THE JOURNAL OF FAMILY PRACTICE

How to refine your approach to peripheral arterial disease

Early recognition, management of comorbid conditions, and appropriate treatment of peripheral arterial disease can help you improve your patient's outcome.

Dustin K. Smith, DO; Michael J. Arnold, MD; Job Larson, MD
Jacksonville Family Medicine Residency Program, Naval Hospital Jacksonville, FL (Dr. Smith); Uniformed Services University of the Health Sciences, Bethesda, MD (Dr. Arnold); Naval Hospital Naples, Italy (Dr. Larson)

dustinksmith@yahoo.com

The authors reported no potential conflict of interest relevant to this article.

The views expressed in this article are those of the authors and do not necessarily reflect the official policy or position of the Department of the Navy, Uniformed Services University of the Health Sciences, Department of Defense, or the United States government.

doi: 10.12788/jfp.0115

PRACTICE RECOMMENDATIONS

› *Use the ankle-brachial index for diagnosis in patients with history/physical exam findings suggestive of peripheral arterial disease (PAD).* (A)

› *Strongly encourage smoking cessation in patients with PAD as doing so reduces 5-year mortality and amputation rates.* (B)

› *Use structured exercise programs for patients with intermittent claudication prior to consideration of revascularization; doing so offers similar benefit and lower risks.* (A)

› *Recommend revascularization for patients who have limb ischemia or lifestyle-limiting claudication despite medical and exercise therapy.* (B)

Strength of recommendation (SOR)

(A) Good-quality patient-oriented evidence

(B) Inconsistent or limited-quality patient-oriented evidence

(C) Consensus, usual practice, opinion, disease-oriented evidence, case series

Peripheral arterial disease (PAD), the progressive disorder that results in ischemia to distal vascular territories as a result of atherosclerosis, spans a wide range of presentations, from minimally symptomatic disease to limb ischemia secondary to acute or chronic occlusion.

The prevalence of PAD is variable, due to differing diagnostic criteria used in studies, but PAD appears to affect 1 in every 22 people older than age 40.[1] However, since PAD incidence increases with age, it is increasing in prevalence as the US population ages.[1-3]

PAD is associated with increased hospitalizations and decreased quality of life.[4] Patients with PAD have an estimated 30% 5-year risk for myocardial infarction, stroke, or death from a vascular cause.[3]

Screening. Although PAD is underdiagnosed and appears to be undertreated,[3] population-based screening for PAD in asymptomatic patients is not recommended. A Cochrane review found no studies evaluating the benefit of asymptomatic population-based screening.[5] Similarly, in 2018, the USPSTF performed a comprehensive review and found no studies to support routine screening and determined there was insufficient evidence to recommend it.[6,7]

Risk factors and associated comorbidities

PAD risk factors, like the ones detailed below, have a potentiating effect. The presence of 2 risk factors doubles PAD risk, while 3 or more risk factors increase PAD risk by a factor of 10.[1]

Increasing age is the greatest single risk factor for PAD.[1,2,8,9] Researchers using data from the National Health and Nutrition Examination Survey (NHANES) found that the prevalence of PAD increased from 1.4% in individuals ages 40 to 49 years to almost 17% in those age 70 or older.[1]

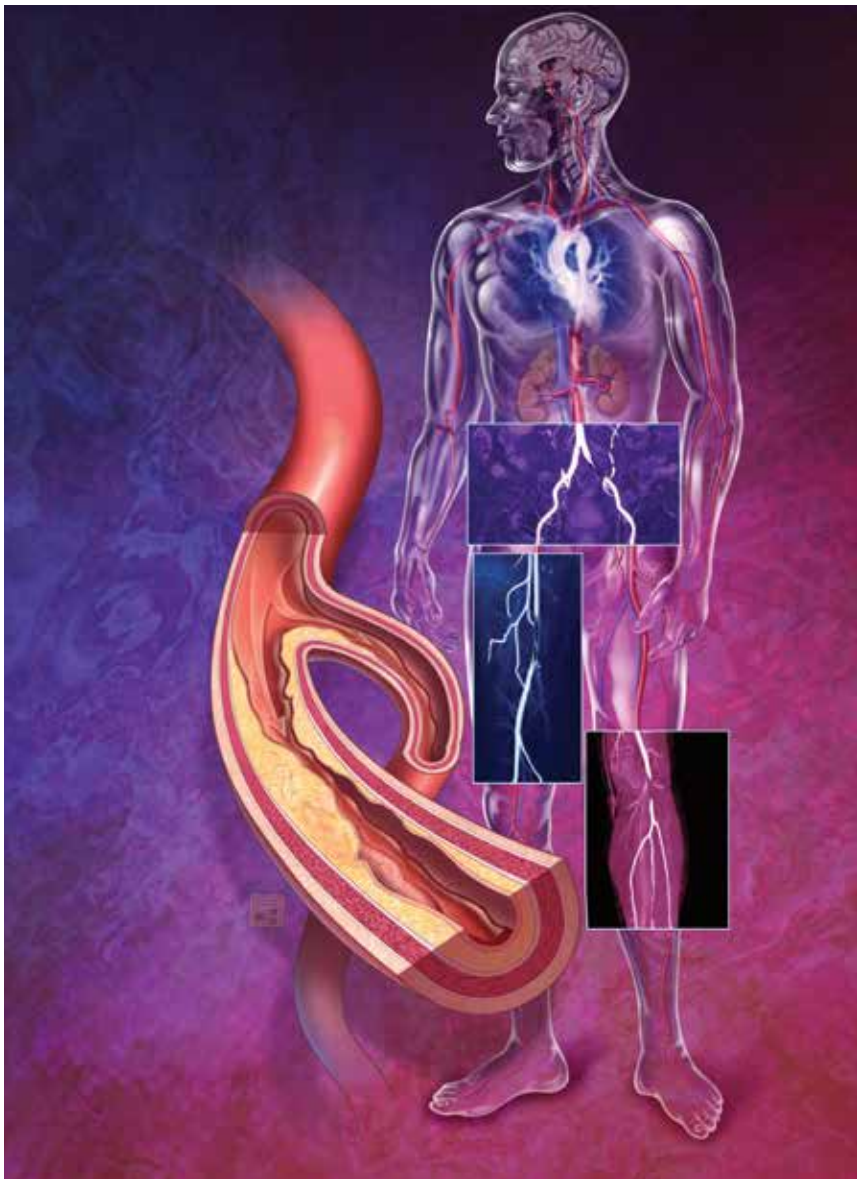

IMAGE: ©KOSTUDIOS

Patients with PAD have an estimated 30% 5-year risk for myocardial infarction, stroke, or death from a vascular cause.

Demographic characteristics. Most studies demonstrate a higher risk for PAD in men.[1-3,10] African-American patients have more than twice the risk for PAD, compared with Whites, even after adjustment for the increased prevalence of associated diseases such as hypertension and diabetes in this population.[1-3,10]

Genetics. A study performed by the National Heart Lung and Blood Institute suggested that genetic correlations between twins were more important than environmental factors in the development of PAD.[11]

Smoking. Most population studies show smoking to be the greatest modifiable risk factor for PAD. An analysis of the NHANES data yielded an odds ratio (OR) of 4.1 for current smokers and of 1.8 for former smokers.[1] Risk increases linearly with cumulative years of smoking.[1,2,9,10]

Diabetes is another significant modifiable risk factor, increasing PAD risk by 2.5 times.[2] Diabetes is also associated with increases in functional limitation from claudication, risk for acute coronary syndrome, and progression to amputation.[1]

Hypertension nearly doubles the risk for PAD, and poor control further increases this risk.[2,9,10]

Chronic kidney disease (CKD). Patients with CKD have a progressively higher prevalence of PAD with worsening renal function.[1] There is also an association between CKD and increased morbidity, revascularization failure, and increased mortality.[1]

Two additional risk factors that are

less well understood are dyslipidemia and chronic inflammation. There is conflicting data regarding the role of individual components of cholesterol and their effect on PAD, although lipoprotein (a) has been shown to be an independent risk factor for both the development and progression of PAD.[12] Similarly, chronic inflammation has been shown to play a role in the initiation and progression of the disease, although the role of inflammatory markers in evaluation and treatment is unclear and assessment for these purposes is not currently recommended.[12,13]

Diagnosis

Clinical presentation

Lower extremity pain is the hallmark symptom of PAD, but presentation varies. The classic presentation is claudication, pain within a defined muscle group that occurs with exertion and is relieved by rest. Claudication is most common in the calf but also occurs in the buttock/thigh and the foot.

However, most patients with PAD present with pain that does not fit the definition of claudication. Patients with comorbidities, physical inactivity, and neuropathy are more likely to present with atypical pain.[14] These patients may demonstrate critical or acute limb ischemia, characterized by pain at rest and most often localized to the forefoot and toes. Patients with critical limb ischemia may also present with nonhealing wounds/ulcers or gangrene.[15]

Physical exam findings can support the diagnosis of PAD, but none are reliable enough to rule the diagnosis in or out. Findings suggestive of PAD include cool skin, presence of a bruit (iliac, femoral, or popliteal), and palpable pulse abnormality. Multiple abnormal physical exam findings increase the likelihood of PAD, while the absence of a bruit or palpable pulse abnormality makes PAD less likely.[16] In patients with PAD, an associated wound/ulcer is most often distal in the foot and usually appears dry.[17]

The differential diagnosis for intermittent leg pain is broad and includes neurologic, musculoskeletal, and venous etiologies. **TABLE 1**[18] lists some common alternate diagnoses for patients presenting with leg pain or claudication.

African-American patients have more than twice the risk for PAD, compared with Whites, even after adjustment for the increased prevalence of associated diseases in this population.

Diagnostic testing

An ankle-brachial index (ABI) test should be performed in patients with history or physical exam findings suggestive of PAD. A resting ABI is performed with the patient in the supine position, with measurement of systolic blood pressure in both arms and ankles using a Doppler ultrasound device. **TABLE 2**[13] outlines ABI scoring and interpretation.

An ABI > 1.4 is an invalid measurement, indicating that the arteries are too calcified to be compressed. These highly elevated ABI measurements are common in patients with diabetes and/or advanced CKD. In these patients, a toe-brachial index (TBI) test should be performed, because the digital arteries are almost always compressible.[13]

Patients with symptomatic PAD who are under consideration for revascularization may benefit from radiologic imaging of the lower extremities with duplex ultrasound, computed tomography angiography, or magnetic resonance angiography to determine the anatomic location and severity of stenosis.[13]

Management of PAD

Lifestyle interventions

For patients with PAD, lifestyle modifications are an essential—but challenging—component of disease management.

Smoking cessation. As with other atherosclerotic diseases, PAD progression is strongly correlated with smoking. A trial involving 204 active smokers with PAD showed that 5-year mortality and amputation rates dropped by more than half in those who quit smoking within a year, with numbers needed to treat (NNT) of 6 for mortality and 5 for amputation.[19] Because of this dramatic effect, American College of Cardiology/American Heart Association (ACC/AHA) guidelines encourage providers to address smoking at every visit and use cessation programs and medication to increase quit rates.[13]

Exercise may be the most important intervention for PAD. A 2017 Cochrane review found that supervised, structured exercise programs increase pain-free and maximal walking distances by at least 20% and also im-

TABLE 1

Differential diagnosis for leg pain or claudication[18]

Condition	Location	Characteristics	Effect of exercise	Effect of rest	Effect of position
Chronic compartment syndrome	Calf muscles	Tight, bursting pain	Usually occurs after prolonged exercise	Subsides very slowly	Relief with rest
Venous claudication	Entire leg, worse in calf	Tight, bursting pain	Occurs after walking	Subsides slowly	Relief speeded by elevation
Spinal stenosis	Often bilateral buttocks, posterior leg	Pain and weakness	May mimic claudication	Recovery variable, usually longer than in claudication	Relief by lumbar spine flexion
Nerve root compression	Radiates down leg	Sharp, lancinating pain	Induced by walking (as well as sitting or standing)	Often present at rest	Improved by change in position
Hip arthritis	Lateral hip, thigh	Aching discomfort	Occurs after varying degree of exercise	Not quickly relieved	Improved when not weight-bearing
Foot/ankle arthritis	Ankle, foot, arch	Aching pain	Occurs after varying degree of exercise	Not quickly relieved	May improve when not weight-bearing
Symptomatic Baker cyst	Behind knee, down calf	Swelling, tenderness	Occurs with exercise	Present at rest	None

TABLE 2

Interpretation of the ankle-brachial index[13]

ABI score	Interpretation	Next step
≤ 0.9	Abnormal	Diagnosis of PAD
0.91 - 0.99	Borderline	Exercise ABI (if high clinical suspicion)
1 - 1.4	Normal	Evaluate for other causes
> 1.4	Noncompressible	TBI

ABI, ankle-brachial index; PAD, peripheral arterial disease; TBI, toe-brachial index

prove physical and mental quality of life.[20] In a trial involving 111 patients with aortoiliac PAD, supervised exercise plus medical care led to greater functional improvement than either revascularization plus medical care or medical care alone.[21] In a 2018 Cochrane review, neither revascularization or revascularization added to supervised exercise were better than supervised exercise alone.[22] ACC/AHA guidelines recommend supervised exercise programs for claudication prior to considering revascularization.[13] **TABLE 3**[13] outlines the components of a structured exercise program.

Unfortunately, the benefit of these programs has been difficult to reproduce without supervision. Another 2018 Cochrane review demonstrated significant improvement with supervised exercise and no clear improvement in patients given home exercise or advice to walk.[23] A recent study examined the effect of having patients use a wearable fitness tracker for home exercise and demonstrated no benefit over usual care.[24]

Diet. There is some evidence that dietary interventions can prevent and possibly improve PAD. A large randomized controlled trial showed that a Mediterranean diet lowered rates of PAD over 1 year compared to a low-fat diet, with an NNT of 336 if supplemented with extra-virgin olive oil and 448 if supplemented with nuts.[25] A small trial of 25 patients who consumed non-soy legumes daily for 8 weeks showed average ABI improvement of 6%, although there was no control group.[26]

CONTINUED

TABLE 3

Elements of a structured exercise program[13]

ACC/AHA guidelines recommend supervised exercise programs for claudication prior to considering revascularization.

Hospital or outpatient facility; can be part of cardiac rehabilitation program
Directly supervised by qualified health care providers
Sessions a minimum of 30-40 min
Sessions performed at least 3 times/wk for at least 12 wk
Warm-up and cool-down included in sessions
Exercise modality–varied between studies
Aerobic exercises
Treadmill walking without avoiding or purposely causing claudication
Treadmill walking, graded to avoid claudication
Walking (outdoors or indoor track)
Cycle ergometer
Arm crank exercises
Polestriding (walking with ski poles in cross-country ski movement)
Anaerobic exercises
Strength training
Calisthenics

ACC/AHA, American College of Cardiology/American Heart Association.

A trial involving 204 active smokers with PAD showed that 5-year mortality and amputation rates dropped by more than half in those who quit smoking within a year.

Medical therapy to address peripheral and cardiovascular events

Standard medical therapy for coronary artery disease (CAD) is recommended for patients with PAD to reduce cardiovascular and limb events. For example, treatment of hypertension reduces cardiovascular and cerebrovascular events, and studies verify that lowering blood pressure does not worsen claudication or limb perfusion.[13] **TABLE 4**[13,27-30] outlines the options for medical therapy.

Statins reduce cardiovascular events in PAD patients. A large study demonstrated that 40 mg of simvastatin has an NNT of 21 to prevent a coronary or cerebrovascular event in PAD, similar to the NNT of 23 seen in treatment of CAD.[27] Statins also reduce adverse limb outcomes. A registry of atherosclerosis patients showed that statins have an NNT of 56 to prevent amputation in PAD and an NNT of 28 to prevent worsening claudication, critical limb ischemia, revascularization, or amputation.[28]

Antiplatelet therapy with low-dose aspirin or clopidogrel is recommended for symptomatic patients and for asymptomatic patients with an ABI ≤ 0.9.[13] A Cochrane review demonstrated significantly reduced mortality with nonaspirin antiplatelet agents vs aspirin (NNT = 94) without increase in major bleeding.[29] Only British guidelines specifically recommend clopidogrel over aspirin.[31]

Dual antiplatelet therapy has not shown consistent benefits over aspirin alone. ACC/AHA guidelines state that dual antiplatelet therapy is not well established for PAD but may be reasonable after revascularization.[13]

Voraxapar is a novel antiplatelet agent that targets the thrombin-binding receptor on platelets. However, trials show no significant coronary benefit, and slight reductions in acute limb ischemia are offset by increases in major bleeding.[13]

For patients receiving medical therapy, ongoing evaluation and treatment should be based on claudication symptoms and clinical assessment.

Medical therapy for claudication

Several medications have been proposed for symptomatic treatment of intermittent claudication. Cilostazol is a phosphodiesterase inhibitor with the best risk-benefit ratio. A Cochrane review showed improvements in maximal and pain-free walking distances

TABLE 4

Medical therapy to address peripheral and cardiovascular events[13,27-30]

Element	Cardiac effect	Limb effect
Hypertension management	Reduce MACE	No harm
High-dose statin	Reduce MACE	Reduce ischemia and amputation
Antiplatelet agent, preferably clopidogrel	Reduce MACE	Reduce chronic limb ischemia

MACE, major acute coronary event.

compared to placebo and improvements in quality of life with cilostazol 100 mg taken twice daily.[32] Adverse effects included headache, dizziness, palpitations, and diarrhea.[29]

Pentoxifylline is another phosphodiesterase inhibitor with less evidence of improvement, higher adverse effect rates, and more frequent dosing. It is not recommended for treatment of intermittent claudication.[13,33]

Supplements. Padma 28, a Tibetan herbal formulation, appears to improve maximal walking distance with adverse effect rates similar to placebo.[34] Other supplements, including vitamin E, ginkgo biloba, and omega-3 fatty acids, have no evidence of benefit.[35-37]

When revascularization is needed

Patients who develop limb ischemia or lifestyle-limiting claudication despite conservative therapy are candidates for revascularization. Endovascular techniques include angioplasty, stenting, atherectomy, and precise medication delivery. Surgical approaches mainly consist of thrombectomy and bypass grafting. For intermittent claudication despite conservative care, ACC/AHA guidelines state endovascular procedures are appropriate for aortoiliac disease and reasonable for femoropopliteal disease, but unproven for infrapopliteal disease.[13]

Acute limb ischemia is an emergency requiring immediate intervention. Two trials revealed identical overall and amputation-free survival rates for percutaneous thrombolysis and surgical thrombectomy.[38,39] ACC/AHA guidelines recommend anticoagulation with heparin followed by the revascularization technique that will most rapidly restore arterial flow.[13]

For chronic limb ischemia, a large trial showed angioplasty had lower initial morbidity, length of hospitalization, and cost than surgical repair. However, surgical mortality was lower after 2 years.[40] ACC/AHA guidelines recommend either surgery or endovascular procedures and propose initial endovascular treatment followed by surgery if needed.[13] After revascularization, the patient should be followed periodically with a clinical evaluation and ABI measurement with further consideration for routine duplex ultrasound surveillance.[13]

Outcomes

Patients with PAD have variable outcomes. About 70% to 80% of patients with this diagnosis will have a stable disease process with no worsening of symptoms, 10% to 20% will experience worsening symptoms over time, 5% to 10% will require revascularization within 5 years of diagnosis, and 1% to 5% will progress to critical limb ischemia, which has a 5-year amputation rate of 1% to 4%.[2] Patients who require amputation have poor outcomes: Within 2 years, 30% are dead and 15% have had further amputations.[18]

In addition to the morbidity and mortality from its own progression, PAD is an important predictor of CAD and is associated with a significant elevation in morbidity and mortality from CAD. One small but well-designed prospective cohort study found that patients with PAD had a more than 6-fold increased risk of death from CAD than did patients without PAD.[41] JFP

ACKNOWLEDGEMENT
The authors thank Francesca Cimino, MD, FAAFP, for her help in reviewing this manuscript.

CORRESPONDENCE
Dustin K. Smith, DO, 2080 Child Street, Jacksonville, FL 32214; dustinksmith@yahoo.com

CONTINUED

For chronic limb ischemia, a large trial showed angioplasty had lower initial morbidity, length of hospitalization, and cost than surgical repair. Surgical mortality was lower after 2 years.

One small but well-designed prospective cohort study found that patients with PAD had a more than 6-fold increased risk of death from CAD than did patients without PAD.

References

1. Eraso LH, Fukaya E, Mohler ER 3rd, et al. Peripheral arterial disease, prevalence and cumulative risk factor profile analysis. *Eur J Prev Cardiol*. 2014;21:704-711.
2. Pasternak RC, Criqui MH, Benjamin EJ, et al; American Heart Association. Atherosclerotic Vascular Disease Conference: Writing Group I: epidemiology. *Circulation*. 2004;109:2605-2612.
3. Hirsch AT, Criqui MH, Treat-Jacobson D, et al. Peripheral arterial disease detection, awareness, and treatment in primary care. *JAMA*. 2001;286:1317-1324.
4. Olin JW, Sealove BA. Peripheral artery disease: current insight into the disease and its diagnosis and management. *Mayo Clin Proc*. 2010;85:678-692.
5. Andras A, Ferkert B. Screening for peripheral arterial disease. *Cochrane Database Syst Rev*. 2014;(4):CD010835.
6. Guirguis-Blake JM, Evans CV, Redmond N, et al. Screening for peripheral artery disease using ankle-brachial index: updated evidence report and systematic review for the US Preventive Services Task Force. *JAMA*. 2018;320:184-196.
7. US Preventive Services Task Force. Screening for peripheral artery disease and cardiovascular disease risk assessment with ankle-brachial index: US Preventive Services Task Force recommendation statement. *JAMA*. 2018;230:177-183.
8. American Heart Association Writing Group 2. Atherosclerotic Peripheral Vascular Disease Symposium II: screening for atherosclerotic vascular diseases: should nationwide programs be instituted? *Circulation*. 2008;118:2830-2836.
9. Berger JS, Hochman J, Lobach I, et al. Modifiable risk factor burden and the prevalence of peripheral artery disease in different vascular territories. *J Vasc Surg*. 2013;58:673-681.
10. Joosten MM, Pai JK, Bertoia ML, et al. Associations between conventional cardiovascular risk factors and risk of peripheral artery disease in men. *JAMA*. 2012;308:1660-1667.
11. Carmelli D, Fabsitz RR, Swan GE, et al. Contribution of genetic and environmental influences to ankle-brachial blood pressure index in the NHLBI Twin Study. National Heart, Lung, and Blood Institute. *Am J Epidemiol*. 2000;151:452-458.
12. Aboyans V, Criqui MH, Denenberg JO, et al. Risk factors for progression of peripheral arterial disease in large and small vessels. *Circulation*. 2006;113:2623-2629.
13. Gerald-Herman MD, Gornik HL, Barrett C, et al. 2016 AHA/ACC guideline on the management of patients with lower extremity peripheral artery disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2017;135:e726-e779.
14. McDermott MM, Greenland P, Liu K, et al. Leg symptoms in peripheral arterial disease: associated clinical characteristics and functional impairment. *JAMA*. 2001;286:1599-1606.
15. Cranley JJ. Ischemic rest pain. *Arch Surg*. 1969;98:187-188.
16. Khan NA, Rahim SA, Anand SS, et al. Does the clinical examination predict lower extremity peripheral arterial disease? *JAMA*. 2006;295:536-546.
17. Wennberg PW. Approach to the patient with peripheral arterial disease. *Circulation*. 2013;128:2241-2250.
18. Norgren L, Hiatt WR, Dormandy JA, et al. Inter-society consensus for the management of peripheral arterial disease (TASC II). *Eur J Vas Endovasc Surg*. 2007;33:S1-S75.
19. Armstrong EJ, Wu J, Singh GD, et al. Smoking cessation is associated with decreased mortality and improved amputation-free survival among patients with symptomatic peripheral artery disease. *J Vasc Surg*. 2014;60:1565-1571.
20. Lane R, Harwood A, Watson L, et al. Exercise for intermittent claudication. *Cochrane Database Syst Rev*. 2017;(12):CD000990.
21. Murphy TP, Cutlip DE, Regensteiner JG, et al; CLEVER Study Investigators. Supervised exercise versus primary stenting for claudication resulting from aortoiliac peripheral artery disease: six-month outcomes from the claudication: exercise versus endoluminal revascularization (CLEVER) study. *Circulation*. 2012;125:130-139.
22. Fakhry F, Fokkenrood HJP, Pronk S, et al. Endovascular revascularization versus conservative management for intermittent claudication. *Cochrane Database Syst Rev*. 2018;(3):CD010512.
23. Hageman D, Fokkenrood HJ, Gommans LN, et al. Supervised exercise therapy versus home-based exercise therapy versus walking advice for intermittent claudication. *Cochrane Database Syst Rev*. 2018;(4):CD005263.
24. McDermott MM, Spring B, Berger JS, et al. Effect of a home-based exercise intervention of wearable technology and telephone coaching on walking performance in peripheral artery disease: the HONOR randomized clinical trial. *JAMA*. 2018;319:1665-1676.
25. Ruiz-Canela M, Estruch R, Corella D, et al. Association of Mediterranean diet with peripheral artery disease: the PREDIMED randomized trial. *JAMA*. 2014;311:415-417.
26. Zahradka P, Wright B, Weighell W, et al. Daily non-soy legume consumption reverses vascular impairment due to peripheral artery disease. *Atherosclerosis*. 2013;230:310-314.
27. Heart Protection Study Collaborative Group. Randomized trial of the effects of cholesterol-lowering with simvastatin on peripheral vascular and other major vascular outcomes in 20536 people with peripheral arterial disease and other high-risk conditions. *J Vasc Surg*. 2007;45:645-655.
28. Kumbhani DJ, Steg G, Cannon CP, et al. Statin therapy and long-term adverse limb outcomes in patients with peripheral artery disease: insights from the REACH registry. *Eur Heart J*. 2014;35:2864-2872.
29. Wong PF, Chong LY, Mikhailidis DP, et al. Antiplatelet agents for intermittent claudication. *Cochrane Database Syst Rev*. 2011;(11):CD001272.
30. 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: randomized, double-blind trial. *J Intern Med*. 2007;261:276-284.
31. Morley RL, Sharma A, Horsch AD, et al. Peripheral artery disease. *BMJ*. 2018;360:j5842.
32. Bedenis R, Stewart M, Cleanthis M, et al. Cilostazol for intermittent claudication. *Cochrane Database Syst Rev*. 2014;(10):CD003748.
33. Salhiyyah K, Forster R, Senanayake E, et al. Pentoxifylline for intermittent claudication. *Cochrane Database Syst Rev*. 2015;(9):CD005262.
34. Stewart M, Morling JR, Maxwell H. Padma 28 for intermittent claudication. *Cochrane Database Syst Rev*. 2016;(3):CD007371.
35. Kleijnen J, Mackerras D. Vitamin E for intermittent claudication. *Cochrane Database Syst Rev*. 1998;(1):CD000987.
36. Nicolai SPA, Kruidenior LM, Bendermacher BLW, et al. Ginkgo biloba for intermittent claudication. *Cochrane Database Syst Rev*. 2013;(6):CD006888.
37. Campbell A, Price J, Hiatt WR. Omega-3 fatty acids for intermittent claudication. *Cochrane Database Syst Rev*. 2013;(7):CD003833.
38. American Surgical Association, New York Surgical Society, Philadelphia Academy of Surgery, Southern Surgical Association (US), Central Surgical Association. Results of a prospective randomized trial evaluating surgery versus thrombolysis for ischemia of the lower extremity: the STILE trial. *Ann Surg*. 1994;220:251-268.
39. Ouriel K, Veith FJ, Sasahara AA. Thrombolysis or peripheral arterial surgery: phase I results. TOPAS Investigators. *J Vasc Surg*. 1996;23:64-73.
40. Bradbury AW, Ruckley CV, Fowkes FGR, et al. Bypass versus angioplasty in severe ischaemia of the leg (BASIL): multicentre, randomised, controlled trial. *Lancet*. 2005;366:1925-1934.
41. Criqui MH, Langer RD, Fronek A, et al. Mortality over a period of 10 years in patients with peripheral arterial disease. *N Engl J Med*. 1992;326:381-386.