

# Diagnosis and management of peripheral artery disease in women

Joy Peacock Walker  
Jade S Hiramoto

Department of Surgery, University  
of California, San Francisco, California,  
USA

**Abstract:** Peripheral artery disease (PAD) is a significant cause of morbidity and mortality in the USA. Not only is it a major cause of functional impairment and limb loss, but it is also strongly associated with an increased risk of myocardial infarction, stroke, and death. Large population studies have demonstrated high rates of PAD in women, but this is not widely recognized by the public or by clinicians. One potential reason for this is that women with PAD are more likely than men to be asymptomatic or have atypical symptoms. In addition, women with PAD experience higher rates of functional decline and may have poorer outcomes after surgical treatment for PAD compared with men. Currently, it is not known if there are sex-specific differences in risk factors for the onset, progression, and surgical outcomes of PAD. This review will focus on the diagnosis and management of PAD in women and examine sex-specific differences in the prevalence, risk factors, presentation, and outcomes of this disease.

**Keywords:** women, peripheral artery diseases, diagnosis, risk factors, management

## Introduction

Peripheral artery disease (PAD) affects approximately 5–10 million people in the USA<sup>1–4</sup> and is a significant cause of lower extremity functional impairment, ulceration, and limb loss. Even without these clinical consequences, PAD is an independent predictor of increased cardiovascular (CV) and all-cause mortality.<sup>5–16</sup> In addition, the economic burden of PAD is higher than one might expect, and comparable to that of coronary artery disease and ischemic stroke.<sup>17,18</sup>

The prevalence and clinical consequences of PAD are similar in magnitude for women and men. Despite this, PAD remains underappreciated in women, and women have been underrepresented in contemporary PAD revascularization studies.<sup>19,20</sup> As a result, sex-specific differences in the risk factors, management, and outcomes of PAD remain unclear, creating a critical need for clinical research to evaluate sex differences in PAD. In recognition of this growing problem, the American Heart Association recently released a “call to action” to raise awareness of the burden of PAD in women.<sup>20</sup> This review will seek to highlight sex differences in the risk factors, presentation, diagnosis, and management of PAD.

## Prevalence of PAD

PAD can be symptomatic or asymptomatic, and can be diagnosed based on several different methods: the ankle brachial index (ABI), duplex ultrasound, computed tomography angiography, magnetic resonance angiography, or catheter angiography. Most population-based estimates of PAD are based on the ABI, the ratio of the

Correspondence: Jade S Hiramoto  
UCSF Vascular Surgery, 400 Parnassus  
Ave, A-581, Box 0222, San Francisco,  
CA 94143-0222, USA  
Tel +1 415 353 4366  
Fax +1 415 353 4370  
Email jade.hiramoto@ucsfmedctr.org

systolic pressure at the ankle compared with that at the arm; this is an accurate and noninvasive method with which to determine PAD.<sup>21–23</sup> Traditionally, most studies have used a cut-off point of an ABI of  $\leq 0.9$  to define PAD; this was based on the association of this ABI level to anatomic findings on catheter angiography. However, there is substantial research demonstrating elevated CV risks and mortality in those with an ABI  $< 1.0$ .<sup>10,15,16,24</sup> As a result, in 2011, the American College of Cardiology Foundation/American Heart Association Task Force updated the guidelines for management of patients with PAD and now considers ABI values of 0.9–1.0 to be abnormal.<sup>25</sup>

Table 1 includes population-based studies where sex-specific PAD prevalence rates could be determined.<sup>2,4,26–39</sup> Even though male sex has traditionally been reported to be a risk factor for the development of PAD,<sup>35,40–42</sup> the prevalence of PAD is similar in women and men (and, in some instances, higher in women). Beyond prevalence, there appears to be an increasing population burden of women with PAD. Using US census data from 2010, Hirsch et al calculated a greater number of women than men with PAD among US adults older than 40 years of age.<sup>20</sup>

## Risk factors

Traditional cardiovascular disease (CVD) risk factors (smoking, hypertension, diabetes mellitus, and hyperlipidemia) are strongly associated with the development and progression of PAD in both women and men.<sup>2,34,43–45</sup>

PAD prevalence increases in both women and men as the population ages, but women tend to be older than men when they present with symptoms of PAD.<sup>46–49</sup> In addition, African-Americans are disproportionately affected with PAD.<sup>1,2,5,31,33,50,51</sup> Although African-Americans have a higher prevalence of obesity, hypertension, and diabetes mellitus compared with Caucasians,<sup>52–55</sup> these traditional risk factors alone do not account for the excess risk of PAD in African-Americans.<sup>37,50,56</sup> The odds for PAD were 1.7 times higher in African-Americans than Caucasians in the Multi-Ethnic Study of Atherosclerosis (MESA)<sup>57</sup> and 2.4 times higher in African-Americans than in Caucasians in the San Diego Population Study.<sup>58</sup> These cross-sectional studies demonstrated that the higher odds for PAD in African-Americans than in Caucasians were only modestly attenuated after adjustment for traditional CVD risk factors as well as several inflammatory biomarkers.

It is plausible that women might have different risk factors for PAD development than men. For example, smoking is one of the strongest risk factors for the development of PAD. However, in a cohort of 15,173 African-American and Caucasian individuals aged 45–64 years old, women who had never smoked were still more likely to develop PAD than men (2.6% vs 0.4%, respectively.) This remained statistically significant even after adjustment for age, low-density lipoprotein cholesterol, hypertension, and diabetes.<sup>31</sup> Another study of 1932 participants free of four traditional CVD risk factors (smoking, diabetes, hypertension, and dyslipidemia)

**Table 1** Prevalence of peripheral artery disease (PAD) in men and women in population-based studies

Study	N	Age (y)	Prevalence in men (%)	Prevalence in women (%)	ABI criteria
Aboyans et al <sup>26</sup>	1932	45–84	4.4	12.3	<1.0
Moussa et al <sup>27</sup>	788	$\geq 70$ or 50–69 with DM or tobacco use	11.6	23.3	$\leq 0.9$
Ostchega et al <sup>4</sup>	3947	$\geq 60$	12.5	12.0	<0.9
Sigvant et al <sup>28</sup>	5080	60–90	9.4	12.6	<0.9
He et al <sup>29</sup>	2334	$\geq 60$	11.7	17.7	<0.9
Kröger et al <sup>30</sup>	4735	45–75	6.4	5.1	<0.9
Zheng et al <sup>31</sup>	15,173	45–64	2.5	3.6	$\leq 0.9$
Diehm et al <sup>32</sup>	6880	$\geq 65$	19.8	16.8	<0.9
Selvin and Erlinger <sup>2</sup>	2174	$\geq 40$	4.5	4.2	<0.9
Collins et al <sup>33</sup>	403	>50	17.4	15.9	<0.9
Murabito et al <sup>39</sup>	3313	$\geq 40$	3.9	3.3	<0.9
Hirsch et al <sup>34</sup>	6417	$\geq 70$ or 50–69 with DM or tobacco use	29.7	28.5	$\leq 0.9^*$
Meijer et al <sup>35</sup>	7715	$\geq 55$	16.9	20.5	<0.9
Stoffers et al <sup>36</sup>	3171	45–74	7.2	6.5	<0.95
Newman et al <sup>37</sup>	5084	$\geq 65$	13.8	11.4	<0.9
Gofin et al <sup>38</sup>	1592	35–64	4.2	5.4	<0.9

**Note:** \*Also includes a history of limb revascularization or documentation of PAD in the medical record.

**Abbreviations:** ABI, ankle brachial index; DM, diabetes mellitus.

in MESA demonstrated there to be a significant association between female sex and low ABI, suggesting that novel risk factors might contribute more to PAD in women than in men.<sup>26</sup>

It is unknown what these novel risk factors are, as there is a lack of published data in this field of study. However, one possible explanation could be differences in the underlying inflammatory profiles in women and men. Inflammation is a known strong risk factor for PAD. C-reactive protein (CRP) is an acute-phase protein that is elevated in individuals with PAD<sup>59,60</sup> and associated with the progression of PAD.<sup>61–64</sup> In addition, CRP levels may differ according to sex. In both MESA<sup>65</sup> and the Dallas Heart Study,<sup>66</sup> women had significantly higher CRP levels than men, despite adjustment for estrogen use, body mass index, and other variables. CRP has been shown in several studies to be an important risk factor for PAD in women. In a prospective cohort study of 27,935 US female health professionals aged over 45 years without baseline vascular disease, CRP was significantly associated with incident symptomatic PAD.<sup>67</sup> Among 1611 US participants aged 40 years or older without CVD, diabetes, or hypertension, higher CRP levels were positively associated with PAD, despite adjustment for multiple potential confounders.<sup>68</sup> In this study, women with CRP values in the highest quartile represented the highest risk group.

Another potential novel risk marker for PAD in women is adiponectin. Adiponectin is the most abundant circulating adipokine and has both anti-atherogenic and anti-inflammatory effects.<sup>69–71</sup> Adiponectin levels are also significantly higher in women than in men,<sup>72–76</sup> even after adjusting for body mass index.<sup>77</sup> In a nested case-control study conducted within the Women's Health Study, baseline adiponectin levels were significantly lower in women who subsequently developed PAD.<sup>78</sup> Further studies are needed to better characterize the possible sex-specific association between adiponectin and PAD.

Chronic kidney disease (CKD) is an independent risk factor for PAD<sup>79,80</sup> as well as an independent predictor of mortality in patients with PAD.<sup>81,82</sup> The prevalence and incidence of PAD is higher among patients with renal insufficiency than among those with normal renal function.<sup>79,83–87</sup> A cross-sectional analysis demonstrated that persons with renal insufficiency were 2.5-fold more likely to have an ABI of <0.9 than those with a normal creatinine clearance, even after adjustment for multiple CVD risk factors.<sup>84</sup> A longitudinal study in the Atherosclerosis Risk in Communities study demonstrated that those with CKD (estimated glomerular filtration rate < 60) had a 1.6 times increased risk for

incident PAD over a mean follow-up of 13.1 years.<sup>88</sup> CKD has become a major public health problem worldwide and, interestingly, there appears to be a higher prevalence of CKD in women than in men. In the National Health and Nutrition Examination Survey, the prevalence of both albuminuria and decreased glomerular filtration rate increased from 1988–1994 to 1999–2004, rising from 8.2% to 11.1% in men, and 12.1% to 15.0% among women.<sup>89</sup> In a recent systematic review of population-based studies, the prevalence of CKD was found to be greater in women than in men, regardless of age and ethnicity.<sup>90</sup> Although CKD is a risk factor for PAD, and CKD prevalence is higher in women than in men, the impact of the association between CKD and PAD according to sex has not yet been thoroughly evaluated.

It was long believed that estrogen was associated with a protective effect against atherosclerotic disease in women. Hence, hormone replacement therapy (HRT) was frequently prescribed to postmenopausal women. The Rotterdam study suggested a protective effect on the risk of PAD in long-term HRT users.<sup>91</sup> In addition, a recent prospective database of 847,982 postmenopausal women associated the use of HRT with a significant decrease in the prevalence of PAD, despite a high number of atherosclerotic risk factors among the women who used HRT.<sup>92</sup> However, large randomized controlled trials – the Heart and Estrogen/Progestin Replacement Study (HERS), Women's Health Initiative (WHI) Estrogen plus Progestin Trial, and WHI Estrogen-Alone Study – demonstrated different results. These randomized studies failed to demonstrate a protective effect of HRT on PAD,<sup>93–97</sup> and the WHI studies demonstrated an increased incidence of early peripheral vascular events in the treatment group. Based on these data, we conclude that HRT does not provide protection against PAD, and may be a risk factor for peripheral arterial events.

## Diagnosis of PAD in women

In both men and women, measurement of ABI is a noninvasive and accurate method with which to assess PAD. An ABI measurement of  $\leq 1.0$  is considered abnormal in both men and women. There is some debate over whether “normal” ABI levels are different between men and women, and across ethnic groups.<sup>98,99</sup> In a fully adjusted model of 1775 healthy participants in MESA, women had approximately 0.02-lower ABI values than men, and African-Americans had about 0.02-lower ABI values than Caucasians.<sup>99</sup> These findings were confirmed in another cohort of middle-aged individuals without PAD.<sup>100</sup> Although women may have a slightly lower “normal” ABI value than men, an ABI of <1.0 is still considered

abnormal in both men and women, and carries considerable risk for adverse CV events in both sexes.<sup>10,15,16</sup>

Should an anatomic assessment of lower extremity arterial occlusive disease be required for surgical treatment of PAD, computed tomography angiography, magnetic resonance angiography, and catheter angiography are all useful methods with which to delineate the nature and extent of PAD in both women and men. Even though women have smaller lower extremity arteries than do men of the same age,<sup>101</sup> these imaging modalities appear equally useful in both women and men. However, catheter angiography may be more useful in defining the smaller vessels of the lower extremity, especially in the infrapopliteal and pedal locations and if there is excessive calcification in the arterial wall.<sup>102</sup>

## Presentation of PAD

The hallmark clinical presentation of PAD is that of intermittent claudication, which is described as calf or thigh muscle fatigue or cramping produced by exercise and relieved with rest. However, it is increasingly recognized that PAD can be present in asymptomatic patients. The “ACC/AHA 2005 Practice Guidelines for the management of patients with peripheral arterial disease” estimates that <10% of PAD patients will present with intermittent claudication, another 50% will have atypical symptoms, and the remaining 40% will be asymptomatic.<sup>40</sup> In addition, women are more likely than men to have asymptomatic PAD.<sup>29,34,35,103–106</sup> In a Swedish population-based study of men and women aged 60–90 years, women were significantly more likely to have an abnormal ABI (<0.9) and be asymptomatic than men (12.6% vs 9.4%, respectively,  $P = 0.03$ ).<sup>28</sup> Similarly, in a longitudinal study of 2327 patients followed for 7.2 years in The Netherlands, the incidence of asymptomatic PAD was 7.8% in men and 12.4% in women.<sup>107</sup>

It is as yet unclear why women with PAD are more likely to be asymptomatic than men. It is possible that women experience walking problems differently, have atypical symptoms, have a lower level of activity, or are just less likely to report symptoms than men. McDermott et al found that leg symptoms and ABI values only correlated in women who walked more than four blocks per week. No association was found between symptoms and abnormal ABI values in less active women.<sup>108</sup> It is also possible that women with PAD are not really asymptomatic but that the PAD symptoms are masked or misinterpreted as symptoms related to arthritis, osteoporosis, or spinal stenosis. For example, in a cross-sectional study of 460 women and men with PAD, women had a higher prevalence of spinal stenosis, which could partially

account for sex differences in lower extremity symptoms.<sup>109</sup> Women with PAD also have poorer lower extremity strength and greater functional impairment than men with PAD. In a longitudinal study of 380 men and women with PAD, women were more likely to become unable to walk for 6 minutes continuously, had greater mobility loss, and faster decline in walking velocity at 4 years of follow-up.<sup>46</sup>

When women do develop lower extremity symptoms and present for PAD treatment, they are more likely to present with advanced disease and critical limb ischemia (CLI).<sup>47,106,110</sup> Women are more likely to require emergent vascular procedures than men<sup>48,49</sup> and are more likely to require amputation as first-line treatment.<sup>106</sup> It is possible that both underdiagnosis and delayed diagnosis of PAD could contribute to these findings. Atypical presentations of this disease may also play a role in this more advanced presentation among women. Thus, it is critical to recognize PAD early in women. Since women with PAD are more likely to be asymptomatic or present with atypical lower extremity symptoms, practitioners should have a high level of suspicion, consider the diagnosis of PAD in all elderly women, and utilize noninvasive testing such as ABI measurement in addition to clinical history, standardized questionnaires, and physical examination. Utilizing all of these measures will probably result in improved detection of PAD in women. For example, in a study of 2334 participants  $\geq 60$  years old, the prevalence of PAD in women was 11.9% as measured by Rose Questionnaire, 16% by ABI < 0.9, and 20.7% when both methods were employed together.<sup>29</sup>

## Treatment of PAD

Treatment of PAD should begin with risk-factor modification, such as smoking cessation, and appropriate treatment of medical comorbidities, especially hypertension, hyperlipidemia, and diabetes mellitus according to the “Inter-Society Consensus for the Management of Peripheral Arterial Disease” guidelines.<sup>111</sup> Antiplatelet therapy is an important therapeutic intervention in the secondary prevention of CV events in those with established atherosclerosis. Aspirin is the most widely used antiplatelet medication and has been extensively investigated in the coronary and carotid circulations. In the initial Antithrombotic Trialists’ Collaboration meta-analysis, PAD patients without evidence of vascular disease in other territories did not have a significant reduction in CV events when treated with aspirin.<sup>112</sup> However, in the more recent meta-analysis of the Antithrombotic Trialists’ Collaboration, which included clopidogrel, ticlopidine, dipyridamole, and picotamide in addition to those studies with aspirin, there was

a 23% reduction in the risk of vascular events in those with PAD treated with antiplatelet medications.<sup>113,114</sup> Aspirin use should be considered in those patients with asymptomatic PAD but without clinical evidence of other forms of CV disease.<sup>111</sup> Aspirin should be given to those patients with symptomatic PAD or in PAD patients with clinical evidence of coronary or cerebrovascular disease.

These recommendations do not differ based on sex; however, women with PAD are far less likely than men to receive the recommended therapy. In the Reduction of Atherothrombosis for Continued Health (REACH) Registry with 8322 PAD patients, women were significantly less likely than men to be treated with optimal risk-factor control.<sup>115</sup> Similarly, in a Swedish population-based PAD study, men were more likely to be treated with lipid-lowering therapy,  $\beta$ -blockers or angiotensin-converting-enzyme-inhibitors, and antiplatelet therapy than women.<sup>116</sup> In a cohort of men and women undergoing non-cardiac vascular surgery (including 1046 lower limb reconstructions), men were more likely than women to receive disease-specific medications.<sup>117</sup> Since improvement in risk-factor control is associated with lower 1-year CV event rates, a more aggressive approach for risk-factor modification needs to be employed, especially in women with PAD.

In those patients with symptoms of intermittent claudication, the approach to treatment should include a structured exercise program in addition to the risk-factor modification already described. The potential mechanisms by which exercise increases walking ability in PAD patients include an increase in collateral blood flow past the area of obstruction, improvement in nitric oxide-dependent vasodilation, and a decrease in systemic inflammation.<sup>118,119</sup> Supervised exercise programs have been shown in multiple prospective studies as well as meta-analyses to significantly increase pain-free walking distance as well as maximal walking time.<sup>119–121</sup> Selected patients may also benefit from pharmacologic treatment. Although several medications have been used for symptom relief from claudication, the drug with the most substantial evidence for effective treatment of claudication in the USA is cilostazol. Cilostazol (Pletal, Otsuka Pharmaceutical Co, Tokyo, Osaka, and Naruta, Japan) is a phosphodiesterase inhibitor that inhibits platelet aggregation and is an arterial vasodilator. A meta-analysis of 1751 patients in six randomized controlled trials demonstrated a benefit of cilostazol over placebo in peak treadmill performance and quality of life.<sup>122</sup> At this time, it is not known if there are sex-specific differences in response rates to either a structured exercise program or cilostazol for treatment of intermittent

claudication. However, the majority of participants in the studies described were men.

## Symptomatic PAD: CLI

Although PAD affects millions of Americans, only 1%–2% of this population will go on to develop CLI, which includes symptoms of lower extremity ischemic pain at rest, foot ulceration, or gangrene. Those who develop CLI are at significantly elevated risk for CV mortality as well as lower extremity amputation. The primary goals of treatment of CLI are to relieve rest pain, heal ulcerations, prevent limb loss, and improve lower extremity function and quality of life. Most patients with CLI will require a lower extremity revascularization procedure in order to meet these goals. Both open surgical bypass procedures and endoluminal angioplasty/stent placement are options for revascularization in women and men.

Even though women with PAD are more likely than men to present for emergent medical attention with CLI,<sup>47–49,106,110,123</sup> fewer vascular surgical procedures are performed on women.<sup>49,124</sup> In an analysis of 2.4 million PAD-related inpatient discharge records from New York, New Jersey, and Florida, women were significantly less likely than men to receive a vascular surgical procedure.<sup>49</sup> In a registry of 5880 infrainguinal arterial reconstructions, only 37% of the procedures were performed on women, and women were more likely than men to undergo surgery for limb salvage.<sup>123</sup> The reasons why this is the case, if the prevalence of PAD is the same in women and men, are as yet largely unknown. It is possible that women with PAD are more likely to be asymptomatic for longer periods of time and then only present for treatment when the disease has become advanced. It is also possible that women with PAD are less likely to be offered a surgical intervention because of atypical symptoms.

## Outcomes after surgical revascularization

Sex-specific data on outcomes after lower extremity revascularization procedures are conflicting, with some reports suggesting that women have worse rates of graft patency than men after lower extremity bypass surgery.<sup>101,125–127</sup> In the largest contemporary series of 9217 patients undergoing lower extremity bypass grafts, female sex was an independent risk factor for early graft failure.<sup>128</sup> In another series of 1646 patients undergoing lower extremity bypass, female sex was an independent risk factor for graft failure and limb loss.<sup>126</sup> In a cohort with CLI, women had a sig-

nificantly higher risk for wound complications, limb loss, and mortality after lower extremity bypass.<sup>129</sup> In contrast, two large registry studies of infrainguinal arterial reconstruction demonstrated no difference in graft patency and mortality in men and women.<sup>123,130</sup> In all of these studies, there were fewer women than men, the women were older, and the women presented with disease at a more advanced stage. There have also been several recent studies examining sex differences in outcomes after endovascular treatment of lower extremity PAD, again with mixed results.<sup>110,131–133</sup> Until women are equally represented in lower extremity revascularization studies, it will be difficult to definitively determine the association between sex and outcomes after lower extremity revascularization.

What has been consistently shown is that female sex is a risk factor for wound complications after lower extremity revascularization procedures. In two separate studies of the National Surgical Quality Improvement Program database, female sex was an independent risk factor for surgical site infection after lower extremity bypass procedures.<sup>48,134</sup> This is an especially important finding since surgical site infections have been associated with prolonged hospital stay, increased early graft loss, and reoperation.<sup>134</sup> In a multi-state hospital discharge database, female sex was independently associated with bleeding and infection after lower extremity vascular interventions.<sup>47</sup>

## Conclusion

Although often overlooked, PAD is a common disease in women. Since the elderly is the fastest growing population in the USA, and women have a longer life expectancy than men, there will be an increasing population burden of women with PAD. Clinicians should have a high degree of suspicion for PAD in women, especially in those with other CV risk factors, since women are more likely to be asymptomatic or present with atypical lower extremity symptoms than men. Efforts should be made to ensure that women with PAD receive appropriate CV risk-factor modification. Women who undergo surgical revascularization for PAD tend to be older and present with more advanced disease than men, have an increased risk of postoperative wound complications, and may have worse rates of graft patency and limb salvage. This should further emphasize the importance of early detection and treatment of PAD in women.

## Disclosure

The authors report no conflicts of interest in this work.

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