Peripheral Arterial Disease in Women

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Women with peripheral arterial disease (PAD) are not well identified in cardiology practice, are undertreated, and have different relative risks for development of PAD than men. Recognizing that PAD is considered a coronary artery disease risk equivalent emphasizes that primary care physicians and cardiologists need to be aggressive for screening and treatment of this disorder. This article reviews the prevalence and risk factors for PAD in women, sex-based differences in development of PAD, and current screening and treatment recommendations.
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Women with peripheral arterial disease (PAD) are not well identified in cardiology practice, are undertreated, and have different relative risks for development of PAD than men. Recognizing that PAD is considered a coronary artery disease (CAD) risk equivalent emphasizes that primary care physicians and cardiologists need to be aggressive in their screening for and treatment of this disorder. This article reviews the prevalence and risk factors for PAD in women, sex-based differences in development of PAD, and current screening and treatment recommendations.

PAD is a significant cause of morbidity and mortality in the United States. Between 5 and 10 million Americans are estimated to have PAD, with a higher prevalence in elderly women.[1,2] Approximately 4.5% of the general population

of both men and women over age 40 are affected by PAD. The prevalence of PAD doubles in patients with diabetes (9.5%).[3] In the PAD Awareness, Risk, and Treatment: New Resources for Survival (PARTNERS) program, which was a multicenter, cross-sectional study looking at 6979 patients over age 70 years or between 50 through 69 years with a history of cigarette smoking or diabetes, 29% of these patients had PAD, defined by an ankle brachial index (ABI) less than 0.9.[4] PAD is more common in men than women in patients under age 70; however, in patients over age 85, PAD is more common in women. Recent estimates show that in patients over age 85, the prevalence of PAD in women increases to 39% in an ambulatory population, compared with only 27% in men.[5,6] Large population-based studies estimate that PAD has an overall prevalence in women of about 12% to 15.6%.[5,7] The development of CAD in women lags approximately 10 years behind men and, therefore, it is not surprising that the prevalence of PAD peaks in women over the age of 80 years.[4]

Fewer than 10% of patients diagnosed with PAD present with intermittent claudication. Approximately 50% of patients present with pain symptoms that are atypical for PAD, and 40% to 60% of all patients are asymptomatic[3,8-10]; women are more likely than men to present with asymptomatic disease.[7] Interestingly, some suggest that the lack of symptoms of PAD may be related to lower activity levels. Vavra and Kibbe[5] and McDermott and colleagues[11] found a linear relationship between exertional leg symptoms and ABI only in patients who walked more than 4 blocks per week. The presence or absence of symptoms does correlate with survival. Patients with symptomatic PAD have a 15-year survival rate of 22%, as compared with a survival rate of 78% in patients without PAD.[12] Because most patients with PAD are asymptomatic, the patient's history is not helpful in the diagnosis of PAD. If physicians rely on the physical examination alone, they will miss 50% of PAD cases, and if they rely on the patient's history, they will miss 85% to 90% of PAD cases.[4,12,13] The progression to critical limb ischemia is rare, but is also more common in women.[7] The incidence of acute limb ischemia is estimated to be 14 in 100,000 cases. In population-based studies, the prevalence of critical limb ischemia is 1.5% in women and 0.9% in men[7]; however, if critical limb ischemia is present, patients have a mortality rate of 25% and a morbidity rate of 20%.[14]

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Risk Factors

Risk factors for development of PAD are similar to traditional CAD risk factors. Patients with PAD have a five- to sixfold increase in risk of morbidity and death from CAD and stroke.[4,5] In fact, in the National Health and Nutrition Examination Survey (NHANES) study, 95% of persons with PAD had at least one of the following risk factors for CAD: current smoking, diabetes, hypertension, and dyslipidemia.[2] Renal failure is also a strong risk factor for development of PAD. In addition to traditional risk factors, nontraditional risk factors such as serum thyrotropin levels, uric acid levels, C-reactive protein (CRP), and elevated homocysteine levels have all been associated with PAD in women.[15-21]

Current smoking is the strongest risk factor for PAD and was associated with a 5.48 odds ratio (OR) for PAD (adjusted for risk factors) in the NHANES survey.[22] A population-based study in the Netherlands looked at young women (aged 18-49 years) on oral contraceptive pills; in this study, smoking was associated with a 19.1 OR for development of PAD.[23] The Atherosclerosis in Communities study also confirmed smoking as one of the strongest risk factors for PAD, regardless of ethnicity.[24] A study in Spanish men showed that starting smoking at age 16 or earlier more than doubles the risk of future symptomatic PAD, regardless of the amount of exposure to cigarette smoking; there were no data for women.[25] The Edinburgh Artery study showed that cigarette smoking was a stronger risk factor for PAD than CAD.[26,27] Cigarette smoking is associated with reduced dietary antioxidant use, reduced high-density lipoprotein cholesterol, reduced diastolic blood pressure, elevated alcohol intake, elevated serum triglycerides, increased blood viscosity, and increased plasma fibrinogen.[28] Insulin resistance is higher in smokers compared with nonsmokers, and hemoglobin A_{1c} is dose-dependently elevated, as is homocysteine.[29,30]

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These comorbid conditions, which are more frequently found in smokers, only partially explain the mechanism for development of PAD. Direct toxic effects, such as increased intracellular and vascular adhesion molecules and elevated fibrinogen levels, are noted in patients with PAD who smoke, showing a mechanism of direct injury to the endothelium in these patients.[31] Unverdorben and colleagues[30] have studied the effects of smoking on the vascular endothelium; they summarized that smoking enhances platelet aggregability, increases blood viscosity, and shifts the pro- and antithrombotic balance toward increased coagulability (eg, fibrinogen, von Willebrand factor, intercellular adhesion molecule-1 and P-selectin).

Other traditional cardiovascular risk factors are associated with development of PAD. Hypertension—specifically elevated systolic blood pressure—was related to PAD in epidemiologic studies.[26] Diabetes is a risk factor for development of PAD.[32] In the Atherosclerosis Risk in Communities Study, a positive association between hemoglobin A_{1c} and risk of PAD (especially symptomatic) was found, which was thought to be related to the microvascular dysfunction in patients with diabetes.[32]

The association of elevated uric acid levels in women with PAD has been suggested in recent studies, independent of serum creatinine levels.[18,20] It is unclear whether elevated serum uric acid may be a surrogate for subclinical renal insufficiency, thus further strengthening the risk of renal failure to the pathophysiology of PAD. In epidemiologic studies, elevated inflammatory markers such as CRP have been identified as a risk factor for development of PAD in women.[5] In a community-based population study, elevated CRP alone did not seem to increase the risk of atherosclerosis, but CRP in addition to other risk factors (namely obesity) increases the risk for developing PAD.[5,33]

Sex-Based Differences

Sex-based differences in the development of PAD have been studied in select populations. In a study on patients with type 2 diabetes in Taiwan, older age and elevated systolic blood pressure were strongly associated with development of PAD in men, and elevated uric acid and insulin therapy were associated with increased risk in women.[19,34] Interestingly, an elevated body mass index was negatively associated with development of PAD in men, both in this study and in others.[34,35] Additional studies have suggested that calf muscle density and area are inversely related to the progression of PAD. When comparing patients in the lowest tertile of calf muscle percent fat to the patients in the highest tertile percent fat, the ORs for incident mobility loss were 0.18 and 3.5, respectively.[36] This begs the question of whether the increased weight carried by obese men could increase calf muscle mass and decrease the development of PAD in men as compared with women. Decreased muscle mass is associated with elevated 2-hour postprandial glucose levels.[37] Women are known to have decreased muscle mass compared with men, regardless of age,[38] and in older women, muscle quality is less than that of men.[39] Larger muscle mass requires more oxygenation and vascularity than fatty tissue. The constant increased demand may promote better collateral blood flow and be a negative risk factor for development of significant lower extremity stenosis. Decreased muscle mass and quality may be why women have an increased risk for development of PAD, despite similar risks, when compared with men, due to both the demand of the muscle and the metabolic effects of more adipose tissue on the peripheral circulation.[34]

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Screening

PAD is defined as a chronic atherosclerotic occlusive disease of the lower extremities defined by an ABI < 0.9. ABI is the most commonly used and preferred diagnostic screening test for PAD. It is also a very useful tool for prediction of cardiovascular risk.[40] ABI is the ratio of systolic blood pressure at the ankle as compared with the arm. Intermittent claudication is the presenting symptom in only about 10% of patients with PAD. Up to 90% of patients may have atypical symptoms or be asymptomatic.[4,7-9] Therefore, screening is recommended for those at high risk for PAD. The American College of Cardiology/American Heart Association (ACC/AHA) 2005 guidelines for the management of patients with PAD suggest screening all patients over 70 years of age, patients 50 to 69 years of age who smoke or have diabetes, patients younger than 50 years with diabetes and one

other risk factor for atherosclerosis, patients with leg symptoms with exertion, abnormal results on vascular examinations of the leg, and patients with coronary, carotid, or renal arterial disease.[9] These recommendations were based on the PARTNERS trial and NHANES data that showed that PAD is found in these populations of patients.

As described above, an ABI is the ratio of systolic blood pressure at the ankle as compared with the arm. A normal ABI is > 0.9. The ABI is a good screening test but it can be unreliable in patients with poorly compressible vessels. Poorly compressible vessels are usually secondary to calcification and are more common in patients with diabetes and chronic kidney disease.[41] In these patients, a toe-brachial index can be a more accurate tool for discovering PAD. The toe-brachial index is similar to the ABI and uses the blood pressure of the great toe as compared with the arm.[42] A normal toe-brachial index is > 0.7. The small arteries of the toe are less susceptible to calcification and provide a more accurate test in patients with calcification.

In patients with a normal ABI at rest and symptoms concerning for claudication, exercise testing should be performed on a treadmill following a standard protocol.[43] ABIs are performed before and after exercise, which causes decreases in peripheral resistance as the systolic blood pressure rises, resulting in a larger pressure gradient, and therefore a lower ABI.

In abnormal ABIs, segmental arterial pressures and pulse volume recordings can help to localize and predict the severity of disease. Significant changes between different segments can help to localize a focal area of stenosis. Pulse volume recordings use a pneumatic pressure cuff and pressure transducer to produce waveforms. In the presence of PAD, there is dampening of these waveforms, as well as decreased amplitude.[44] An abnormal ABI can be further evaluated anatomically with duplex ultrasonography, magnetic resonance angiography, computed tomographic angiography, and contrast angiography.

Screening for abdominal aortic aneurysms (AAA) in women is controversial. Current guidelines utilizing the US Preventative Services Task Force recommend screening for men aged 65-75 years with a history of smoking. There are no guidelines recommending screening for AAA in women. A recent cohort study evaluating more than 3 million individuals screened for abdominal aortic aneurysm in the United States estimated that using current guidelines, only 33.7% of large AAAs would be detected.[45] This is of concern because, using current guidelines, no women would ever be screened for AAA, despite estimates that 11% of large AAAs (> 5 cm) occur in women.[45] Although the incidence of aortic aneurysm is much lower in women than men, a higher percentage of women present with rupture, and the in-hospital mortality rate for women is much higher than for men. A recent model was developed, based on this cohort study, giving points to women who had a family history of abdominal aortic aneurysm, a personal history of PAD, CAD, high blood pressure, smoking (with escalating points in relation to amount smoked), high cholesterol, obesity, and age. Negative points were applied to factors that were considered to be protective against AAA, which included diabetes, exercise, and Hispanic and African American race.[45] In clinical practice, a woman over age 60 with multiple risk factors suggesting a high risk of AAA, such as family history, heavy smoking (> 0.5 packs per day), presence of PAD and CAD, and obesity, should be advise to get screened for AAA with ultrasound. Women with multiple risk factors are estimated to have a prevalence of AAA of 6.4%.[46] Unfortunately, until guidelines change, these screenings will need to be paid out-of-pocket by the patient.

Treatment

The major goal in the treatment of PAD is aggressive risk factor modification, to slow the rate of progression, reduce the associated cardiovascular morbidity and mortality, and improve quality of life by improving symptoms (Figure 1).[47] Risk factor modifications include both lifestyle changes and pharmacologic therapies. This includes smoking cessation, aggressive lipid-lowering therapy, and control of diabetes and blood pressure.

Smoking is the most significant risk factor for the development and progression of PAD. Patients who quit smoking have been shown to have a lower risk of developing critical limb ischemia and an increased survival rate when compared with those who continue to smoke.[48] Lipid therapy has been shown to reduce progression of claudication symptoms and reduce the risk of adverse cardiovascular events in patients with PAD.[49,50] The National Cholesterol Education Program Adult

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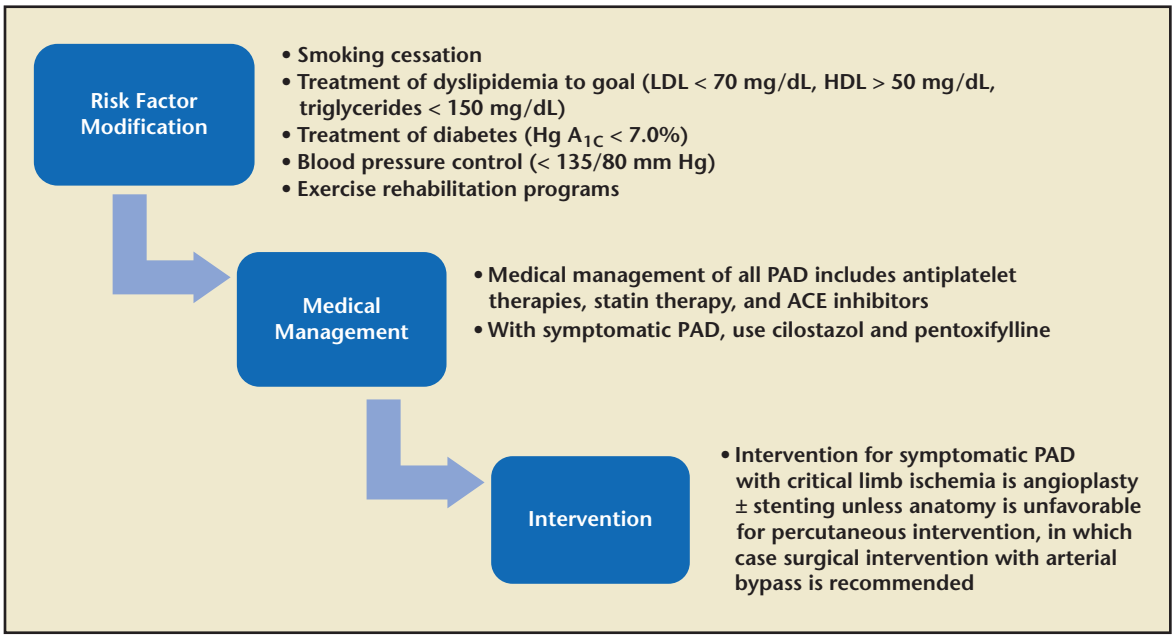

Figure 1. *Treatment of peripheral arterial disease (PAD) in women. ACE, angiotensin-converting enzyme; HDL, high-density lipoprotein; Hg A_{1C}, glycated hemoglobin; LDL, low-density lipoprotein.*

Treatment Panel III considers PAD a "coronary risk equivalent," and should be treated with the most aggressive lipid guidelines. Treatment with high-dose simvastatin was shown to increase walking distance by more than 60% compared with a 38% increase in placebo-treated patients in the Treatment of Peripheral Atherosclerotic Disease with Moderate or Intensive Lipid Lowering study.[51] Diabetes is another known risk factor in the development of PAD. Studies, including the Diabetes Control and Complications Trial, showed a reduction in cardiovascular events with intensive insulin therapy.[52] In the UK Prospective Diabetes Study, intense glycemic control decreased diabetes-related endpoints and diabetes-related deaths; however, it was not associated with a significant reduction in the risk of amputation due to PAD.[53] ACC/AHA 2005 guidelines for PAD still recommend that patients be treated aggressively to achieve a hemoglobin A_{1C} of < 7%.[54] Optimization of blood pressure is important in the management of PAD. Angiotensin-converting enzyme inhibitors have been shown to decrease cardiovascular morbidity in patients with PAD.[55] Ramipril was also found to improve pain-free walking distance in patients with PAD.[56] β-blockers were previously thought to be contraindicated in patients with PAD due to a theoretical risk of worsening claudication symptoms, which has not been proven in randomized controlled trials; however, β-blockers have been shown to reduce mortality in patients with CAD. Therefore, given the relative lack of evidence against the use of β-blockers in patients with PAD, they can be used in instances of mild to moderate PAD.[57]

Supervised exercise rehabilitation programs have been shown to reduce claudication symptoms. A meta-analysis of randomized controlled trials discovered that exercise increased maximum walking time and average distance walked before developing symptoms.[58,59] The most successful exercise regimens include 30 to 60 minutes of treadmill or track exercise per session with at least 3 sessions per week and a program length greater than 3 months.[10] Most patients can expect improvement in their symptoms within 2 months. Several mechanisms have been suggested for the improvement in claudication symptoms, including improved endothelial function by increases in nitric oxide synthase,[60] induction of vascular angiogenesis,[61] improved muscle metabolism,[62] reduced local inflammation by decreasing free radicals,[63] and increased exercise pain tolerance.[64]

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prevention of CAD and stroke. The Antithrombotic Trialists' Collaboration performed a meta-analysis showing that antiplatelet therapy with aspirin was associated with a significant decrease in the risk of myocardial infarction, stroke, or vascular death.[65] However, aspirin showed no statistically significant benefit on claudication symptoms.[66] Other antiplatelet agents, including ticlopidine, clopidogrel, and aspirin in combination with dipyridamole, have shown increases in walking distance. In the Clopidogrel Versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) trial, clopidogrel was more effective than aspirin in preventing vascular events.[67] Aspirin is still the drug of choice for the treatment of PAD, but clopidogrel may be an alternative in selected patients with symptomatic PAD, and in those who cannot tolerate aspirin.

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There are limited medications for the treatment of symptomatic PAD. Currently two medications are US Food and Drug Administration-approved for the treatment of intermittent claudication. Pentoxifylline works by decreasing blood viscosity and improving erythrocyte flexibility. Studies have revealed conflicting results of efficacy of pentoxifylline and show it is less effective than cilostazol.[68] Cilostazol is a phosphodiesterase inhibitor, working as a direct arterial vasodilator. It also suppresses platelet aggregation. In a meta-analysis of patients with stable moderate to severe claudication, 12 to 24 weeks of therapy with cilostazol increased maximal and pain-free walking distances by 50% and 67%, respectively.[69] Therefore, a therapeutic trial of cilostazol is recommended in patients with intermittent claudication, specifically if antiplatelet therapy and exercise rehabilitation are ineffective. Oral phosphodiesterase inhibitors used for inotropic therapy in heart failure lead to increased mortality; therefore, cilostazol is contraindicated in patients with heart failure.[70]

When medical therapy has failed or if the patient develops limb-threatening ischemia, peripheral or surgical revascularization can be offered. Balloon angioplasty, with or without stenting, can be useful for symptoms related to PAD. The long-term success of percutaneous transluminal angioplasty (PTA) depends on the site and length of the lesion. In general, patency is best in larger vessels with short, focal stenoses or occlusions. Disease of the aortoiliac vessels is considered "inflow" disease, and uncomplicated iliac stenosis has an initial PTA success rate of 90%, with a 70% 5-year patency rate.[71,72] PTA outcomes, with or without stenting, are comparable with surgical outcomes in long-segment aortoiliac disease and bilateral iliac occlusions.[73] Primary stenting is most commonly used when there is iliac occlusion, eccentric and/or calcified lesion, or disease involving a long segment.[74] The femoropopliteal segment is the most common site for treatable arterial disease. Balloon angioplasty is usually performed without stenting with procedure success exceeding 90%. However, long-term patency rates are poor, with 2-year patency rates ranging from 42% to 58%. This loss of patency may be higher in long or eccentric calcified lesions, occlusion instead of stenosis, and poor distal runoff.[75,76] Balloon expandable steel stents are not used in femoropopliteal arteries due to significant restenosis rates. The risk of restenosis is reduced with a nitinol stent compared with a steel stent.[77] PTA and surgery have similar outcomes for amputation-free survival and PTA is less expensive; therefore, PTA is recommended as first-line therapy for femoropopliteal disease.[78] Infrapopliteal disease is most often associated with diffuse disease, and physicians must take into account the extent, severity, and disease of the proximal vessels when considering revascularization. Inflow lesions should be treated first and symptoms re-evaluated, as symptoms may improve with better proximal flow. Technological advances of equipment have improved PTA success rates, up to 90%.[79] Currently, the goal of infrapopliteal percutaneous intervention is limb salvage[78]; however, as technology progresses and success and patency rates improve, PTA may be a reasonable option in the near future.

The 2005 ACC/AHA guidelines on the management of PAD recommend initial revascularization with surgery only when the arterial anatomy is not favorable for a percutaneous approach.[10] Patients who benefit from elective surgical revascularization are < 70 years of age, are not diabetic, and have limited distal disease. Inflow disease can be treated with aortobifemoral bypass, which has excellent long-term surgical results, and there is a lower threshold to intervene at this level. When extra-anatomic surgical procedures are used, there are lower long-term patency rates. Compared with aortobifemoral or aortoiliac bypass, which has an 85% to 90% patency rate at 5 years, the femoral-femoral bypass has 70% patency rate at 5 years, and the axillofemoral has 50% to 80% patency at 3 years.[10] Infrainguinal bypass is generally reserved for treatment of critical limb ischemia, and vein grafts have better long-term patency rates than synthetic grafts.

Preventing graft failure is an important issue with surgical revascularization. Treatment with antiplatelet or antithrombotic therapy appears to help prevent graft failure. Studies have shown that antiplatelet therapy may be more beneficial in prosthetic grafts and anticoagulation with warfarin in vein grafts.[80] Recommendations from the 2008 American College of Chest Physicians guidelines state that aspirin therapy should be started preoperatively and continued indefinitely in patients with infrainguinal bypass. Warfarin or other anticoagulants are not recommended, except in those at high risk for bypass occlusion and limb loss.[81]

Conclusions

In summary, PAD is underrecognized and undertreated in women. Primary care physicians, as well as cardiologists, need to consider screening women more aggressively with ABIs, as many women are asymptomatic. Risk factors differ between men and women. Cigarette smoking is the strongest risk factor for development of PAD in women. Treatment of asymptomatic PAD is similar to secondary prevention for CAD. Treatment of symptomatic arterial disease includes medical therapy, rehabilitation, and percutaneous revascularization. Surgery is reserved for those with unfavorable anatomy. It is hoped that increased recognition and treatment will reduce the morbidity and mortality associated with this disease in women. ■

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Main Points

- Women with peripheral arterial disease (PAD) are not well identified in medical practice, are undertreated, and have different relative risks for development of PAD than men.
- Patients with PAD have a five- to sixfold increase in risk of morbidity and death from coronary artery disease and stroke.
- Current smoking is the strongest risk factor for PAD.
- An ankle brachial index is the most commonly used and preferred diagnostic screening test for PAD.
- The major goals in the treatment of PAD are aggressive risk factor modification to slow the rate of progression, reduce the associated cardiovascular morbidity and mortality, and improve quality of life.

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