0.76; 95% confidence interval [CI] 0.66–0.86; \( P = .001 \)) compared with the rivaroxaban-alone cohort (hazard ratio = 0.90; 95% CI 0.79–1.03; \( P = .12 \)), but more major bleeding events occurred in patients on rivaroxaban plus aspirin (3%) compared with rivaroxaban alone (1.9%). The secondary composite outcome of ischemic stroke, myocardial
infarction, acute limb ischemia, or cardiovascular death also favored rivaroxaban-plus-aspirin therapy, with emphasis on screening for bleeding.

Figure 1 outlines a frequently used approach to antithrombotic therapy showing that all patients with symptomatic PAD should receive aspirin or clopidogrel or aspirin with rivaroxaban. In patients with asymptomatic PAD, aspirin should be considered especially if disease is present in another vascular bed.

**Summary of risk reduction therapy for patients with PAD**

The American College of Cardiology/American Heart Association 2016 guidelines on the management of patients with lower extremity PAD advise that reduction of risk for major adverse limb events should include healthy lifestyle modifications, tobacco cessation, achieving target blood pressure goals, glucose lowering therapy, LDL-C lowering using a statin or ezetimibe or a PCSK9 agent, and antiplatelet therapy. The Further Cardiovascular Outcomes Research With PCSK8 Inhibition in Subjects With Elevated Risk (FOURIER) trial provides insight into LDL-C levels and outcomes in patients with PAD. Of the 27,564 patients in the FOURIER trial, 13.2% had PAD and by lowering LDL-C to a median of 31 mg/dL in patients with symptomatic PAD, major adverse cardiovascular events and major adverse limb events were reduced significantly. Evolocumab plus a statin to reduce LDL-C levels reduced the risk of major adverse limb events (ie, limb ischemia or loss of limb) by 42% in 2 study populations.

For some patients with more advanced disease, aspirin together with rivaroxaban (2.5 mg twice daily) or ticagrelor (60 mg twice daily) or clopidogrel (75 mg once daily) with or without vorapaxar (2.08 mg once daily) is appropriate. Claudication therapy with cilostazol (100 mg twice daily) can be used for patients without heart failure.
**PERIPHERAL ARTERY DISEASE**

**Approach to Antithrombotic Therapy in Peripheral Artery Disease**

- **Asymptomatic**
  - Consider Aspirin
    - Particularly if disease in another vascular bed
  - All Patients
  - Recent Coronary Stent or Acute Coronary Syndrome
- **Symptomatic**
  - Aspirin or Clopidogrel OR Aspirin + Rivaroxaban
    - Rivaroxaban 2.5 mg BID added to aspirin reduces major adverse cardiovascular or cerebrovascular events and minor adverse limb events but increases bleeding
  - Dual Antiplatelet Therapy (DAPT)
    - Weigh ischemic and bleeding risks for long-term use
  - DAPT for 1-6 Months
  - Aspirin or Clopidogrel OR Aspirin + Rivaroxaban
    - High Limb Risk
      - Intensify Antithrombotic Therapy
        - Consider aspirin + rivaroxaban, vitamin K antagonist, or DAPT after bypass.
        - Consider prolonged DAPT after endovascular procedure. Weigh limb and bleeding risks.
  - Revascularization
    - Surgical
    - Endovascular

**Figure 1.** Therapeutic approach for patients with peripheral artery disease.

BID = 2 times per day; MI = myocardial infarction

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**REFERENCES**

1. Hiatt WR, Goldstone J, Smith SC Jr, et al. Atherosclerotic Peripheral Vascular Disease Symposium II: nomenclature for vascular diseases. [published correction appears in Circulation 2009; 119(25):e604]. Circulation 2008; 118(25):2826–2829. doi:10.1161/CIRCULATIONAHA.108.191171

2. Hirsch AT, Murphy TP, Lovell MB, et al. Gaps in public knowledge of peripheral arterial disease: the first national PAD public awareness survey. Circulation 2007; 116(18):2086–2094. doi:10.1161/CIRCULATIONAHA.107.725101

3. Criqui MH, Frohlich 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; 71(3):516–522. doi:10.1161/01.cir.71.3.516

4. Gerhard-Herman MD, Gornik HL, Barrett C, et al. 2016 AHA/ACC Guideline on the Management of Patients With Lower Extremity Peripheral Artery Disease: Executive Summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines [published correction appears in J Am Coll Cardiol 2017; 69(11):1520]. J Am Coll Cardiol 2017; 69(11):1465–1508. doi:10.1016/j.jacc.2016.11.008

5. Society for Vascular Medicine. Peripheral arterial disease (PAD). Society for Vascular Medicine website. http://myperipheralarterydisease.com/health-care-providers. Accessed March 5, 2020.

6. Hirsch AT, Haskal ZJ, Hertzer NR, et al. ACC/AHA 2005 Practice Guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease): endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; and Vascular Disease Foundation. Circulation 2006; 113(11):e463–e654. doi:10.1161/CIRCULATIONAHA.106.174526
Vorapaxar in patients with peripheral artery disease: results from TRA2°P-TIMI 50. Circulation 2013; 127(14):1522–1529. doi:10.1161/CIRCULATIONAHA.112.000679

Bonaca MP, Scirica BM, Creager MA, et al. Antithrombotic therapy for peripheral artery disease: recent advances. J Am Coll Cardiol 2018; 71(21):2450–2467. doi:10.1016/j.jacc.2018.03.483

CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). CAPRIE Steering Committee. Lancet 1996; 348(9038):1329–1339.

Critical Leg Ischaemia Prevention Study (CLIPS) Group; Catalano M, Born G, Peto R. Prevention of serious vascular events by aspirin amongst patients with peripheral arterial disease: randomised, double-blind trial. J Intern Med 2007; 261(3):276–284. doi:10.1111/j.1365-2796.2006.01763.x

Hiatt WR, Fowkes FGR, Heizer G, et al. Ticagrelor versus clopidogrel in symptomatic peripheral artery disease. N Engl J Med 2017; 376(1):32–40. doi:10.1056/NEJMoa1611688

Cacoub P, Bhatt DL, Steg PG, Topol EJ, Creager MA; CHARISMA Investigators. Patients with peripheral arterial disease in the CHARISMA trial. Eur Heart J 2009; 30(2):192–201. doi:10.1093/eurheartj/ehn534

Patel MR, Becker RC, Woydyla DM, et al. Cardiovascular events in acute coronary syndrome patients with peripheral arterial disease treated with ticagrelor compared with clopidogrel: data from the PLATO Trial. Eur J Prev Cardiol 2015; 22(6):734–742. doi:10.1177/2047487314533215

Bhatt DL, Bonaca MP, Bansilal S, et al. Reduction in ischemic events with ticagrelor in diabetic patients with prior myocardial infarction in PEGASUS-TIMI 54. J Am Coll Cardiol 2016; 67(23):2732–2740. doi:10.1016/j.jacc.2016.03.529

Franzone A, Piccolo R, Gargiulo G, et al. Prolonged vs. short duration of dual antiplatelet therapy after percutaneous coronary intervention in patients with or without peripheral arterial disease: a subgroup analysis of the PRODIGY randomized clinical trial. JAMA Cardiol 2016; 1(7):795–803. doi:10.1001/jamacardio.2016.2811

Secemsky EA, Yeh RW, Kerenikes DJ, et al; Dual Antiplatelet Therapy Study Investigators. Extended duration dual antiplatelet therapy after coronary stenting among patients with peripheral arterial disease: a subanalysis of the dual antiplatelet therapy study. JACC Interv 2017; 10(9):942–954. doi:10.1016/j.jcin.2017.02.013

Bonaca MP, Scirica BM, Creager MA, et al. Vorapaxar in patients with peripheral artery disease: results from TRA2P-TIMI 50. Circulation 2013; 127(14):1522–1529. doi:10.1161/CIRCULATIONAHA.112.00679

Jones WS, Tricoci P, Huang Z, et al. Vorapaxar in patients with peripheral artery disease and acute coronary syndrome: insights from Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome (TRACER). Am Heart J 2014; 168(4):588–596. doi:10.1016/j.ahj.2014.06.017

Warfarin Antiplatelet Vascular Evaluation Trial Investigators; Anand S, Yusuf S, et al. Oral anticoagulant and antiplatelet therapy and peripheral arterial disease. N Engl J Med 2007; 357(3):217–227. doi:10.1056/NEJMoa0659583

Eikelboom JW, Connolly SJ, Bosch J, et al; COMPASS Investigators. Rivaroxaban with or without aspirin in stable cardiovascular disease. N Engl J Med 2017; 377(14):1319–1330. doi:10.1056/NEJMoa1709118

Belch J, MacCuish A, Campbell I, et al; Prevention of Progression of Arterial Disease and Diabetes Study Group, Diabetes Registry Group, and Royal College of Physicians Edinburgh. The prevention of progression of arterial disease and diabetes (POPADAD) trial: factorial randomised placebo controlled trial of aspirin and antioxidants in patients with diabetes and asymptomatic peripheral arterial disease. BMJ 2008, 337:a1840. doi:10.1136/bmj.a1840

Fowkes FGR, Price JF, Stewart MCD, et al; Aspirin for Asymptomatic Atherosclerosis Trialists. Aspirin for prevention of cardiovascular events in a general population screened for a low ankle brachial index: a randomized controlled trial. JAMA 2010; 303(9):841–848. doi:10.1001/jama.2010.221

Butch Bypass Oral Anticoagulants or Aspirin (BOA) Study Group. Efficacy of oral anticoagulants compared with aspirin after infragenual bypass surgery (The Dutch Bypass Oral Anticoagulants or Aspirin Study): a randomised trial [published correction appears in Lancet 2000; 355(9201):346–351.

Belch JFF, Dormandy J, CASPAR Writing Committee, et al. Results of the randomised, placebo-controlled clopidogrel and acetylsalicylic acid in bypass surgery for peripheral arterial disease (CASPAR) trial. J Vasc Surg 2010; 52(4):825–833. doi:10.1016/j.jvs.2010.04.027

Tepe G, Bantleon R, Brechtel K, et al. Management of peripheral arterial interventions with mono or dual antiplatelet therapy—the MIRROR study: a randomised and double-blind clinical trial. Eur Radiol 2012; 22(9):1998–2006. doi:10.1007/s00330-012-2441-2

Bonaca MP, Nault P, Giugliano RP, et al. Low-density lipoprotein cholesterol lowering with evolocumab and outcomes in patients with peripheral artery disease: insights from the FOURIER Trial (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk). Circulation 2018; 137(4):338–350. doi:10.1161/CIRCULATIONAHA.117.032235

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