



T.T.T. Huynh, M.D.

LIMB SALVAGE IN WOMEN

Tam T.T. Huynh, M.D.;^a Lori Choi, M.D.^b

^aThe University of Texas MD Anderson Cancer Center, Houston, Texas; ^bThe University of Texas Medical Branch, Galveston, Texas

Abstract

The prevalence of peripheral arterial occlusive disease (PAD) in women and men is equal. Studies to date present conflicting data of gender effects on the risk factors, clinical presentation, and treatment outcomes. Clinical trials have often failed to analyze results by gender or to recruit sufficient women to enable such an analysis. This review summarizes the management and outcome of limb salvage therapy with a particular focus in women.

Introduction

Cardiovascular diseases remain the number one cause of death in industrialized countries. For decades, it was thought that cardiovascular diseases affect men predominantly. Whether due to better disease recognition, increased numbers of women smoking tobacco, or other socioeconomic or environmental factors, the reported incidence of cardiovascular diseases in women began to rise in the early 1980s. In 2007, more women died from cardiovascular diseases than men (421 918 vs. 391 886, respectively);¹ in fact, according to the National Center for Health Statistics, the annual number of cardiovascular deaths for women in the United States has consistently exceeded those for men since 1984. During the same period, a rise in the incidence of peripheral arterial occlusive disease (PAD) was also observed in women. Published PAD studies have reported conflicting results on the outcome for limb salvage, morbidity, and mortality in women compared to men. Factors such as older age, late presentation, delayed diagnosis, smaller-size vessels, and other gender-related biases have been postulated to account, at least in part, for the portended less-favorable outcome in women with PAD. However, until recently, most studies on PAD have had low enrollment rates for women. Fortunately, the gender disparity in the management of PAD has been recognized, and more effort and resources have been dedicated to study this issue. In this article, we provide an up-to-date review on PAD in women, focusing on the similarities and differences compared to men with regard to clinical presentation and limb-salvage treatment.

Epidemiology, Risk Factors, and Clinical Evaluation

Prevalence of PAD in Women

PAD affects approximately 8 to 12 million people in the United States.² The prevalence of PAD varies depending on what is defined as PAD and the age of the study population. Through mechanisms not yet well defined, premenopausal women are thought to be relatively protected from arteriosclerosis. However, arterial occlusive disease in women increases significantly during menopause and after. As such, the incidence of disease in women and men in their sixth and seventh decades is at least identical. The prevalence of PAD rises with age in both men and women.

The current age-adjusted prevalence is estimated at approximately 12%, affecting men and women equally.^{2,3} In the Cardiovascular Health Study, 11.4% of 2870 asymptomatic women aged ≥ 65 years had PAD.⁴ Approximately 10-20% of people with PAD identified in epidemiological studies are symptomatic, and among these persons, classic intermittent claudication was present in only 11%.^{5,6} The prevalence of symptomatic PAD is highest in elderly patients, estimated at 26% in one study of 2464 women with mean age of 81 years living in a nursing home.⁷ Notwithstanding the risk of limb loss, women with PAD are at increased risk for all-cause mortality, cardiovascular mortality, and cardiovascular events.⁵ Criqui et al. showed that PAD is a predictor for increased all-cause mortality and mortality from cardiovascular disease, with a risk ratio of 2.5 and 4.8, respectively, in a group of 258 women.⁸ This increased mortality risk is highest in patients with critical leg ischemia.^{5,6}

Risk Factors for PAD in Women

Well-defined risk factors of PAD include older age (>65 years), cigarette smoking, systemic hypertension, diabetes, dyslipidemia, and homocysteinemia.^{2,3} The patient's ethnicity and socio-economic status have been associated with higher PAD complications. In a German population-based study, participants with low and median educational levels had higher odds of suffering from PAD compared to participants with high educational levels.⁹ In this study, the association of lower socioeconomic status and PAD was more influenced by current smoking status, diabetes, and obesity rather than by actual financial income.⁹ In a retrospective review of a cohort of more than 1500 patients, Robinson et al. showed that Hispanic race was an independent risk factor for limb loss in patients undergoing infrainguinal bypass surgery.¹⁰ In the posthoc analysis of the PREVENT III trial, a multicenter randomized trial that evaluated the results of leg bypass surgery for critical ischemia using venous conduits, graft failure and amputation rates were highest in black women, suggesting a synergistic effect of gender and race on outcome.¹¹

Clinical Presentation and Evaluation of PAD in Women

Symptoms of PAD range from intermittent leg claudication and ischemic rest pain to tissue loss or necrosis. However, the

majority of men and women with PAD are asymptomatic, defined as having an ankle-brachial index (ABI) of less than 0.9 without leg symptoms. Interestingly, in a cohort study of 460 PAD participants, 187 women were more than twice as likely to report atypical leg symptoms with exertion that sometimes begin at rest.¹² In the same study, women with PAD were found to have poorer leg strength and greater walking impairment than their male counterparts.¹² A thorough review of PAD risk factors, comorbid medical illnesses and current medications is of paramount importance. The standard physical exam of the woman with PAD focuses on the palpation of peripheral pulses, the presence or absence of signs of vascular insufficiency (such as hair loss, muscle atrophy, or thickened nail), and the presence or absence of tissue loss and necrosis (Figures 1 A, B). Although much has been reported on the higher incidence of cardiovascular events in patients with asymptomatic PAD, the natural history with regard to limb outcome in these patients is not well defined. Fortunately, it has been observed that only a small percentage of patients with asymptomatic PAD or intermittent claudication will develop progressive disease or critical limb-threatening ischemia. Several PAD reports have found women to be older (typically by 3 to 4 years) and to present with more severe or advanced disease compared to men. Brevitti et al. reported on a cohort of 231 men and women with PAD.¹³ The authors found that women had a higher incidence of metabolic syndrome, obesity, diabetes mellitus, and hypertension but were less likely to have smoked or continue to smoke tobacco compared to men.¹³ Women with PAD may also demonstrate a faster functional decline and greater mobility loss than men, as recently shown by McDermott et al.¹⁴



Figure 1. The right foot of a 56-year-old woman with aggressive metastatic non-small cell lung cancer who developed acute onset of progressive right forefoot critical ischemia. (A) dorsal view showing discoloration at base of first toe and tips of toes with colored nail polish. (B) plantar view revealing dry necrosis of tip of fifth toe.

The diagnostic work-up for PAD includes physiologic studies, duplex ultrasound, and computed tomography (CT) or magnetic resonance (MR) angiography. The image quality of all three modalities has improved remarkably over the years, permitting an accurate assessment of the patient's arterial anatomy and disease lesions (Figure 2). Selective digital subtraction angiography is now rarely indicated for diagnostic confirmation but is used instead for therapeutic endovascular interventions. There are no gender-specific differences in the diagnostic evaluation for PAD. After a complete assessment, it is helpful to determine the extent of disease according to the TransAtlantic InterSociety Consensus (TASC) anatomical classification to plan therapeutic intervention and for reporting.¹⁵

Medical Therapy for PAD in Women

Modification of risk factors and medical therapy remain the first line of treatment for all patients with PAD.^{5, 16, 17} In brief,

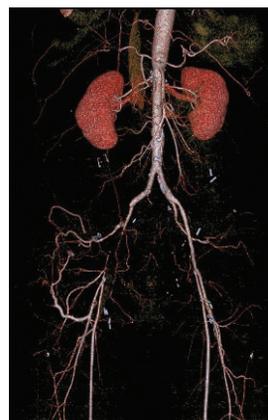


Figure 2. Three-dimensional volume rendering of reconstructed CT angiogram of a 57-year-old woman with ischemic rest pain in the right leg, demonstrating chronic occlusion of the right common and external iliac and common femoral arteries. The patient had previously undergone (failed) endovascular intervention and cross-over left-to-right femoral-femoral artery bypass.

a smoking cessation program should be instituted in all active smokers. Continued tobacco smoking has been associated with a higher risk of amputation in patients with intermittent claudication, lower patency in leg bypass grafts, and increased risk of myocardial infarction and death.¹⁸⁻²⁰ Patients with intermittent claudication should be encouraged to continue to exercise. Furthermore, participation in a supervised exercise program has been shown to produce superior symptomatic improvement in these patients compared to unsupervised exercise.^{21, 22} Medical therapy aims at keeping the HgbA_{1c} level to less than 7% in diabetic patients, reducing serum low-density lipoprotein cholesterol level to less than 70 mg/dL in patients with hypercholesterolemia, and lowering the blood pressure to less than 130/80 mm Hg in hypertensive patients.²³⁻²⁶ In addition, antiplatelet, statin, angiotensin-converting enzyme inhibitor, and β -blockade agents have all been shown to be beneficial in PAD patients.²⁶⁻³² We therefore recommend prescribing these agents to all PAD patients unless otherwise contraindicated. Moreover, the addition of cilostazol, a phosphodiesterase inhibitor, can further improve exercise capacity and increase walking distance in patients with intermittent claudication.^{33, 34}

We found no reported significant differences regarding medical treatments for PAD in women compared to men. However, there are two important points related to prescription medications to consider. First is the observation that hormone replacement therapy, either as estrogen alone or in combination with progesterone, has been shown to increase cardiovascular risk without improving PAD.^{35, 36} Additionally, it has been shown that lower income is associated with worse PAD outcomes.³⁶ A retrospective analysis stratifying patients with femoropopliteal atherosclerotic disease by low vs. high income reported worse outcomes in the lower income patients, who were also statistically less likely to be taking a statin medication.³⁷

Lower Extremity Revascularization and Outcome for PAD in Women

In Figure 3, we outline the algorithm for the management of PAD in women. The majority of patients with either asymptomatic PAD or intermittent claudication fare well with medical therapy and have a low risk of limb loss. Candidates for revascularization are patients with disabling claudication or those who have evidence of critical limb-threatening ischemia as manifested by the presence of ischemic rest pain, nonhealing wounds, or tissue necrosis. Revascularization can be surgical or endovascular based on the extent of the occlusive lesions and the patient's clinical characteristics. According to TASC guidelines on PAD treatment

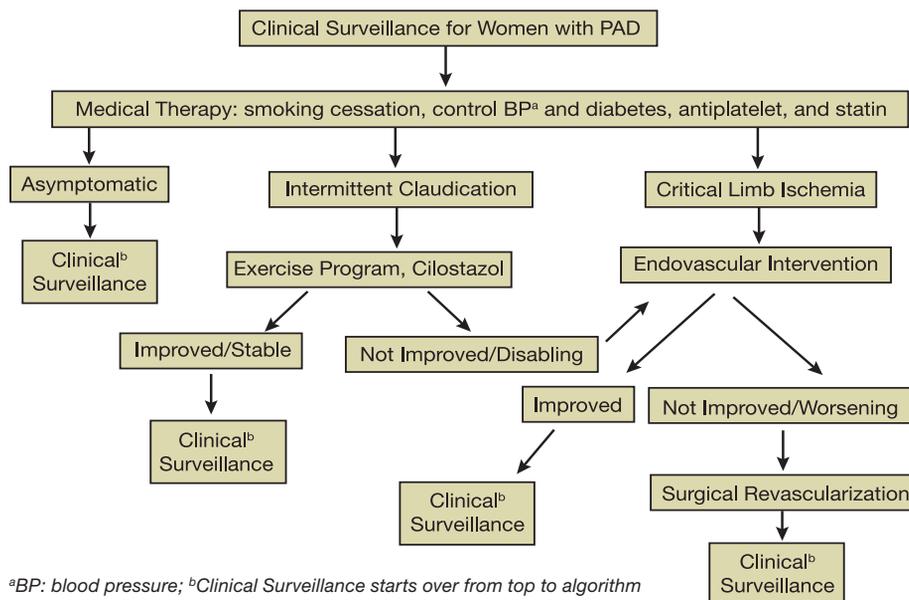


Figure 3. Algorithm outlining the management of peripheral arterial disease (PAD) in women.

strategies, endovascular revascularization is the treatment of choice for TASC A/B lesions, and surgical intervention is reserved for TASC C/D lesions. However, with evolving technological advances and physician experience, recent reports are demonstrating the efficacy of endovascular treatment for the more extensive TASC C/D lesions.

Numerous cohort studies have shown that women are more likely to be older and present with more advanced disease (critical limb-threatening ischemia and multilevel disease) compared to men.^{38,39} Pooled conclusions from large cohort series and review studies have included marginally worse outcomes regarding the rates of limb salvage, morbidity, and mortality for women undergoing lower extremity revascularization when compared to men.⁴⁰⁻⁴³ The authors have postulated that the older age, higher rate of diabetes, and more extensive occlusive disease may account for the higher complication rates in women.⁴⁰⁻⁴³ In their analysis of the large inpatient discharge database of New York state, Vouyouka et al. reported a slightly higher risk of bleeding (10.6% vs. 8.2%), infection (3.2% vs. 2.9%), and amputations (9.8% vs. 8.8%) in women compared to men undergoing endovascular and open surgical procedures.³⁶ In contrast, other authors have reported equivalent outcomes and limb-salvage rates in women and men, although women presented with more advanced disease.^{38,44-47} In our experience, the most challenging revascularization cases for limb salvage have been in women with smaller diameter native vessels, whether using endovascular or open surgical techniques, although this has not been consistently characterized in the literature.

Aortoiliac Occlusive Disease in Women

Men and women with aortoiliac occlusive disease are usually half a decade younger than patients with infrainguinal disease at presentation. In general, women have smaller diameter vessels compared to men, a characteristic that is particularly more pronounced in the aortoiliac segments. This may be in part the reason for the reported higher rate of graft thrombosis in women compared to men undergoing aortobifemoral bypass. In his experience with aortofemoral reconstructions for 339 men and 197 women over a 28-year period at the Cleveland Clinic, Hertz et al. reported that women were more likely to sustain graft thrombosis (OR 3.2, $P < .005$).⁴¹ Valentine et al. demonstrated that although

women have smaller aortic diameters compared to men, gender was not a predictor for graft failure in a subgroup of younger patients (mean age of 44 years) undergoing surgical aortofemoral revascularization.⁴⁸ In this study, the mean infrarenal aortic diameter was significantly smaller in the occluded grafts (14.5 mm in women vs. 18.1 mm in men) compared to the patent grafts (15.7 mm vs. 19.2 mm, respectively), indicating the influence of native inflow vessel size on graft patency that is independent of gender.⁴⁸ In their early experience with endovascular iliac interventions, Ballard et al. showed that aortoiliac artery balloon angioplasty and stenting was inferior to surgical reconstruction in a cohort of 119 women and men.⁴⁰ Multivariable analysis identified female gender as an independent predictor of bypass graft or stent thrombosis.⁴⁰ However, the authors did not provide details differentiating between the women with graft thrombosis and those with stent thrombosis. Orr et al. reported their results of iliac angioplasty and stenting for limb salvage in a comparative cohort study of 40 men and 44 women with aortoiliac occlusive disease.⁴⁹ Despite having smaller iliac arteries (mean luminal diameters of 6.5 mm and 8.2 mm for women and men, respectively) and a higher incidence of native iliac artery occlusion (21% vs. 6%, respectively), women had comparable primary, primary-assisted patency, and limb-salvage rates after a median follow-up of 13 months.⁴⁹ A subsequent single-institution cohort study compared stenting versus open reconstruction for 169 patients (~39% women) with aortoiliac occlusive disease.⁵⁰ In this study, the authors showed similar results for limb salvage and immediate-term secondary patency in patients after iliac stenting or open surgery, with no significant gender differences.⁵⁰

Infrainguinal Disease in Women

In a large retrospective study of 5880 patients (37% women) undergoing surgical infrainguinal arterial reconstructions using autogenous venous conduits preferentially, Roddy et al. showed excellent limb salvage rates of 93% for women and 88% for men at 10 years.⁴⁵ They found no significant differences in long-term survival, primary rate, and secondary patency rates between women and men.⁴⁵ Similar to other reports, women in this study were significantly older (71 years vs. 66 years), more often diabetic (53% vs. 50%), and less often smokers (27% vs. 44%)

compared to men.⁴⁵ A more recent report from Ballotta et al. showed comparable excellent results for 496 women and 837 men undergoing open infrainguinal arterial bypass with preferential autogenous vein graft.³⁸ There were no significant differences in morbidity and mortality rates between the two groups despite the fact that women were again a mean 3 years older than men and had a higher incidence of diabetes.³⁸ Ten-year limb salvage rates exceeded 90% in both men and women.³⁸ Other investigators have reported worse limb salvage rates for women of Hispanic and Black races compared to Caucasian women and men,^{10,11} although the underlying explanation for this race-based disparity has yet to be determined. AhChong et al. reported poorer primary and secondary graft patency rates in 93 women compared to 98 men undergoing infrainguinal bypass for critical limb ischemia. The authors postulate that the smaller-diameter target artery in women compared to men (median diameter 2.01 mm vs. 2.45 mm, respectively, $P = .03$) may be contributing, at least in part, to the worse patency outcome.⁵¹

Currently, percutaneous endovascular interventions have emerged as the revascularization modality of choice for patients with infrainguinal occlusive disease, including those with critical limb-threatening ischemia. Surgical reconstruction is generally reserved as a second-line or salvage therapy. Several studies have demonstrated low complication rates and good limb-salvage rates following endovascular interventions on occluded femoropopliteal and tibial arteries, with comparable results for men and women.^{46,52,53} DeRubertis and coauthors showed equivalent limb salvage and patency rates in women and men undergoing endovascular interventions for infrainguinal occlusive disease, even though the women had a higher prevalence of more advanced TASC C and D lesions (71% vs. 62%) and of critical limb ischemia (62% vs. 47%).⁴⁶ Pulli et al. showed similar findings with excellent limb salvage rates and low periprocedural complication rates in both women and men.⁵³ As shown in these series and numerous others, endovascular interventions for infrainguinal arterial lesions generally achieve limb salvage rates greater than 80-90%; however, the patency rates remain relatively low compared to those for iliac interventions, averaging a 40-50% primary patency rate at 1 to 2 years and between 50-80% primary-assisted patency rates. It is well recognized that repeated interventions on infrainguinal arterial lesions may be necessary to achieve long-term patency and limb salvage (Figure 4). We find tibial interventions for limb salvage particularly challenging. These patients are often older with multilevel arterial occlusive disease. Target vessels are smaller and less forgiving. In a recent publication, Domenick et al. reported tibial interventions in 201 patients (40% women) and showed an

overall limb salvage rate of 88% and a primary patency rate of 62% at one year.⁵² Gender and age >80 years did not play a significant factor in the outcome.⁵²

We identified two noteworthy reports in the literature indicating that women may have superior outcomes over men following endovascular interventions for infrainguinal arterial occlusive disease. Gallagher et al. reviewed their results of 537 patients (229 male and 308 female) undergoing infrainguinal percutaneous interventions between 2004-2009 and found no differences between genders in lesion characteristics.⁵⁴ Although women were more likely to have interventions for critical limb ischemia, they actually had better patency rates after interventions for superficial femoral artery and tibial lesions.⁵⁴ In a recent report by Tye et al., women were also found to have superior primary and patency rates following infrageniculate arterial endovascular interventions.⁵⁵ In this cohort of 38 men and 43 women, more men had TASC C and D lesions than women. However, female gender remained an independent predictor of superior outcome even after controlling for the gender-related differences in TASC grade.⁵⁵ All in all, for infrainguinal arterial occlusive disease, there appear to be conflicting findings in the literature with regard to gender disparities in outcome: most studies showed no differences, some demonstrated worse outcomes for women following open surgical revascularization, and some suggested superior results in women with endovascular treatment. Admittedly, some of the published studies may have been underpowered to identify a gender effect on outcomes, which hence underscores the importance for further research.

Major Lower Extremity Amputation in Women

Studies have shown lower survival rates for PAD patients requiring lower extremity amputations compared to those with successful revascularization, in part because of selection bias.^{56,57} For example, a major leg amputation would be recommended over a revascularization for a patient with high medical risks (Figure 5), and those requiring major amputation are more likely to have more advanced and extensive PAD. There is limited information on gender differences in the incidence and outcome of patients undergoing major lower extremity amputations for ischemic complications. In a literature review, Peek reports on current evidence indicating that men are more likely to undergo diabetes-related lower extremity amputation but that women have higher immediate and long-term mortality after amputation.⁵⁸ It is estimated that women have more deaths per 1000 amputations compared to men (37.7 vs. 29.7, respectively).⁵⁸ In addition, men are younger than women at the time of amputation regardless of the level of amputation.⁵⁸ In one retrospective analysis of the

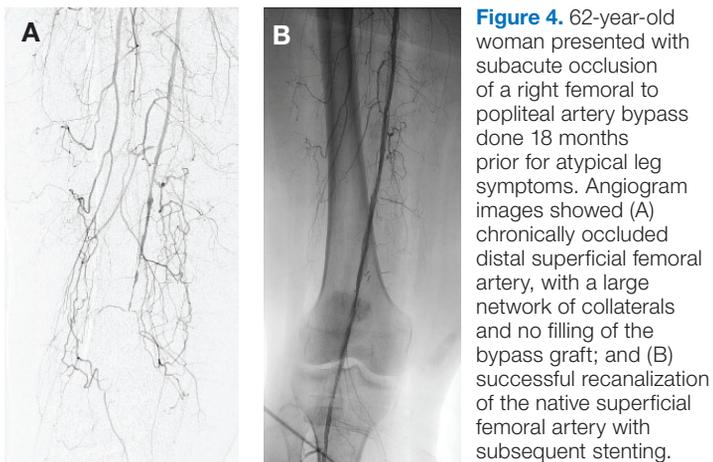


Figure 4. 62-year-old woman presented with subacute occlusion of a right femoral to popliteal artery bypass done 18 months prior for atypical leg symptoms. Angiogram images showed (A) chronically occluded distal superficial femoral artery, with a large network of collaterals and no filling of the bypass graft; and (B) successful recanalization of the native superficial femoral artery with subsequent stenting.



Figure 5. Extensive chronic foot wound in a frail 72-year-old diabetic woman with metastatic cholangiocarcinoma and severe infrainguinal arterial occlusive disease. Revascularization was not attempted, and the patient underwent successful rehabilitation after primary below-knee amputation.

Nationwide Inpatient Sample database for 2007, Lefebvre and Chevan reported that more men had below-knee than above-knee amputation (59% vs. 41%, respectively), whereas more women had above-knee than below-knee amputation (47% vs. 53%, respectively).⁵⁹ The authors postulate that the higher rate of above-knee amputations among women may indicate poorer outcomes in the presence of PAD compared to men.

Summary

Although conflicting results can be found in the literature, our review shows that while women with PAD can differ from men in their clinical presentation, their management and outcome are similar. In particular, women have smaller vessels and are older at the time of diagnosis. Future research studies to evaluate pharmacological, surgical, or device-related interventions in limb salvage must enroll women at a rate that reflects the increased prevalence of women with PAD. The widespread adoption of optimal medical management of asymptomatic disease will require large-scale educational efforts directed at both primary care providers and the public to increase the awareness of PAD in women.

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