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Sex Differences in Peripheral Artery Disease

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Abstract

Peripheral artery disease (PAD) is a prevalent condition that confers substantial morbidity and mortality and remains underdiagnosed as well as undertreated in the overall population. Although PAD prevalence is similar or higher in women compared to men, associations of traditional and non-traditional risk factors with PAD and clinical manifestations of PAD differ by sex and may contribute to delayed or lack of diagnosis in women. Such sex-based differences in the manifestation of PAD may arise from sexual dimorphism in the vascular substrate in health as well as sex variation in the responses to vascular stressors. Despite the availability of proven therapies for improving symptoms and reducing risk of ischemic cardiovascular and limb events among patients with diagnosed PAD, important sex differences in treatment and outcomes have been observed. We provide an overview of current knowledge regarding sex differences in the epidemiology, pathophysiology, clinical presentation, and management of PAD.

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Introduction

Peripheral artery disease (PAD) generally refers to arterial diseases of the non-coronary vasculature that can arise from atherosclerotic, aneurysmal, inflammatory, or a combination of pathologies.¹ To focus on the most prevalent form of peripheral vascular disease, we herein refer to PAD as atherosclerotic narrowing of the peripheral arteries that classically affects the lower extremities. Defined as such, PAD prevalence has not only persisted but in fact doubled over the last three decades, in part due to lengthening life expectancy, rising incidence of risk factors such as obesity and diabetes, and increased screening and detection.² Importantly, presence versus absence of PAD confers a three-fold greater risk for mortality^{3,4} and an overall similar or worse risk for ischemic cardiovascular events compared to individuals with only coronary artery disease.⁵ Notwithstanding these statistics, PAD remains underdiagnosed and, in turn, undertreated when compared to other cardiovascular disease (CVD) conditions. In this context, women are especially vulnerable. Despite similar or higher prevalence of PAD, clinical recognition is often delayed or deferred in women compared to men.² Even among diagnosed patients, sex-based differences in PAD treatments and outcomes are evident. Therefore, we summarize current knowledge regarding sex differences in the epidemiology, pathophysiology, clinical presentation, and management of PAD – with the aim of increasing awareness and highlighting opportunities to improve outcomes for both women and men with PAD.

Epidemiology

An estimated 236 million adults are diagnosed with PAD, accounting for 5.6% of the worldwide population.⁶ In the United States, an estimated 4-10% of adults age 40 years or older are affected.⁷⁻¹⁰ Importantly, PAD incidence substantially increases with age, doubling with each advancing decade of life – affecting 1 in 10 adults aged 70 years or older. With the mean age of the population increasing, the number of PAD cases is rapidly rising: between 2000 to 2015, the prevalence of PAD grew by 45% worldwide.¹¹ Importantly, asymptomatic and under-recognized PAD represent almost 90% of all cases,¹² with true disease prevalence likely underestimated.

The gold standard screening modality for PAD is the ankle-brachial index (ABI) and its definition affects epidemiologic estimates of disease.¹³ Numerous epidemiologic studies have identified a lower range of ABI values in women than in men, which is not accounted for by sex differences in height or other potential confounders.¹⁴ Recognizing that sex-specific ranges can obscure population estimates, the Atherosclerosis Risk in Communities study showed that changing the definition of PAD to an ABI <0.85 can eliminate sex differences.¹⁵ However, too lower of a threshold can miss important disease. In fact, PAD defined using the <0.90 cutoff has been shown to correspond with ~90% sensitivity and ~80% specificity for 50% diameter stenosis,¹⁶ leaving many patients with ABIs in the apparently normal range and under-recognized PAD with associated excess cardiovascular

and mortality risk.^{17–20} Given these challenges, true population-level PAD prevalence remains difficult to accurately estimate for both sexes.

For women, the true prevalence of PAD is likely higher than available estimates for reasons that extend beyond the screening challenges.²¹ Women commonly manifest atypical claudication symptoms or no symptoms at all.²² Among the 35% of women with ABI <0.90 in the Women's Health and Aging, only 1 in 6 were aware of having PAD.²² Accordingly, data from the Global Burden of Disease Study suggests that PAD cases in women outnumber those in men across all age groups,² particularly among younger women in low-income countries, even after controlling for cardiovascular risk factors. The prevalence of PAD has also been observed to be higher among women of non-white compared with white race.^{7,8,23,24} Of particular interest is the finding of at least similar, if not higher (3 to 29%,) prevalence of PAD in women compared to men despite women having relatively lower historical rates of smoking.^{25,26} This sex paradox concerning the most substantial modifiable risk factor for PAD underscores the high likelihood of sex dimorphic factors contributing to the pathogenesis of PAD.

Pathophysiology

Sex differences in the clinical manifestation of vascular disease, including PAD, arise from not only sexual dimorphism in the vascular substrate in health but also sex variation in the types and responses to stressors experienced over the life course (Figure 1 and Figure 2). Mounting evidence suggest that sex chromosomes play an important role in the development of vascular and dysfunction atherosclerosis. For example, women with monosomy X (Turner syndrome) have increased LDL cholesterol levels and particle size.²⁷ In reality, however, the majority of sex differences arise from the complex interplay between sex hormones and sex chromosome complement. This concept was elegantly demonstrated in a recent study using male transgenic mice with deletion of *Sry* from the Y-chromosome. Depending on the presence/absence of testosterone, in male mice infused with AngII, an XY sex chromosome complement promotes diffuse aortic aneurysmal disease, while an XX sex chromosome complement contributes to focal aneurysms.²⁸ Further studies will be required to fully appreciate the complex mechanisms by which sex chromosome complement influences lipid profiles and vascular integrity.

Sex differences in PAD, in particular, are preceded by sex differences in arterial pathophysiology. Endothelial dysfunction is an initial step in the pathogenesis of atherosclerosis and development of PAD.²⁹ A notable feature of endothelial dysfunction is impairment in macro- and micro-vascular endothelium-dependent vasodilation, partly due reduced nitric oxide (NO) bioavailability. In men, the measurable impairment in endothelial function occurs in the 4th decade, whereas in women the impairment occurs about a decade later (around the time of menopause) with subsequent acceleration to similar impairment seen in men.^{30–32} The sex difference in the age-based onset of impaired endothelial function has been attributed to changes in sex hormones with menopause, particularly estradiol (E₂) in women.^{30–32} Indeed, treatment with E₂ improves endothelial function in postmenopausal women,^{33–36} while surgically or chemically decreasing E₂ in premenopausal women induces

endothelial dysfunction that is reversed with E₂ treatment.^{37–39} Collectively, these findings suggest that E₂ modulates endothelial function in women.

There are multiple potential mechanisms by which E₂ decline may contribute to the endothelial dysfunction that presages atherosclerosis and PAD in women. In healthy women, the decline in E₂ with menopause appears to trigger excess reactive oxygen species (ROS) production, subsequently impairing NO-mediated vasodilation.^{37,39,40} In experimental studies involving women treated with gonadotropin-releasing hormone antagonists to mimic ovarian suppression, vitamin C improves endothelial dependent vasodilation, but the beneficial effect was not present in those also treated with estradiol.^{39,41} Such findings suggest that estrogen decline may be a key physiological event leading to increased oxidative stress-mediated endothelial dysfunction in women. The modulatory role of sex hormones on oxidative stress-mediated endothelial dysfunction in men are unknown, although evidence suggests oxidative stress contributes to endothelial dysfunction in men with low testosterone.⁴² Beyond antioxidant effects, estrogen also has anti-inflammatory effects on the vascular endothelium that are particularly evident in a healthy artery.⁴³ Estrogen can antagonize the effects of pro-inflammatory cytokines by inhibiting nuclear factor-kappa-B, consequently reducing endothelial activation and the release of other inflammatory cytokines and ROS.⁴⁴ Inflammation appears to be a key determinant of endothelial function, as animal and human studies have demonstrated that administration of the TNF- α receptor blocker etanercept enhanced endothelium-dependent vasodilation in ovariectomized animals and in postmenopausal women not treated with estradiol.^{35,45}

The vascular endothelium also releases endothelin-1 (ET-1), a potent vasoconstrictor produced and released from endothelial cells that acts on two receptor subtypes, ET_A and ET_B, located on the vascular smooth muscle. ET_B receptors are also located on the endothelium and mediate vasodilation. Mounting evidence suggest that sex differences may be related to ET_B receptors.⁴⁶ Indeed, ET-1 responsiveness differs between men and women,^{47,48} preferentially binding to ET_B receptors in women.⁴⁹ More recent data also suggests that ET_B receptor function shifts with menopause, favoring vasoconstriction and contributing to overall vascular impairment with age in women.⁵⁰

Endothelial dysfunction represents an early step in the formation of atherosclerotic plaque by altering the hemostatic mechanisms increasing both the adhesiveness and permeability with respect to leukocytes and platelets.⁵¹ These changes produce a procoagulant effect along with inflammation, which if left unabated, start a cascade that includes stimulation and proliferation of smooth muscle cells, as well as an increase in macrophages, lymphocytes, cytokines, and chemokines. Estrogen alters the immune response during atherosclerosis, resulting in sex-specific disease phenotypes.^{52–54} Eventually, a fibrous cap is formed that overlies a lipid rich plaque with a necrotic core. The vessel accommodates this process by dilating, however once dilation is no longer feasible, the plaque may protrude into the vessel and limit flow.

Data are limited regarding sex differences in the formation of atherosclerosis. Many pre-clinical studies have not reported the sex of the animals, and even when available, sex was not used as a key variable in analyses.⁵⁴ In limited animal studies, males appear to have

more inflamed plaque but smaller plaque volume when compared to females.⁵⁴ In humans, imaging and histology studies suggest that men develop plaque earlier and have greater plaque burden compared to women, even when controlling for risk factors. However, since many of these studies were performed in patients younger than 60 years of age, it is unclear how increased plaque burden may lead to the “catch up” events seen in women over age 60 years.

Risk Factors

Both traditional and non-traditional risk factors contribute to the development of PAD through various pathophysiologic mechanisms (Figure 2). In addition to genetic factors underlying propensity for PAD,⁵⁵ a number of non-genetic and environmental exposures have been implicated along with sex variation in their associations with disease outcomes.

Traditional Risk Factors—Smoking is perhaps the most well-recognized of all risk factors. Across epidemiologic studies, prior or current smoking status was a predominant characteristic, especially among individuals with symptomatic PAD. The impact of smoking on PAD development can persist up to 30 years after smoking cessation,⁵⁶ with both quantity and duration corresponding to greater risk.⁵⁷ In countries where ~30% of the population are smokers, half of PAD cases are attributed to tobacco use.⁵⁸ Men with PAD more commonly have a history of smoking than women with PAD.⁵⁹ The relative effects of smoking on overall CVD risk are especially pronounced in women, and the PAD-specific risk is also at least similar if not potentially also higher in women.^{60,61} In the Women’s Health Study, past and current smokers had a 3-fold and more than 10-fold greater risk for PAD, respectively, compared to never smokers.

Diabetes is well-recognized as second only to smoking in its attributable risk for PAD. Diabetes is associated with twice the risk of developing PAD^{62,63} as well as greater risk for the most severe forms of PAD, including chronic limb-threatening ischemia (CLTI) and amputation.⁶⁴ Women compared to men with diabetes have a greater sex-specific risk for overall atherosclerotic disease.^{65–68} The evidence for sex-specific diabetes related risk for PAD is less clear. While results from a recent meta-analysis suggested relatively equal diabetes-related risk for PAD by sex,⁶⁵ a prior Framingham Heart Study analysis found that impaired glucose tolerance posed greater risk for PAD in women than in men.⁶⁹ It is possible that sex differences in dysglycemia related risk for PAD are more evident earlier in the course of systemic metabolic disease,⁷⁰ and further studies are needed.

Hypertension is another important risk factor for PAD and, as is the case for other CVD conditions, there is a dose-exposure relationship with worsening blood pressure values being associated with greater risk for PAD in women and men.^{71,72} In the Women’s Health Study, hypertension was related to a 2–3-fold higher risk of developing symptomatic PAD, with a linear relationship between the degree of hypertension and the risk of PAD.⁷³ Similar increments of elevated blood pressure have been shown to be associated with a greater risk in women than in men for a number of subclinical and clinical CVD outcomes including left ventricular hypertrophy, diastolic dysfunction, coronary heart disease, heart failure, and stroke.^{74–77} Although similar sex-specific outcomes data for PAD are lacking, there is

evidence that hypertension is more common among women than men with PAD.^{78–80} The relationship between hypertension and claudication symptoms is also more pronounced in women than men.⁶⁹ While additional investigations are needed, emerging data suggest that effects of elevated blood pressure on the vasculature may be different in females compared to males, in part due to intrinsic dimorphism in arterial physiology, anatomy, or both⁸¹ and with downstream effects on arterial pathophysiology that could lead to greater propensity for PAD.

Hyperlipidemia is a well-recognized risk factor for atherosclerotic cardiovascular disease, including PAD.^{82–84} In the Health Professionals Follow-Up Study, men with hyperlipidemia were found to have higher risk of developing PAD after 25 years later.⁶³ Among patients with PAD, women appear to have a higher prevalence of hyperlipidemia than men.⁸⁰ However, the lipid panel composition varies by sex, with men tending to have lower high-density lipoprotein levels than women across all age groups. Interestingly, a recent prospective study showed that in young women, elevated levels of small LDL particle concentration rather than total LDL cholesterol were associated with a higher risk for developing PAD. Additional lipid-based analyses may uncover sex specific markers to help clarify risks for PAD.⁸⁵

Non-Traditional Risk Factors—Non-traditional risk factors may also contribute to PAD, although data are limited. For example, a history of pregnancy complications such as hypertensive disorders of pregnancy are known risk enhancing factors for CVD, including PAD.^{86–88} Also, patients with autoimmune diseases such as rheumatoid arthritis, the majority of whom are women, are at higher risk for noncardiac vascular disease including PAD.⁸⁹ Chronic kidney disease (CKD) patients are at higher risk for atherosclerotic disease in general; among CKD patients under the age of 70 years, the incidence of PAD is 50% greater in women than men.^{90,91} Psychologic risk factors are related to higher cardiovascular disease risk,⁷⁷ and women with PAD have higher burden of depressive symptoms as compared to men with PAD.^{92,93} There may also be a link between PAD and bone density, as postmenopausal women with osteoporosis have lower ABIs as compared to women with osteopenia.⁹⁴

Social Determinants of Health—A growing body of evidence has linked socioeconomic factors with health disparities. Studies have shown an inverse relationship between socioeconomic status and incidence of CVD.^{95–97} Historically, women have been more vulnerable to healthcare and socioeconomic disparities compared to men.⁷⁷ This may partially explain the disproportionate excess of CVD in women with lower socioeconomic status⁹⁸ and the higher absolute number of CV deaths of women as compared to men.⁹⁹ For PAD in particular, environmental pollution, lower socioeconomic status and lower education level have been associated with higher disease incidence.^{100–103} Long-term exposure to airborne particulate matter has been related to subclinical atherosclerotic disease, including PAD in population studies.¹⁰⁴ There is also an association of long-term traffic exposure, in particular residential proximity to main roads, and increased prevalence of PAD.^{105,106} Notably, the association was more pronounced in women and inconsistent in men.¹⁰⁶ Several studies have also demonstrated that lower income and lower education level are

associated with worse PAD outcomes.^{100,107–109} Among possible causes for this heightened risk is limited access to resources and opportunities that improve overall health while being exposed to chronic psychosocial stress.¹⁰⁹

Biomarkers—Given the known limitations of ABI, numerous studies have sought to identify blood biomarkers that might assist with screening, shed light on pathophysiology, and also improve risk estimates. These include markers of inflammation, endothelial dysfunction, angiogenesis, lipid metabolism, oxidative stress, and coagulation.¹¹⁰ Amidst emerging data on sex differences in cardiovascular biomarker associations in general, data specific to PAD are still limited. One study that followed 15,737 adults over two decades in Scotland assessed biomarker predictors of PAD versus coronary artery disease and found that triglycerides, hsCRP, tobacco metabolites, and GGT were more prominently associated with PAD in women whereas fibrinogen, NT-pro-BNP, and 25-OH vitamin D were more prominently associated with PAD in men.⁶¹ The extent to which female PAD risk may be more dependent on metabolic and inflammatory pathways, and male risk more related to coagulopathies and other factors requires further investigation.

Hormone Therapy—Relationships between hormone therapy and PAD outcomes are inconsistent. Prospective observational studies report lower prevalence of PAD in women using hormone therapy. In the Rotterdam Study, postmenopausal women taking hormone therapy for 1 year had a lower risk of PAD (defined as ABI <0.9).¹¹¹ Another study similarly demonstrated that hormone therapy was associated with lower PAD risk, despite a higher prevalence of risk factors (i.e., smoking, hypertension and hypercholesterolemia) in women who used hormone therapy.¹¹² In contrast to the apparently protective exposure effect seen in observational studies, prospective data from randomized trials have not suggested benefit. In the Women's Health Initiative (WHI) estrogen plus progestin and estrogen alone trials^{113,114} and the Heart and Estrogen/Progestin Replacement (HERS) secondary prevention study, there were no reported differences in PAD outcomes for postmenopausal women treated with hormone therapy compared to placebo.^{115,116} Rather, a non-significant trend toward risk of peripheral arterial events was seen in the estrogen alone WHI trial.

Importantly, adverse effects of hormone therapy have also been reported in studies of outcomes following PAD interventions. In a study of postmenopausal women undergoing infra-inguinal bypass grafting, hormone therapy use was associated with reduced primary graft patency.¹¹⁷ Similarly, in postmenopausal women undergoing iliac artery stenting, those treated with hormone replacement therapy had lower rates of primary patency than those not using hormone therapy,¹¹⁸ suggesting that adverse outcomes could be related to thromboembolic effects of hormone therapy.¹¹⁷ Accordingly, in premenopausal women, oral contraceptive pill use has been associated with increased PAD risk.¹¹⁹ On balance, the clinical findings to date suggest that while estrogen deficiency may be a predisposing factor for the development of PAD, currently available formulations of hormone replacement are not likely to offer therapeutic benefit at least in the setting of clinically manifest disease.

Outcomes

PAD patients have the highest rates of cardiovascular (CV) death and major CV events among patients with atherosclerotic disease, suggesting that diagnosing PAD is an important marker of overall atherosclerotic burden.¹²⁰ After 1 year of follow up, PAD patients had 21% risk of major adverse cardiovascular events (MACE) and CV death compared to 15% in patients with CAD or CVA history.¹²⁰ Similarly, women with PAD have an increased risk of all-cause mortality and MACE as compared to women without PAD.¹²¹ Women with an ABI <0.90 have a 3-fold increased risk of all-cause mortality^{3,122} and this risk is comparable to their male counterparts.^{3,80,122,123} However, some studies have shown higher risk of mortality in males with PAD as compared to women.^{124,125} Women also have similar risk of major adverse limb events (MALE) including acute limb ischemia⁸⁰ and higher rates of above the knee amputation¹²⁶ as compared to men. Among women with PAD, Black and Native American women also have higher risk of morbidity and mortality relative to White and Hispanic women.⁸

CLTI is one of the most severe manifestations of PAD and is characterized by chronic inadequate tissue perfusion leading to intractable foot pain at rest and/or tissue necrosis which can lead to limb loss if not treated urgently.¹²⁷ Among PAD patients, CLTI patients have the highest morbidity and mortality risk, with reports of 20-40% with an amputation within a 1-year period and 20% dead within 6 months.^{128,129} Although women tend to present with more severe PAD, including CLTI, than men, mortality associated with CLTI is similar in men and women with PAD.¹²⁸ However, Black race and female gender have been associated with increased odds of receiving an above the knee amputation.¹²⁶

Clinical Presentation

Clinical presentations vary and symptoms does not necessarily correlate with severity of PAD, as some patients may have atypical symptoms, higher thresholds for pain, or more robust collateral circulation.¹³⁰ Less than one third of patients have typical intermittent claudication, and the majority have atypical symptoms or are “asymptomatic” with respect to lower extremity symptoms.¹³¹ Importantly, PAD, even in the absence of leg symptoms, has been associated with functional decline, including decline in walking endurance.¹³² Patients with borderline ABI (0.90-0.99) have been shown to have greater mobility loss than patients with normal ABI after 5 years of follow up.¹³³

Differences in symptoms and presentation have been observed between women and men with PAD (Table 1). Women with PAD commonly present with atypical symptoms or are asymptomatic with respect to limb symptoms.^{121,134-136} In the Women’s Health and Aging study, only 14% of women with PAD had a history of IC, and 64% were asymptomatic.¹³⁷ Early symptoms are also underrecognized in women as they may be masked by other musculoskeletal conditions prevalent in this population like osteoporosis and osteoarthritis, in addition to the erroneous belief that PAD is more prevalent in men.¹³⁸ Compared to men, women are more likely to be older,¹³⁸⁻¹⁴⁰ to present with more advanced Rutherford class,^{136,139-141} and to have multivessel atherosclerotic disease identified at revascularization.^{139,142} Among patients presenting with CLTI, female gender has been shown to be an independent predictor of femoropopliteal disease.^{142,143}

Important sex-based differences in physical function have also been observed. Relative to men, women have a faster functional decline¹⁴⁴ and are at higher risk for reduced quality of life.¹⁴⁵ Relative to men with similar ABI values, women with PAD have poorer functional status, greater ambulatory limitations and reduced lower extremity strength.¹⁴⁶ One study showed that women with PAD had 18% lower daily physical activity level than men.¹⁴⁷ Another study showed that women walked fewer blocks per week, had lower 6-min walk performance, smaller calf muscle area, lower calf muscle density, and poorer knee extension strength as compared to men with PAD of similar age.¹⁴⁴ The Walking Impairment Questionnaire (WIQ) is a tool that measures patient perceived mobility by assessing walking endurance, walking speed and stair-climbing ability in the community and has been validated in men and women with PAD.¹⁴⁸ Female sex has been related to lower scores in all the WIQ parameters.^{149,150}

Diagnosis

Several tests can be used for the diagnosis of PAD. The ABI is the diagnostic test of choice, due to its low cost, noninvasiveness, and wide availability.¹⁵¹ Additional testing modalities used to confirm the diagnosis of PAD and define arterial anatomy include duplex ultrasonography, computer tomographic angiography, and magnetic resonance angiography. Invasive angiography remains the gold standard for diagnosing PAD but is generally performed when non-invasive methods are not feasible or inconclusive or when revascularization is planned. Despite observed smaller caliber arteries in women versus men,¹⁵² no studies have shown sex-based differences in imaging accuracy for PAD. An important barrier in diagnosing PAD in women remains clinician bias and failure to recognize atypical symptoms.

Management

The goals of managing PAD are to improve functional capacity, preserve limb viability, and reduce MACE and mortality risk.¹⁵³ As discussed in current guidelines, management options include medical treatments (e.g. lipid-lowering and antithrombotic therapies), exercise therapy, and revascularization.¹³¹ However, use of guideline-recommended therapies in the overall PAD population has been consistently low,^{5,154–157} with variations arising in part from sex disparities.

Lipid-Lowering Therapies—Lipid lowering therapies (LLT) have revolutionized the primary and secondary prevention of CVD, including PAD. LLT has been shown to reduce MACE and limb events, as well as improve function, in patients with PAD,^{158–165} Furthermore, a relationship between lower LDL levels and lower risk of limb events has been demonstrated,¹⁶⁶ suggesting that specifying lipid targets may be important to reduce adverse outcomes in PAD patients.

Despite the relevance of LLT in the management of PAD patients, the use of LLT remains underutilized especially when compared to patients with atherosclerotic disease in other territories.⁵ Only about 34% of the PAD patients are on a statin,⁵ and in a recent study, one-quarter of PAD patients were on high intensity statin.¹⁶⁷ This suboptimal utilization of LLT is even more prominent in women with PAD as compared to men^{168,169} with

disparities even more pronounced in minority groups such as African American women.¹⁷⁰ In a post-hoc analysis of the COMPASS trial of patients with stable atherosclerotic CVD, including PAD, women were less often treated with LLT.¹⁷¹ Among patients with PAD, female sex is associated with lower odds of treatment with any statin^{172,173} and achieving target LDL-C.¹⁶⁷ Among CLTI patients, a high risk subgroup, women are undertreated with statins and revascularization compared to men.¹²⁸

Anti-Hypertensive Therapies—Anti-hypertensive therapies, in particular angiotensin-converting enzyme (ACE) inhibitors have been associated with improved maximum walking distance in patients with PAD irrespective of sex.^{174–176} Despite this, PAD patients also tend to be undertreated for hypertension as compared to patients with other known CVD.^{155,177} Although the incidence of hypertension in women with PAD is higher than in men with PAD, men are more likely to achieve blood pressure control¹⁷⁸ and are 1.3 times more likely to receive an ACE inhibitor than women.¹⁷³

Antithrombotic Therapy—Antithrombotic therapy is a key component of medical treatment of PAD to reduce the risk for atherothrombotic cardiovascular and limb events,¹³¹ and sex-based outcomes have been reported for several relevant trials. The EUCLID trial showed that ticagrelor was not superior to clopidogrel for reducing cardiovascular events in patients with stable PAD.¹⁷⁹ In subgroup analysis, women had similar rates of MALE but reduced mortality and MACE events compared with men; no sex modification was seen for the ticagrelor versus clopidogrel effect on MACE.¹⁸⁰ The COMPASS trial demonstrated significant reductions in MACE, the primary endpoint, and MALE with low dose rivaroxaban (2.5 mg twice daily) plus aspirin versus aspirin alone in patients with stable atherosclerotic cardiovascular disease, including PAD.^{181,182} In COMPASS, there was no effect modification by sex, with similar benefits for MACE and similar risk of bleeding associated with combination therapy in women and men.¹⁷¹ The regimen of rivaroxaban 2.5 mg twice daily plus aspirin versus aspirin alone was most recently shown in VOYAGER PAD to reduce the risk of severe limb and cardiovascular events in patients undergoing lower extremity revascularization;¹⁸³ consistent benefit and risk of bleeding were demonstrated in women and men.¹⁸³ Additionally, in VOYAGER PAD, rivaroxaban appeared safe and efficacious in patients with impaired renal function, a significant proportion of whom were women.¹⁸⁴

A novel antiplatelet agent, vorapaxar, is also approved by the FDA for the treatment of symptomatic PAD based on the results of TRA2P-TIMI 50 trial. In the overall population of patients with stable atherosclerotic cardiovascular disease, vorapaxar versus placebo added to aspirin and a P2Y₁₂ inhibitor reduced MACE; in the subgroup of patients with stable, chronic PAD, vorapaxar did not reduce MACE but did reduce acute limb ischemia and need for peripheral revascularization.¹⁸⁵ Although not designed to detect sex-based differences, a post-hoc analysis among patients with impaired renal function (who were more likely to be women) showed similar net clinical benefit for cardiovascular events and bleeding with vorapaxar in this population.¹⁸⁶

Studies consistently demonstrate sex-based differences in use of antithrombotic therapy in PAD. Overall, among patients with PAD, men are 1.5 times more likely than women to be

treated with antiplatelet agents.¹⁷³ Even after lower extremity revascularization, a setting associated with higher risk for ischemic limb events, women are less likely to be discharged on evidence based medical therapies from the hospital including antiplatelet therapy, statins, or ACE-inhibitors/ARBs.¹⁸⁷ As women tend to be older when diagnosed with PAD, it is thought that frailty and/or bleeding concerns may play a role in decision-making regarding antithrombotic therapies. However, in a study of veteran patients with PAD, young women were also less likely to receive antiplatelet therapy than men (59% vs 78% respectively).¹⁸⁸ These findings support the need for further investigation into differential use by sex of this important class of therapies proven to reduce risk of atherothrombotic events in PAD.

Cilostazol—While the above therapies focus on reducing MACE or MALE in PAD patients, cilostazol is approved by the FDA to help with symptom relief and has been shown to help improve functional capacity.¹⁸⁹ Pooled analyses of nine randomized controlled trials showed that cilostazol can increase maximal walking distance and quality of life over 24 weeks in patients with PAD.^{190,191} Notably, the benefit of cilostazol was significant and similar in men and women in subgroup analysis.¹⁹⁰

Exercise Therapy—Supervised exercise therapy (SET) is well known to improve symptoms, exercise capacity, and quality of life¹⁸⁹ and, although gender specific data are lacking, small studies suggest benefits of SET are lower in women than men.^{192–195} Gardner et al. reported 100% of men (both diabetic and non-diabetic) with PAD showed an increase in claudication onset time after the completion of either a supervised or home-based exercise program compared to only 81% of non-diabetic and 37% of diabetic women with PAD.¹⁹³ Though incompletely understood, this sex disparity may relate to greater baseline limitations in women that manifest as earlier-onset claudication pain, longer time-to-recover calf muscle hemoglobin oxygen saturation after exercise, and more limited daily ambulatory activity.¹⁹³ Attenuated responses in women with PAD could also be due to diminished effects of exercise training on vascular function. Evidence from exercise training studies in healthy postmenopausal women not taking estrogen-based hormone therapy report that endurance exercise training effects on endothelial function and limb blood flow are diminished or absent compared to middle-age and older men.^{33,196,197} Further investigations of sex-specific outcomes, particularly in response to exercise, has been identified an AHA/ACC research priority for exercise interventions in individuals with PAD.¹⁹⁸

Revascularization—Lower extremity revascularization is an important treatment option for patients with PAD. . Historically, women have undergone lower extremity revascularization for PAD at lower rates than their male counterparts, despite the fact that PAD affects men and women at least equally.^{136,199} In the 1980s, men were twice more likely than women to be selected for revascularization.²⁰⁰ Fortunately, by 2006-2008, gender was no longer an independent predictor of revascularization for lower extremity PAD.²⁰¹ Trends in revascularization strategies for women reflect an overall transition to an endovascular-first approach, with rates of endovascular treatment that are nearly equal between men and women.²⁰² In fact, Nationwide Inpatient Sample data from 1998-2006 indicated that, along with yearly increases in endovascular procedures for both sexes,

women made up less than half of acute admissions for PAD and were more likely to undergo endovascular as opposed to open surgical revascularization when compared to men.²⁰³

Data regarding post-revascularization outcomes by sex show mixed results. Although higher mortality for women after revascularization has been reported,²⁰² most studies do not show a statistically different rate of in-hospital death by sex^{139,204} with at least equivalent limb salvage rates despite the presence of more multilevel disease in women.^{142,143} Surgical data yield conflicting results. In comparisons of surgical versus endovascular therapy for aortoiliac disease, women had higher rates of both bypass failure and stent thrombosis in multivariate analysis²⁰⁵ along with poorer patency at all prosthetic graft sizes.²⁰⁶ In randomized data examining autologous vein grafting for CLTI, black women experienced the greatest disparity in overall graft patency.²⁰⁷ Several studies on infra-inguinal bypass for CLTI have shown similar limb salvage rates in women despite lower patency rates,^{152,208,209} although other studies have shown no effect of gender on patency.^{210–212} Overall long-term patency rates of surgical bypass are lower in women,^{209,213} owing at least in part to smaller native arterial diameters than for men of matched age.¹⁵²

Outcomes data by sex after endovascular peripheral vascular intervention (PVI) are limited, but women generally have higher peri-procedural complication rates without increased rates of major adverse limb events. Large registry data have consistently shown that women are at higher risk of procedural or access site complications than men but not for reintervention, amputation, or death.^{138,139,214} Despite women presenting with more advanced disease, in a statewide California database, women were shown to have improved amputation-free survival compared to men.²¹⁵ In contrast, data from a national Korean registry showed that women undergoing PVI had higher rates of peri-procedural complications, myocardial infarction, major amputation, and death compared to men.²¹⁶ A meta-analysis by Matsi and colleagues reported increased bleeding risk among women undergoing lower extremity PVI.²¹⁷ Patency outcomes after PVI by sex are less well-characterized. In general, men and women appear to have similar primary patency rates after infra-inguinal PVI¹⁴¹ and femoropopliteal stenting,^{218–221} although one study did report poorer secondary patency after femoropopliteal stenting²²² and infra-popliteal PVI for CLTI among women versus men.¹⁴²

Overall, outcomes after revascularization in women are mixed and are likely related to complex interactions between age, risk factors, Rutherford class at presentation, and anatomic factors including presence of microvascular disease.²²³ Importantly, the lifetime prevalence of PAD is at least equal between men and women, and although women present at older age with more complex, multilevel disease, their post-revascularization outcomes are at least as good as men – when revascularization therapies are offered and applied for women.

Conclusion

Not only is PAD a highly prevalent condition associated with significant morbidity and mortality, it is a condition that affects women as often or more commonly than men. Sex-based differences in pathophysiology and risk factors may contribute to the later-onset

and often atypical presentation of women with PAD, in addition to the overall disease burden. Importantly, while underdiagnosis and undertreatment of PAD affects the quality of care and outcomes for all patients, these challenges are especially profound for women – with data consistently demonstrating less frequent use of evidence-based therapies in women compared to men. Studies examining outcomes in PAD among women and men have shown mixed results, likely reflecting the complexity of sex-specific interactions that are relevant to pathophysiology, risk factors, and treatment. Additional efforts are needed to increase awareness of and to better understand sex-based differences in PAD development, diagnosis, and management so that improved outcomes can be achieved in this vulnerable, high-risk population. In particular, sex-specific analyses from translational PAD studies in conjunction with clinical trial findings reported by sex will help to address the persistent unmet need.

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Nonstandard Abbreviations and Acronyms:

ABI	Ankle-brachial index
ACE	Angiotensin-converting enzyme
CKD	Chronic kidney disease
CLTI	Chronic limb-threatening ischemia
CV	Cardiovascular
CVD	Cardiovascular disease
E₂	Estradiol
ET	Endothelin

ET-1	Endothelin-1
HERS	Heart and Estrogen/Progestin Replacement
LLT	Lipid lowering therapies
MACE	Major adverse cardiovascular events
MALE	Major adverse limb events
NO	Nitric oxide
PAD	Peripheral artery disease
PVI	Peripheral vascular intervention
ROS	Reactive oxygen species
SET	Supervised exercise training
WHI	Women's Health Initiative
WIQ	Walking Impairment Questionnaire

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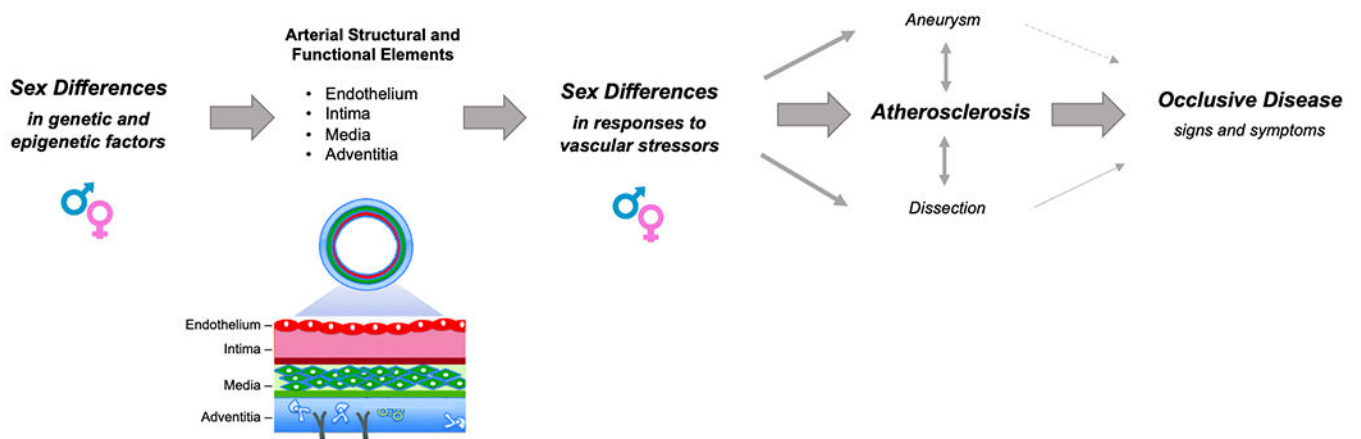


Figure 1. Sex Differences in Responses to Vascular Stressors and Sequelae.

A conventional paradigm proposes that when the same arterial structural and functional substrate is exposed to stressors, sex differences in response to these stressors lead to variations in manifest peripheral vascular disease including the predominance of aortic aneurysm and dissection in men as well as the likely higher prevalence of classic atherosclerotic lower extremity disease in women that also tends to present more as multivessel disease in women compared to men. Emerging evidence suggests that intrinsic sex differences in the arterial substrate, arising from genetic or epigenetic factors, likely also contribute to sexual dimorphism in vascular disease phenotypes.

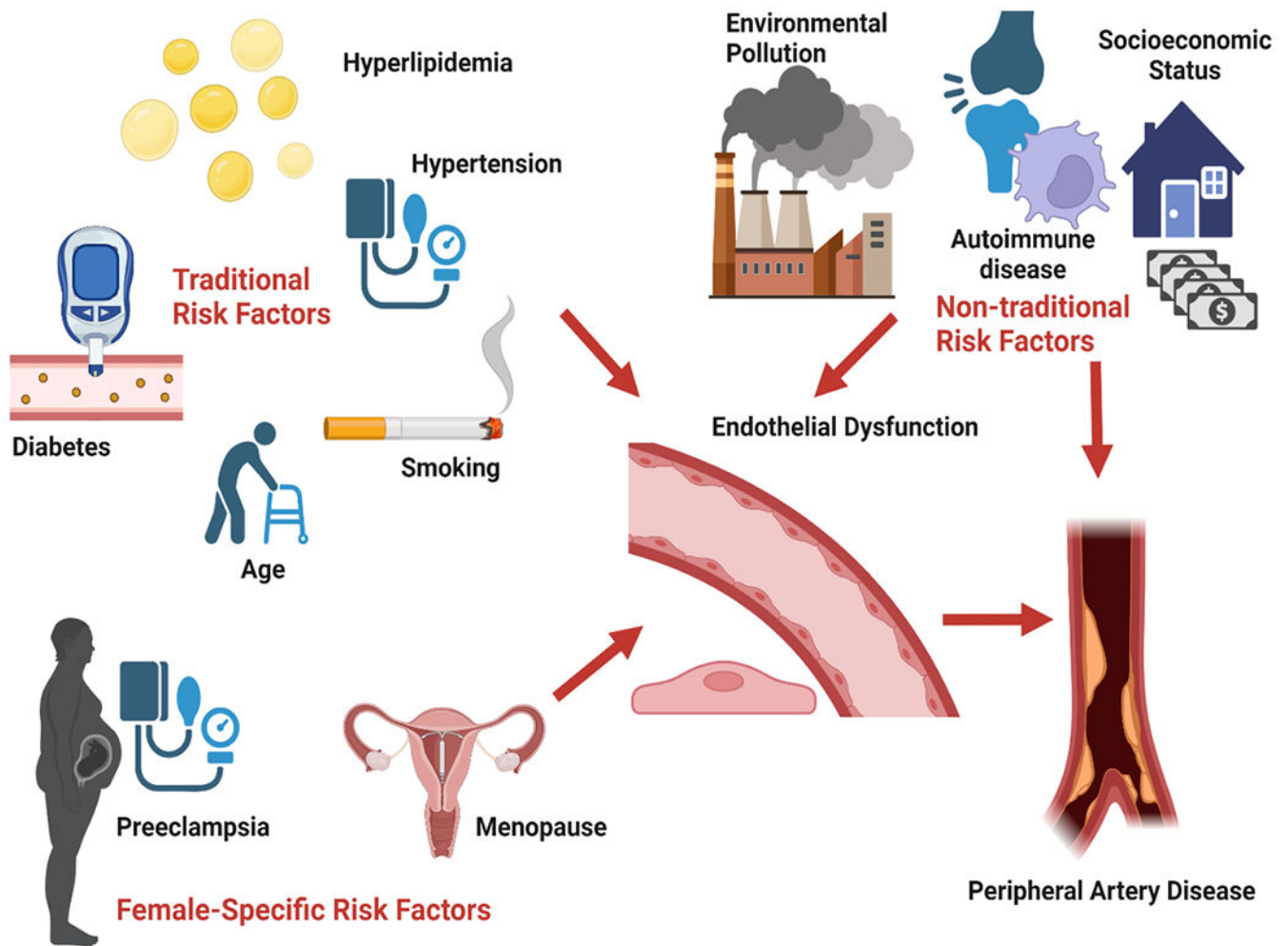


Figure 2. Sex-Agnostic and Sex-Specific Risk Factors for Peripheral Arterial Disease.

A number of sex-agnostic risk factors for peripheral arterial disease have been identified, with smoking being among the most prominent and potentially contributing a more substantial burden of disease risk in women compared to men, based on analyses of tobacco metabolite associations. The excess burden and multivessel predominance of peripheral arterial disease in women may also arise from a sex-specific predisposition for endothelial dysfunction and, in turn, arterial dysfunction and disease in the setting of age-related estrogen deficiency occurring either with or without a preceding vascular disorder of pregnancy event.

Table 1.

Sex Differences in PAD Presentation and Management

	Sex Differences in PAD
Clinical Presentation	
<i>Symptoms</i>	Women more likely to have no or atypical leg symptoms
<i>Examination</i>	Women more likely to have greater functional decline and reduced walking parameters and quality of life
<i>Diagnostics</i>	Women more likely to present with multilevel disease
Management	
<i>Hyperlipidemia</i>	Women less often treated with lipid-lowering therapies, and female sex associated with lower odds of achieving target LDL-C
<i>Hypertension</i>	Men more likely to be treated with an ACE inhibitor and to achieve target blood pressure
<i>Antithrombotic therapy</i>	Lower use of antiplatelet therapy consistently observed among women
<i>Supervised exercise therapy (SET)</i>	Small studies suggest less response to SET in women than men, though data are sparse
<i>Revascularization</i>	Older data suggest lower use of revascularization in women, but more recent data show similar use between women and men

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