Peripheral arterial disease in women

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Peripheral arterial disease (PAD) affects a significant portion of the United States population, and much research has been conducted on identifying populations at risk for PAD, evaluating appropriate diagnostic modalities for PAD, studying the effect of risk factor reduction on PAD progression, and determining the best method of treatment for symptomatic PAD. However, most PAD research and clinical trials have focused on whole populations, or populations consisting mostly of men. Little data exist with respect to PAD in women. The goal of this review is to highlight what is known about gender-related differences for PAD. (J Vasc Surg 2013;57:18S-26S.)

Peripheral arterial disease (PAD) is a considerable public health burden because it impairs quality of life and leads to high rates of morbidity and mortality. It currently affects between 5 and 10 million Americans, with the expectation that these numbers will greatly increase as the population ages and becomes more obese and more likely to suffer from diabetes. At the time patients are diagnosed with PAD, >50% present with asymptomatic disease or complain of atypical leg pain. A smaller percentage of patients who have PAD also have intermittent claudication distinguished by cramping pain, discomfort, or a sensation of weakness in the legs that occurs with exertion and is relieved by rest. Although claudication symptoms remain stable in 70% to 80% of patients, approximately 10% to 20% worsen and 1% to 2% of patients will progress to critical limb ischemia (CLI) over a 10-year period.[1]

Some patients experiencing amputations because of CLI have not had PAD symptoms 6 months before being diagnosed with CLI. Thus, it is now believed that PAD does necessarily advance through the traditional stages of the classification schemes. In addition to the functional impairment, PAD is a strong marker for cardiovascular events. Patients with PAD have a fivefold to sixfold increased risk of death or morbidity from other atherosclerotic disease processes such as stroke or coronary artery disease (CAD).[2] Interestingly, although the risk of death is higher in those with PAD vs without, it is similar in both asymptomatic and symptomatic patients.[3]

Caucasian men historically develop PAD. Although former studies detail a lower frequency of PAD in women, current data suggest PAD frequency in women may be equal to and perhaps greater than in men. PAD is generally underdiagnosed, but gender bias may result in a reduction of screening and management of predisposing risk factors for women. Differences between the sexes in the time it takes to diagnose PAD may also contribute to the worse outcomes observed after treatment for women. Hence, the intent of this review is to provide an update on gender-based variations in PAD and show how these differences may influence PAD-related outcomes in women.[4]

PREVALENCE OF PAD IN WOMEN

The American Heart Association estimates that PAD affects ~8 million Americans aged >40 years.[5] Furthermore, it is widely recognized that the prevalence of PAD increases with age; in patients aged <60 years, the prevalence is ~3%, but in patients aged >70, the prevalence can approach 15% to 20%.[6,7] The American College of Cardiology (ACC)/American Heart Association (AHA) 2005 practice guidelines for the management of patients with PAD maintain male sex as a PAD risk factor; however, these data were from 1985.[1] More recent studies have reported conflicting results, with the prevalence of PAD in women being similar or higher than that of men.[8-11] Population studies yielded a prevalence of PAD of 16.5% and 19.2% in men and women, respectively, which was not statistically different.[8] However, there was a significant sex-based presentation for asymptomatic PAD, with a higher prevalence among women than in men (13% vs 9%; $P < .03$). Several factors may exist in these studies that contribute to sex-based differences in prevalence.

Selection bias may contribute to whether the disparities between genders are mirrored in the groups of patients. A study from Vogt et al[12] showed that in women aged >60 years with PAD, 6.5% refused ankle blood pressure and were thereby excluded from the study. Along similar lines, data were omitted for nearly 20% of the participants in the National Health and Nutrition Examination Survey (NHANES) study. Among these individuals, there were more women and the patients were older.[13] Although the investigators for NHANES did not provide an explanation for this discovery, some have suggested that women with the diagnosis of PAD may suffer from more functional impairment from their disease, leading them to stay at

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home more and less likely to seek care from a physician or enroll in a clinical research study.

Skewed data may also be caused by oversampling of subjects in certain demographic groups. Because the occurrence of PAD escalates with age, most research tends to concentrate on older patients, generally those aged >50 years. Yet, PAD frequency among women may differ within elderly age groups. As such, a study of demographic data from PAD patients evaluated at a vascular laboratory revealed that women were 3.3 years older than men and made up a larger percentage of the patients aged >65 years (69% women vs 57% men).[14] Other studies, while reporting a greater frequency of patients with PAD at age ≥65 years, have reported a higher prevalence of PAD among women.[8,15] Diehm et al[9] noted in their study that men (19.8%) had a higher incidence of PAD than women (16.8%). However, for women, the prevalence of PAD increased with age more than it did with men. In patients aged <70 years, the occurrence of PAD was 12% for women and 17% for men. Interestingly, for patients aged >85 years, women had a higher prevalence of PAD (39%) than men (27%).[9]

It is possible that the prevalence of PAD in men may be due to a bias in screening and diagnosis. Results of a survey recently conducted of Texan female veterans found that women are not as likely to talk about a diagnosis of PAD with doctors.[16] Even though 47% of the respondents were at high risk for cardiovascular disease (CVD), two-thirds reported not discussing vascular-related issues or disease with their doctor. Women are also reported to be disproportionately under-represented in randomized controlled trials for vascular disease.[17] Specifically, for trials on lower extremity revascularization, women represented 22.4% of study participants, yet the Nationwide Inpatient Sample data showed that women actually represented 41.3% of this population, indicating that randomized controlled trials on lower extremity revascularization under-represented women by ~50%. Thus, under-representation of women and under-reporting of symptoms from women contribute to the conflicting data on prevalence of PAD in women.

RISK FACTORS FOR PAD AMONG WOMEN

The risk factors for PAD and CAD are comparable and include smoking, age, diabetes mellitus, hypertension, and dyslipidemia.[5] Among these risk factors, diabetes and smoking are associated with the highest odds ratios for developing PAD (3.0 and 4.0, respectively).[5] Although risk factors such as diabetes mellitus, hypertension, hyperlipidemia, and tobacco use are more frequent in African American populations than in Caucasian populations, these risk factors have been mostly reported to be similar for men and women, with a few exceptions. Vouyouka et al[18] found that among >370,000 inpatient surgical hospitalizations for PAD, women were more likely to be older, obese, and black. Others have shown that women presenting with PAD tend to be older and have dyslipidemias.[15,19]

Supporting the role for obesity among women with PAD, Lu et al[20] found that among women, a positive relationship existed between the waist-to-thigh ratio and the waist circumference and PAD. Urine and blood levels of cadmium were associated with PAD in men and women, but the odds ratio for women was significantly lower than for men.[21]

Lastly, as an independent association between hypothyroidism and CAD has been demonstrated, Mazzeffi et al[22] investigated whether hypothyroidism is associated with PAD as well. They found a gender effect that it is positively associated in men but negatively in women.[22] Although it is unknown why some of these gender-based differences in risk factors may exist, it has been reported that gender-based differences exist for the management of these risk factors.

The Reduction of Atherothrombosis for Continued Health (REACH) registry recruited >68,000 outpatients aged >45 years.[23] Unfortunately, risk factor control was much less frequent for patients with the diagnosis of PAD than for patients with a diagnosis of CAD. This included the management of blood pressure, glycemia, total cholesterol, and smoking cessation. Upon further evaluation, men were found to be nearly twice as likely than women to have optimal risk factor control. Similarly, an observational population-based study of patients with PAD from Quebec found that more men than women were treated with statins, angiotensin-converting enzyme (ACE) inhibitors, and antiplatelet agents.[24] Lastly, a study by Klein-Weigal et al[25] evaluated risk factor management among medical physicians vs vascular surgeons and found that medical doctors treated more women than men compared with vascular surgeons. Medical doctors were also more likely to document smoking and diabetes and prescribe statins than vascular surgeons. Thus, gender-based disparities with risk factor modification in patients with PAD exist and could ultimately affect the progression of PAD in women, especially as the women age.

Patients who smoke increase the odds of developing symptomatic PAD by fourfold compared to nonsmokers.[26] Cigarette smoking remains the most important risk factor for the development of PAD. The probability of PAD multiplies with the amount of smoking exposure and may be stopped by smoking cessation.[11] He et al[11] conducted a study in China and discovered that smokers who quit smoking ≤10 years had a sustained risk of developing PAD. The risk was minimal if the patient quit for >10 years.[11]

According to the Centers for Disease Control, the prevalence of cigarette smoking from 2003 to 2007 in Americans was ~20%, a relatively stable number over time. The frequency of women who smoke is between 17% and 19%, which is below average.[27] Interestingly, women with a diagnosis of PAD are more apt to have smoked or are current smokers than women without PAD. However, some reports show a lower prevalence of tobacco use among women with PAD than among men.[28-30]

There is a connection between the development of PAD and C-reactive protein (CRP) levels.[31] Elevated levels

of CRP may be a marker for PAD severity. Vidula et al[32] recently reported that an increase in D-dimer and CRP, both inflammatory markers, was predictive of 1-year all-cause and cardiovascular mortality. The Multiethnic Study of Atherosclerosis (MESA) results showed women had higher levels of CRP than men, even after adjustment for comorbidities, hormone status, and age. Decedents were more likely to be male in the report by Vidula et al.[33] Finally, the specific role of inflammatory markers has yet to be established in the diagnosis or management of PAD patients.

With respect to other coexisting conditions that may affect the risk for developing PAD, such as diabetes mellitus or hypertension, data suggest that the risk is similar between the sexes. However, some evidence suggests that CVD not related to PAD is less prevalent in women than in men.[34] The PAD Awareness, Risk and Treatment: New Resources for Survival (PARTNERS) study, enrolled 6979 patients aged >50 and <70 years old with a medical history of tobacco use or diabetes mellitus to ascertain the relationship between CVD and PAD. Within this group of patients, 53% had a past medical history of CVD or PAD. Of the PAD-only group, 61% were women compared with 44% of the PAD and CVD group.[2] Because patients with PAD and CVD typically receive more aggressive management of risk factors, such as hyperlipidemia and hypertension, than patients with only PAD,[2] a diminished identification of PAD in female patients may result in less risk factor modification. Patients with PAD from both sexes possess an overall higher risk of CVD-associated morbidity and mortality.[35]

Estrogen and other sex hormones have vasoprotective properties that lower the prevalence of atherosclerosis in women of a younger age, yet estrogen is a risk factor for the development of CVD in women of an older age. After menopause, therapy with estrogen can cause adverse changes, such as increased triglycerides and low-density lipoproteins and a concurrently decreased high-density lipoprotein in the lipid profile.[36] Women have also been found to have a better vasodilation response to nitric oxide compared with men, but this diminishes after menopause.[37] Premenopausal women have also been found to have significantly more circulating endothelial progenitor cells than age-matched men and menopausal women.[38] The mechanism that accounts for these differences in premenopausal women is thought to be secondary to the actions of estrogen. Mendelsohn et al[39] demonstrated that the estrogen-estrogen receptor (ER) complex can increase the protein expression of endothelial nitric oxide synthase (eNOS), the enzyme that synthesizes NO in endothelial cells. Because one of the main cardioprotective molecules is NO, this may be one mechanism by which estrogen lowers the risk of developing CVD.

Observational studies have suggested that hormone replacement therapy (HRT) over the long term may be beneficial, even though cardiovascular event risk may be higher over the short term. The Rotterdam study consisted of 2196 women (aged 55-80 years). Women who used HRT for >1 year had a 52% decreased risk of PAD. The risk of developing PAD was not affected with HRT use for ≤1 year.[40] However, larger well-designed trials like the Heart and Estrogen/Progestin Replacement (HERS) and Women's Health Initiative (WHI) have not demonstrated a benefit from using HRT with respect to PAD or CVD.[41-43] Two WHI trials: estrogen alone and the estrogen plus progestin trial revealed more events related to PAD or reinterventions related to PAD at early time points.[44,45] Neither study, however, discovered an increase in PAD incidence in those taking HRT, and the HERS trial reported no change in the rate of events related to peripheral vascular disease.[42,44-46]

In summary, the use of inflammatory markers, such as CRP, to diagnose or manage PAD is still investigational. The prevalence of diabetes mellitus, hypertension, hyperlipidemia, and tobacco use remain similar in men and women who have PAD. However, because women more often present with asymptomatic PAD and are less often diagnosed with CVD risk factors, they may not receive the same risk factor modification therapy as men. Lastly, HRT does not appear to reduce the odds of developing PAD in postmenopausal women and may even increase the risk of morbidity from vascular interventions.

PRESENTATION OF PAD AMONG WOMEN

Variability exists in the presentation of PAD. Symptoms of PAD are classified according to the Fontaine or Rutherford classifications, but patients do not always present as a logical progression through these classifications or stages. In accordance with the 2005 ACC/AHA practice guidelines for the management of patients with PAD, intermittent claudication will manifest in <10% of patients with PAD[1,2] Approximately 50% of patients with PAD will manifest atypical symptoms of pain, and the remainder of patients (40%) will be asymptomatic. Most studies have shown that asymptomatic disease is more prevalent in women than in men.[2,15,47]

Furthermore, an interview-based study at the University of Minnesota found subtle differences in how men and women described their symptoms of claudication, with twice as many women as men describing their symptoms with pathophysiologic descriptions.[48] However, studies have suggested that variation exists among women, in the frequency of different symptoms. McDermott et al[47] reported that in a study of disabled elderly women, 63% presented with no complaints of leg pain. A study of Swedish patients reported that a larger percentage of women presented with intermittent claudication vs American and Dutch groups, although women (12.9%) with the diagnosis of PAD were more prone than men (9.4%) to present with no leg pain symptoms ($P = .03$).[8]

Activity level is possibly related to the higher occurrence of asymptomatic disease in women. Recently, McDermott et al[49] reported a linear relationship between disease severity and the presence of exertional leg symptoms in asymptomatic women with PAD, but only among patients who walked >4 blocks per week. This linear

correlation was not observed in less active women who walked <4 blocks per week.[49] Also, women may present with unusual signs that are ascribed to other comorbidities, such as spinal stenosis. Because a substantial number of patients are diagnosed by primary care providers who draw on patient history more often than noninvasive vascular testing of the ankle-brachial index (ABI), the patient's activity level should be ascertained during screening for those patients who are suspected to have PAD; this will help establish whether a lack of symptoms is an indicator of the presence of disease.

An increase in asymptomatic disease, associated with a decrease in recognition and later intervention, may produce a higher percentage of women who present with CLI and severe disease than men. A study from Northwestern University reported that when patients were sent to the vascular laboratory for evaluation of suspected PAD, women were more likely than men to be diagnosed with severe disease based on the ABI.[14] A study from Italy demonstrated a similar finding, that women who were sent to the vascular laboratory for evaluation of PAD more often presented with symptoms of CLI than men (13% vs 4%).[15]

Treatment of patients with CLI requires substantial resources, because CLI eventually necessitates intervention; fortunately, this represents a small proportion of all patients who have PAD. In addition, a significant problem associated with the delay in presentation or presentation with more severe disease in women is that this may account for why women undergo fewer revascularization procedures and more amputations than men (see below).

When compared with men, data suggest that women more often present with advanced disease, have a poorer quality of life, and baseline lower extremity function. In a 403-patient study by Collins et al,[16] women were more likely to have impaired walking scores compared with men with PAD and women without PAD. Furthermore, physical function and general health scores were lower for women with PAD than men with PAD.[16] Comparable results were reported in a study by McDermott et al.[50] In a group of 273 men and women with PAD, women had lower walking speeds, shorter 6-minute walking distances, and lower performance scores, even after adjusting for comorbidities and leg symptoms.[50] The authors proposed that a correlation between lower extremity impairment and leg strength may exist and that leg exercises to strengthen the legs may be helpful for patients with PAD.

Most recently, Gardner et al[51] showed that women with intermittent claudication ambulated slower than men in a community setting. Specifically, they found that women had a lower adjusted daily maximal cadence for 5 minutes of ambulation, 1 minute of ambulation, and for intermittent ambulation. These changes in women correlated with changes in their calf muscle oxygen saturation during exercise. Thus, although women who have PAD may have worse function of the lower extremities than men, the question remains whether this decreased lower extremity function can prognosticate outcomes.

Although research has failed to demonstrate that diminished function of the lower extremities in individuals diagnosed with PAD is related to adverse clinical outcomes, data appear to suggest that a relationship exists between function and quality of life in individuals diagnosed with PAD. A decrease in quality of life among patients diagnosed with PAD has been reported with women who carry the diagnosis of PAD compared with men, when functional status is controlled for.[52] A study from the University of California at Los Angeles found that among patients with PAD, after controlling for disease severity, women described more physical dysfunction, pain, and mood disturbances than men, leading to lower overall quality of life. The authors ascribe these finding to sex-based differences because the results were established despite disease severity, comparable age, and an increased occurrence of associated comorbidities in the men, which can negatively affect quality of life.[52] The decreased quality of life may be related to depression.

Smolderen et al[53] reported that women with newly diagnosed PAD experienced a fourfold greater odds of baseline depression as well as development of subsequent depressive symptoms than men aged ≥65 years. Because worse outcomes after revascularization of an affected limb have been associated with depression, these data may have real clinical importance.[54]

Exercise may enhance quality of life in patients with diminished function of the lower extremity in the setting of PAD. In addition, exercise is known to reduce overall cardiovascular risk for death. McDermott et al[55] recently conducted a randomized controlled trial that found that treadmill exercise and resistance training in patients with PAD, with and without symptoms, improved walking performance, stair climbing, and quality of life. However, no gender analysis was performed for this study.

DIAGNOSIS OF PAD

Most patients with PAD are asymptomatic, although the use of screening questionnaires for the presence of symptoms can help to discover PAD. Physical examination can be informative, especially the findings of carotid or other bruits, differential blood pressure measurements, and diminished or absent peripheral pulses. Use of more noninvasive testing that is objective is necessary if patients are at high risk for developing PAD. The World Health Organization/Rose Claudication questionnaire can be used. However, although it has been found to have a high specificity for the detection of PAD, it has a low sensitivity.[6] Several studies maintain that using only symptoms to diagnose PAD can result in a high proportion of false-negative results.[9,11] He et al[11] conducted a study of Chinese patients for which PAD prevalence was 12% when diagnosed by the Rose Questionnaire but 16% when an ABI <0.9 was used. Prevalence was increased to 20.7% when using a combination of the two methods.[11] Therefore, although patient history and physical examination are helpful for the general diagnosis of PAD and to

assess cardiovascular risk, objective studies are important when forming a definitive diagnosis.

The ABI is the standard screening study for the diagnosis of PAD. The Inter-society Consensus for the Management of PAD (TASC II) document details the standard measure of ABI.[56] An ABI <0.9 indicates the patient has PAD. Used in combination with segmental plethysmography or pulse volume recordings (PVRs) increased the accuracy to 95%.[7] However, the ABI is not without challenges, because it can be falsely elevated to values >1.4 in patients with PAD but noncompressible calcified arteries, often observed in patients with diabetes mellitus. Most studies usually exclude patients with ABI elevated >1.3 to 1.4. A review of ABIs performed as part of the PARTNERS program showed that male sex was positively associated with a high ABI.[57] Furthermore, those with a high ABI were shown to be at an increased risk for foot ulcers and neuropathy.

Exercise testing using heel raises or a treadmill and measurement of the ABI may improve the sensitivity for patients with exertional leg symptoms and a normal resting ABI.[58] In a 396-patient study of patients who were referred to a vascular laboratory for rest pain, intermittent claudication, and ulceration, the ABI was <0.9 in 31%, and 46.2% of the patients had an ABI >0.9 at rest. After a 5-minute walk on a treadmill set with a 12% incline at 2.0 miles/h, the ABI fell <0.9 in 31%, which confirmed the diagnosis of PAD.[59]

For the ABI, 0.9 is typically the cutoff for the diagnosis of PAD, with values <0.9 indicating the presence of PAD. Although different ABI thresholds for the diagnosis of PAD are not standard, some research has suggested that the limit should be different between the sexes. The Multiethnic Study of Atherosclerosis used an ABI limit of 0.88 to reevaluate the PAD prevalence in women. The prevalence of PAD in women dropped from 3.5% to 2.2% and the ratio for women to men inverted from 1.3 to 0.8. Thus, the authors suggested that the use of an ABI of 0.9 to indicate PAD may overestimate PAD prevalence by 37% in non-Hispanic Caucasian women and by 36% in black women.[60] Use of a lower ABI limit in women has been suggested to be necessary due to smaller-sized arteries in women[61] or to the relationship between ABI and height. Results of the Atherosclerosis Risk in Communities (ARIC) study found differences in the average ABI between men and women, but after adjusting the ABI values for height, the differences were eliminated.[62] Nevertheless, given that the standard error from measurement to measurement with the ABI is ~0.15, these differences may not be great. Thus, most physicians use an ABI <0.9 to diagnose PAD, regardless of the patient's sex.[1]

The reason for using the ABI as a criterion is because the ABI has been shown to be related to PAD severity. For instance, patients with ABIs of <0.5 have been found to have a greater risk for CLI, and ABIs of <0.4 are associated with rest pain or tissue loss, or both.[1] Increased mortality is associated with a lower ABI. A recent study of 1101 patients from the Prevalence of PAD in Patients with Acute Coronary Syndrome registry showed that patients with an ABI of <0.9 and acute coronary syndrome were more likely to have other cardiovascular risk factors, such as diabetes mellitus and stroke. These patients also had a greater risk of death and were more likely to develop heart failure than patients with an ABI of >0.9.[63]

The Ankle Brachial Index Collaboration group conducted an epidemiologic review to determine if the ABI would improve the cardiovascular risk assessment of the Framingham risk score (FRS). Interestingly, the study reported a higher 10-year risk of death for both men and women when using the ABI and even after adjusting for the FRS. The effect was most dramatic for women.[64] Thus, the authors concluded that incorporation of the ABI into cardiovascular risk stratification assessment may improve the accuracy of the prediction and lead to better risk factor modification.

Duplex ultrasound imaging is a safe and effective method of determining the presence and location of stenoses and occlusions in the periphery without radiation. B-mode imaging provides a two-dimensional image of the artery wall and displays plaque characteristics, which may be important in determining risk. Color-flow Doppler and pulsed-wave Doppler evaluations define the degree of stenosis according to velocity measurements.[65] Because the test is inexpensive and risk-free, ultrasound imaging has great utility as a means of identifying subclinical atherosclerosis before the development of symptoms. Ultrasound screening of carotid and femoral arteries in a population with low or intermediate FRS was undertaken to determine whether patients who would benefit from intensive risk modification could be identified. Unlike men, in whom the presence or absence of risk factors did not predict the frequency of finding plaque, only a small number of women without risk factors and aged <50 years demonstrated the presence of plaque. This indicates that screening for PAD in this group provides little advantage.[19]

Other imaging, such as magnetic resonance imaging (MRI) or computed tomography (CT), is normally obtained for patients with a PAD diagnosis to more precisely determine the location of disease and determine if the anatomy is amenable to revascularization. The gold standard for the diagnosis of PAD remains contrast angiography; however, this evaluation modality is invasive and associated with risks, including contrast-induced nephropathy, local injury to the artery, and radiation exposure. MR angiography (MRA) is not used for first-line screening because it is costly, time-consuming, and exposes the patient to risks, such as contrast-induced nephropathy and anxiety, for patients who are claustrophobic. MRA also requires special software for postimaging processing and knowledge of how to use this software. However, MRA does have a sensitivity of 90% to 94% and a specificity of 90% to 94% for the diagnosis of PAD.[2]

TREATMENT AND OUTCOMES

The treatment goals in patients with PAD have two intents: decrease cardiovascular morbidity and mortality

and improve limb-related symptoms, thus improving the quality of life. These goals are achieved by a combination of reduction of risk factors, medical treatment of claudication, and revascularization when indicated. Smoking cessation is imperative. Treatment of coexisting medical disease, such as diabetes mellitus, hyperlipidemia, and hypertension, has been reported to reduce morbidity and mortality in patients diagnosed with PAD.[36] An example is the use of ACE inhibitors for hypertension. ACE inhibitors have been reported to lower the risk of cardiovascular events in PAD patients.[66] Statin use may improve walking distance and speed in claudicants as well as slow progression of disease.[67] In the HERS trial, statin use in women decreased the risk of CAD and myocardial infarction and appeared to abrogate some of the detrimental effects of HRT.[68]

The research on the effect of antiplatelet agents on the progression of PAD is not as clear. The Clopidogrel vs Aspirin in Patients at Risk of Ischemic Events (CAPRIE) study in 1996 enrolled nearly 20,000 patients, including 6,452 who were diagnosed with PAD. Patients were randomized to receive clopidogrel or aspirin for ~2 years. Clopidogrel reduced the risk of myocardial infarction, stroke, or vascular death for patients with symptomatic PAD by 24% compared the cohort that received aspirin.[69] More recently, a meta-analysis was performed of randomized controlled trials using aspirin in patients diagnosed with PAD. This study found that the risk of nonfatal stroke was reduced by aspirin alone or in combination with dipyridamole, but the risk of cardiovascular events, nonfatal myocardial infarction, cardiovascular mortality, and all-cause mortality was not reduced.[70]

TASC II recommended the use of antiplatelet therapy, particularly aspirin, for patients with PAD; however, the data only conclusively supported use in patients with cerebrovascular disease or CAD.[56] No recommendations were made based on sex in the TASC II document for patients with PAD.

Research has also found that PAD patients with a concomitant diagnosis of CAD are more prone to be treated with an antiplatelet drug, ACE inhibitor, or statin than those who do not have a concomitant diagnosis of CAD.[71] In the American Vascular Association Screening Program, of the 2,446 people enrolled, PAD was diagnosed in 9%. Of those patients with PAD, only 47% were found to be receiving statins or antiplatelet agents, and more men (58%) were receiving antiplatelet agents than women (40%). A similar pattern was observed for statin use, with 87% of the men and 63% of the women reporting use.[71]

Sigvant et al[34] recently conducted a study in Sweden and reported a similar pattern. Women diagnosed with PAD were less likely to seek pharmacologic treatment for risk factor reduction. When compared with women, the odds ratio for men receiving pharmacologic therapy was 1.3 for β-blockers or ACE inhibitors, 1.3 for lipid-lowering therapy, and 1.6 for antiplatelet therapy.[34] These findings are similar to a study undertaken in Canada evaluating differences in the use of antiplatelet agents, statins, and ACE inhibitors between men and women. Although antiplatelet therapy was similar for men and women, men were much more likely to receive all three treatments (22.4% vs 18.2%; $P < .005$), and more women than men used only one agent (33.4% vs 30.0%).[24]

A program of supervised exercise is recommended for patients with intermittent claudication. Research has established that following a regular exercise regimen can improve the total distance PAD patients can walk.[72] Two medications, pentoxifylline and cilostazol, have been approved by the U.S. Food and Drug Administration for use in claudication. The response to pentoxifylline is small. Cilostazol, a phosphodiesterase III inhibitor, has improved peak treadmill performance and quality of life in multiple randomized trials.[73] Revascularization may be indicated for patients who have more advanced disease or progression of symptoms.

Clear indications for revascularization include ischemic rest pain, ischemic ulceration, gangrene, or symptomatic disabling claudication. The decision to pursue or not pursue revascularization in women may be influenced by their higher rate of asymptomatic presentation. A study from Northwestern University reported that men were more likely to undergo an intervention for their PAD than women, even when considering only patients with CLI. Men were also more likely to be selected for intervention than women, even after controlling for potential confounding factors.[14] Fortunately, a recent reassessment of patients evaluated in the vascular laboratory at this same institution was just conducted (15 years after the first publication). These data indicate that this gender bias has been rectified since the earlier study, possibly because of increased awareness of the original data.[74]

Women are usually older compared with men and have worse disease when they have lower extremity revascularization. Procedural outcomes for women could be negatively affected because of these factors.[75,76] In a study of patients from Albany, of 5,880 procedures, 13% of men but only 8% of women underwent interventions for intermittent claudication. However, 90% of women vs 81% of men underwent intervention for limb salvage.[75] Evaluating procedural outcomes, this study indicated that graft patency was the same between men and women. Ahchong et al[77] analyzed 211 infrainguinal bypass procedures in China and reported contrasting results: women had worse 3-year graft patency results (33%) than men (49%). They postulated that this was secondary to the fact that women had smaller infrapopliteal arteries and vein conduits than men (2.0 vs 2.5 mm; $P = .03$).[77] These findings were supported by an analysis of the clinical database Project of Ex Vivo Vein Graft Engineering via Transfection III (PREVENT III) database in which women had more adverse events, including graft failure and limb loss, after vascular bypass grafting compared with men.[78]

Hormone replacement therapy in postmenopausal women has been associated with worse outcomes after lower extremity revascularization in women. Timaran et al[79] analyzed outcomes of women after iliac angioplasty

and stenting that showed a significant decrease in 5-year primary patency rates when using HRT (HRT 49% vs non-HRT 74%; $P = .02$).[79] A different study from the same institution observed that HRT had a similar effect on patency in women after femoropopliteal bypass grafting.[80] As noted by the HERS study, patients receiving HRT are at an increased risk for developing venous thromboembolic events.[46] The conclusions from this study may help to clarify the increased risk of peripheral arterial events observed in the WHI studies.[44,45] From these studies, authors have suggested that women with PAD taking HRT should consider discontinuing the HRT 4 to 6 weeks before a vascular intervention.[36,46]

Although a high rate of postoperative wound complications in women after revascularization was noted in some sex-based outcomes studies, there was no significant difference in mortality between men and women.[75,81] The PREVENT study, which included 1400 patients who received lower extremity revascularization for CLI, reported a 39% wound complication rate by 30 days.[81] Female gender and oral anticoagulation were the only variables that independently predicted wound complications, with an odds ratio of 1.4. Although wound complications were associated with more deaths and limb loss, they were not associated with graft patency. Other investigators have proposed that women with diabetes are at greater risk for complications than men with diabetes.[82,83] Nguyen et al[81] suggested that hormonal factors, and the amount and distribution of body fat, may be factors in the increased risk for women; however, these variables were not quantified.

Vouyouka et al[18] did find a higher postoperative mortality in women of 5.26% vs 4.21% in men ($P < .0001$). In addition, all types of vascular surgery, including endovascular and open revascularizations and major amputation, were statistically more likely to be complicated by bleeding in women, with an odds ratio of 1.33. A higher rate of periprocedural infection was observed after open revascularizations, a combination of open and endovascular procedures, and major amputations. No difference in infection rates between men and women were found after strictly endovascular procedures, but the overall infection rate for these interventions is low.

CONCLUSIONS

Female sex has an important effect on the diagnosis and treatment of PAD. Women with PAD are more likely to present without symptoms. As a consequence, their vascular disease has been underdiagnosed and undertreated. As the population ages, the prevalence of PAD will increase significantly. Among the elderly, there are more women than men, with the disparity being greatest in the oldest age groups; consequently, morbidity and mortality from PAD will become increasingly common for women. There has been an increased effort to delineate the effects of sex on the clinical burden and risks presented by PAD. Better knowledge of these effects will hopefully result in the development of strategies to achieve sex-specific cardiovascular risk reduction and improvement in overall quality of life for women.

AUTHOR CONTRIBUTIONS

Conception and design: VT, AV, MK
Analysis and interpretation: VT, AV, MK
Data collection: VT, AV, MK
Writing the article: VT, AV, MK
Critical revision of the article: VT, AV, MK
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