Prevalence, clinical significance, and management of peripheral arterial disease in women: is there a role for postmenopausal hormone therapy?

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Abstract: Peripheral arterial disease (PAD), like coronary heart disease, is a clinical manifestation of atherosclerosis and is associated with increased mortality. Although atherosclerotic cardiovascular disease is the leading cause of death for women as well as for men, PAD in women has received less attention than coronary heart disease or stroke. This paper reviews the prevalence of PAD, its risk factors, clinical significance, and management in women. One gender-specific therapeutic issue of particular interest to practitioners and the lay public is the role of postmenopausal hormone therapy. Prior to completion of the Heart and Estrogen/Progestin Replacement Study and the Women's Health Initiative Hormone Trials, postmenopausal hormone therapy was believed to exert antiatherosclerotic effects and to thereby reduce coronary heart disease risk in women on the basis of case-control and cohort studies. This review particularly focuses on the role, if any, of postmenopausal hormone therapy for prevention or treatment of PAD, which was a pre-specified secondary outcome for these three randomized trials.

Keywords: women, estrogen, peripheral arterial disease

Introduction

Atherosclerotic peripheral arterial disease (PAD) can be categorized as aortic or involving arterial beds supplying the lower extremities, upper extremities, brain, or viscera such as the kidneys or intestine. This review will focus on lower extremity disease in women with particular focus on the role of postmenopausal hormone therapy.

Diagnosis

The prevalence of PAD varies with its definition and with approaches to screening. Clinical diagnosis of PAD is traditionally made by history of claudication or absent or diminished pulses. The Rose questionnaire (Rose et al 1982), which has been widely used to screen for claudication, will not detect asymptomatic disease. The ratio of ankle systolic blood pressure to arm systolic blood pressure at rest, the so-called ankle-brachial index, is an inexpensive approach to screening for asymptomatic PAD (Table 1) and can be accurately conducted in the primary care setting (Raines et al 2004). An ankle-brachial index of ≤0.90 has been reported to have 90% sensitivity and 98% specificity for arterial stenosis ≥50% (Greenland et al 2000).

In the Rotterdam Study, 36 (5%) of 742 women with ankle-brachial index <0.9 reported claudication on the Rose questionnaire (Meijer et al 1998). Symptoms of

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Table 1 Measuring ankle-brachial index

The patient should lie supine for 5 minutes in a comfortable room and position.

Measure brachial pressure

1. Place an appropriate sized blood pressure cuff (Table 2) above the elbow; apply ultrasound gel over brachial artery.
2. Move the vascular Doppler ultrasound probe across the brachial area until the arterial sound is identified; adjust probe to obtain loudest signal. Steady your hand on the patient.
3. While maintaining this position, inflate the blood pressure cuff until 10–20 mmHg above the point where arterial flow is no longer audible. Slowly deflate the cuff; the pressure at which the arterial sound returns is the brachial pressure. Repeat for the other arm.

Measure ankle pressure

1. In general, posterior tibial pressure is preferred to dorsalis pedis pressure. If values for both sites are obtained, use the highest value to calculate the index.
2. Place appropriate size blood pressure cuff just above the ankle. For the posterior tibial pressure, apply ultrasound gel behind the ankle bone (medial malleolus). Abduct the foot to make the medial ankle more accessible. Slowly scan behind the ankle bone until the arterial sound is identified; adjust probe to obtain loudest signal. Steady your hand on the patient.
3. For the dorsalis pedis pressure, position the probe on top of the foot, halfway between the tips of toes and ankle, between the big toe and second toe. Press lightly, as pressure may occlude the artery. Once you identify the arterial sound, adjust probe position to find the loudest signal.
4. While maintaining this position, inflate the blood pressure cuff until 10–20 mmHg above the point where arterial flow is no longer audible. Slowly deflate the cuff; the pressure at which the arterial sound returns is the ankle pressure. Repeat for the other ankle.

Calculate ankle-brachial index

Left ankle-brachial index = highest left ankle pressure ÷ highest brachial pressure

Right ankle-brachial index = highest right ankle pressure ÷ highest brachial pressure

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Table 2 Choosing the appropriate blood pressure cuff size (Perloff 1993)

Limb circumference		Cuff size
Cm	Inches	
27–34	≤13.4	Standard adult
35–44	13.7–17.3	Large adult
45–52	17.7–20.4	Adult thigh cuff

NOTE: An extra-large (XL) cuff is available for limbs 17–26 inches in circumference, and extra-extra-large (XXL) for those 26–35 inches in circumference (see www.amplestuff.com).

measurement in all individuals being evaluated for PAD, with a reminder that patients with diabetes may have heavily calcified vessels, artificially elevating ankle pressure (Sacks 2003). In that setting, toe pressure determinations may more accurately reflect peripheral perfusion.

Prevalence

The prevalence of PAD depends upon the characteristics of the population studied and the definition of PAD used. The Framingham Offspring Study defined PAD as ankle-brachial index <0.9 and identified it in 3.9% of 1554 men and 3.3% of 1759 women in their predominantly white cohort (Murabito 2002).

A recent assessment of PAD prevalence was conducted by the National Health and Nutrition Examination Survey (NHANES), which measured ankle-brachial index in a probability sample of 2381 United States residents over the age of 40 years from 1999–2000 (Gregg 2004). Oversampling of the elderly, low-income persons, non-Hispanic blacks, and Mexican Americans was undertaken to permit more reliable estimates in these subpopulations. In NHANES, the prevalence of PAD, defined as ankle-brachial index <0.90 in either leg, was 4.3% (95% confidence interval [CI] 3.1%–5.5%). Peripheral arterial disease was identified with similar frequency in men (4.5%, 95% CI 2.8%–5.6%) and women (4.2%, 95% CI 2.9%–6.1%) and increased with age. Extrapolating from the random NHANES sample to the United States' population, approximately 5 million adults, half of them women, have abnormal ankle-brachial indices.

Clinical significance of peripheral arterial disease

Both symptomatic and asymptomatic PAD predict functional decline (McDermott 2004). Annual decline in 6-minute walk performance was more marked among asymptomatic patients with ankle-brachial index <0.9 (–77 feet, 95% CI –135 to –19 feet) than among healthy

claudication were reported by a slightly higher proportion of men with ankle-brachial index <0.9, 37 of 424 (9%). Claudication was reported by few women (15/3023, 0.5%) or men (18/2135, 0.8%) with normal ankle-brachial indices.

Thus, reliance on claudication symptoms as a screening approach for detection of PAD provides high specificity, but poor sensitivity. Ankle-brachial index provides excellent overall diagnostic accuracy without incurring the expense associated with imaging studies such as ultrasound or magnetic resonance angiography (Greenland et al 2000). Nonetheless, the procedure is not reimbursed by many third-party payers, including Medicare in the United States. American Diabetes Association guidelines for preventive foot care include a recommendation that ankle-brachial index be considered in all patients with type 2 diabetes (American Diabetes Association 2004). The Society of Interventional Radiology recommends ankle-brachial index

controls (–9 feet, 95% CI –37 to +20 feet; p = 0.04). Annual decline was even greater among patients with abnormal ankle-brachial index and claudication (–111 feet, 95% CI –173 to –50 feet; p = 0.004).

A small minority of patients with PAD will develop critical leg ischemia over 5 years (~5%), with 1%–4% progressing to amputation (Faxon 2004). In addition to the impact of lower extremity atherosclerosis on downstream tissue, PAD may be considered a general marker of atherosclerosis; angiographic coronary disease is identified in about 85%; and carotid stenosis, defined as >30% by ultrasonography, is identified in about 60% of patients with PAD (Faxon 2004).

The presence of PAD has prognostic significance both for coronary heart disease and death (Criqui 1992; Hooi 2004). Criqui et al (1992) followed 565 men and women prospectively for 10 years. Among the 33 women with PAD identified by either ankle-brachial index or Doppler ultrasound, 33% died during follow up, compared with 26 of 225 (12%) of women without PAD. After multivariate adjustment, the relative risk for all-cause mortality was 3.1 (95% CI 1.9–4.9) for individuals with prevalent PAD. Relative risk for coronary death was 6.6 (95% CI 2.9–14.9).

The relationship between low ankle-brachial index and cardiovascular disease was confirmed in the Cardiovascular Health Study, a population-based cohort that included 3282 women aged ≥65 years (Newman 1999). Among individuals without prevalent cardiovascular disease at baseline, the hazard ratio in multivariate-adjusted Cox proportional hazards models was 1.40 (95% CI 0.90–2.17) for myocardial infarction, 1.12 (95% CI 0.74–1.70) for stroke, and 2.03 (95% CI 1.22–3.37) for cardiovascular death (Newman 1999).

The stroke risk with low ankle-brachial index was stronger in the Framingham Heart Study, in an analysis carried out when study participants' mean age was 80 years (Murabito 2003). In multivariate-adjusted Cox proportional hazards analysis, the hazard ratio for stroke was 2.0 (95% CI 1.1–2.7) among individuals with ankle-brachial index <0.9. The incidence of stroke was about 1.7% per year in this analysis, compared with 0.6% per year in the Cardiovascular Health Study (Newman 1999).

The relationship between ankle-brachial index and stroke was also examined in the Atherosclerosis Risk in Communities Study, which included 2450 black and 5776 white women, aged 45–64 years (Tsai 2001). The incidence of stroke was low among women in this middle-aged cohort, 0.2% per year. In Cox proportional hazards analysis adjusted for age, race, gender, center, blood pressure, diabetes, smoking, cholesterol, and prevalent coronary heart disease, ankle-brachial index did predict stroke risk (p-value for trend 0.03).

Thus, epidemiologic data from a variety of cohort studies strongly supports the relationship between low ankle-brachial index and increased risk of myocardial infarction, stroke, and death.

Peripheral arterial disease risk factors

Risk factors associated with PAD are similar to those of other atherosclerotic diseases. In NHANES, multivariate-adjusted logistic regression models identified current smoking as the strongest predictor of abnormal ankle-brachial index (odds ratio [OR] 4.23, 95% CI 1.95–9.17) (Gregg 2004). Other independent predictors of PAD included diabetes mellitus (OR 2.08, 95% CI 1.01–4.30), total cholesterol ≥240 mg/dL (OR 1.67, 95% CI 1.01–2.74), glomerular filtration rate <60 mL/min/1.73 m^2 (OR 2.17, 95% CI 1.10–4.30), and non-Hispanic black ethnicity (OR 2.39, 95% CI 1.11–5.12). Overweight (body mass index 25–30 kg/m^2) and obese individuals (body mass index >30 kg/m^2) were less likely to have abnormal ankle-brachial index, OR 0.87 and 0.54, respectively, compared with normal weight individuals (referent), although body mass index was not an independent determinant of abnormal ankle-brachial index.

Risk factors for PAD in women were assessed in the Heart and Estrogen/Progestin Replacement Study (Hsia 2000), a cohort of 2763 postmenopausal women with coronary heart disease. Independent predictors of peripheral arterial revascularization or amputation among women assigned to placebo for 4.1 years included hypertension (relative risk 2.66, 95% CI 1.60–4.44) and diabetes (relative risk 1.98, 95% CI 1.27–3.11). Negative predictors in Cox proportional hazards models included body mass index (relative risk 0.70, 95% CI 0.56–0.88) and high-density lipo-protein cholesterol (relative risk 0.76, 95% CI 0.60–0.96).

The relationship between chronic kidney disease and PAD has been identified in both a random sample of United States residents and in a cohort of women with coronary heart disease (O'Hare, Glidden, et al 2004; O'Hare, Vittinghoff, et al 2004). In the Heart and Estrogen/Progestin Replacement Study, the rate of lower extremity re-vascularization or amputation was inversely related to creatinine clearance. After multivariate adjustment, the relative risk among women with creatinine clearance

30–59 mL/min/1.73 m^2 was 1.63 (95% CI 1.04–2.54) compared with women with creatinine clearance $\geq$ 60 mL/min/1.73 m^2 (referent). Among women with creatinine clearance < 30 mL/min/1.73 m^2, relative risk was 3.24 (95% CI 1.20–8.78) (O'Hare, Vittinghoff, et al 2004).

Treatment

Peripheral arterial disease is a marker of systemic atherosclerosis; consequently, aggressive management of conventional atherosclerotic risk factors should be undertaken, especially smoking cessation. Exercise is also an important component of clinical management in patients with lower extremity arterial atherosclerosis (Menard 2004); supervised exercise, even once weekly, appears to improve long-term outcomes compared with exercise advice alone (Cheetham 2004). Potential mechanisms underlying the benefits of exercise training include improved oxygen extraction and utilization, better walking biomechanics, enhancement of collateral blood flow, favorable effects on endothelial function, arterial compliance, free radical formation, and inflammation (Stewart 2002; Falcone 2003).

Pharmacologic interventions can: (1) improve claudication symptoms; (2) reduce cardiovascular events in patients with PAD; or (3) reduce incident peripheral arterial events in individuals with or without PAD at baseline. Gender-specific data is generally not available, so these agents are briefly summarized. The one therapeutic area specifically studied in women is the role of postmenopausal hormone therapy, which is discussed in more detail.

Lipid-lowering agents

A secondary analysis of the Scandinavian Simvastatin Survival Study, a cohort of 4444 coronary heart disease patients including 827 women, identified new or worsening intermittent claudication in 2.3% of participants assigned to simvastatin 40 mg daily compared with 3.6% of those assigned to placebo during median follow up of 5.4 years, a relative risk of 0.62 (95% CI 0.44–0.88) (Pederson 1998).

Both simvastatin (Aronow 2003; Mondillo 2003) and atorvastatin (Mohler 2003) have been evaluated in patients with claudication. In a group of 86 patients with claudication and hypercholesterolemia randomized to simvastatin 40 mg or placebo for 6 months, pain-free walking distance was increased by simvastatin (+90 meters, 95% CI 64–116 meters, p < 0.005) (Mondillo 2003). In a trial of 354 patients with claudication, including 81 women (23%) randomized to atorvastatin 10 mg, atorvastatin 80 mg, or placebo for

12 months, pain-free walking time improved by 63% (91 ± 15 seconds) in the atorvastatin 80 mg group compared with 38% (39 ± 8 seconds) in the placebo group (p = 0.025) (Mohler 2003). Although quality of life measures did not differ among treatment groups, the combined atorvastatin groups had significantly fewer clinical peripheral vascular events (2 events in the atorvastatin 80 mg group, 1 in the atorvastatin 10 mg group, 9 in the placebo group, p = 0.003).

Angiotensin-converting enzyme (ACE) inhibitors

Ramipril reduced cardiovascular events in patients with peripheral vascular disease in the Heart Outcomes Prevention Evaluation trial, which randomized 9297 high-risk patients (2480 women) to ramipril or placebo for 4.5 years (Yusuf 2000). Among women enrolled, 49.4% had PAD at baseline defined as claudication, > 50% stenosis by angiography, prior peripheral revascularization, or ankle-brachial index < 0.9. In women, ramipril reduced the primary end point (myocardial infarction, stroke, or cardiovascular death) from 14.9% to 11.3% (relative risk 0.77, 95% CI 0.62–0.96) (Lonn 2002).

Antiplatelet agents

Aspirin, clopidogrel, and ticlopidine have all been demonstrated to reduce cardiovascular events in patients with PAD, but gender-specific analyses are lacking. In meta-analysis of patients with PAD, aspirin reduced the OR for major vascular events from 7.1% to 5.8% (p < 0.004) (Antithrombotic Trialists' Collaboration 2003).

The Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events trial randomized 19 185 patients with cardiovascular disease, including 6452 with PAD at baseline, to clopidogrel 75 mg daily or aspirin 325 mg daily for a mean of 1.9 years (CAPRIE Steering Committee 1996). Among those with PAD at study entry, the primary outcome (stroke, myocardial infarction, or vascular death) was identified in 3.7% per year in the clopidogrel group vs 4.9% per year in the aspirin group, an adjusted risk reduction of 23.8% (95% CI 8.9%–36.2%).

Although ticlopidine has also been shown to reduce coronary and cerebrovascular events in patients with claudication (relative risk reduction 0.66, 95% CI 0.45–0.96) (Janzon 1990), this agent is not widely used because of gastrointestinal symptoms, neutropenia, and thrombotic thrombocytopenic purpura.

Postmenopausal hormone therapy

During the two years preceding menopause, women's low-density lipoprotein cholesterol rises by 10%, high-density lipoprotein cholesterol falls by 6%, and triglycerides rise by 11% (Jensen 1990). Until recently, postmenopausal hormone therapy, which ameliorates these unfavorable lipid changes (The Writing Group for the PEPI Trial 1995), was believed to prevent atherosclerosis.

The association of postmenopausal hormone therapy with ankle-brachial index was studied in a population-based observational study of 2196 Dutch women, aged 55–80 years (Westendorp 2000). Recent postmenopausal hormone use was reported by 31 women and remote use by 320 women. Duration of therapy ranged from 1 to more than 15 years; 9% of hormone users had taken progestin in addition to estrogen. Ankle-brachial index < 0.9 was identified in 284 women (13%). In logistic regression analyses adjusted for age, smoking, and education, women who reported using postmenopausal hormones for at least one year were less likely to have abnormal ankle-brachial index (relative risk 0.48, 95% CI 0.24–0.85) compared with never users (referent). When short- and long-term hormone users were combined, relative risk of abnormal ankle-brachial index was 0.65 (95% CI 0.44–0.98).

Other observational studies found that women taking postmenopausal estrogen had less severe carotid athero-sclerosis, assessed by ultrasound (Jonas 1996; Le Gal 2003).

Recent randomized trials of postmenopausal hormone therapy have underscored the limitations of observational studies in evaluating the risks and benefits of estrogen. Peripheral arterial disease has been less intensively studied than coronary heart disease or stroke, but some data is available from randomized trials.

In one randomized trial using an intermediate outcome of change in intima-medial thickness assessed by ultrasound, unopposed estradiol reduced progression of carotid disease (Hodis 2001). Another trial, using combination estrogen with progestin found no effect on progression of ultra-sonographic carotid atherosclerosis (Byington 2002).

Three large randomized trials with clinical end points have now assessed the impact of postmenopausal hormone therapy on clinical cardiovascular end points, with PAD as a prespecified secondary outcome. The Heart and Estrogen/Progestin Replacement Study randomized 2763 women with documented coronary heart disease to conjugated estrogens (6.25 mg daily) with continuous medroxyprogesterone acetate (2.5 mg daily) or to placebo.

Peripheral arterial disease, assessed as peripheral arterial revascularization or amputation, was a prespecified secondary outcome. During 4.1 years of follow up, 143 lower extremity arterial events were identified, 77 among women assigned to placebo, and 66 in women assigned to conjugated estrogens with progestin (Hsia 2000). The age-adjusted relative risk for lower extremity events with combination hormone therapy was 0.88 (95% CI 0.58–1.35); multivariate-adjusted relative risk was 0.85 (95% CI 0.56–1.31).

For all types of PAD (aortic, carotid, and lower extremity), the relative hazard with combination estrogen/progestin was 0.87 (95% CI 0.66–1.44); the annual incidence of peripheral arterial events was 2.9%. Independent predictors of peripheral arterial events differed in the two treatment groups; among placebo recipients, hypertension and diabetes were positive determinants, whereas high-density lipoprotein cholesterol and body mass index were negative determinants of incident peripheral arterial events. In contrast, among women assigned to combination hormone therapy, diabetes and current smoking were positive predictors of peripheral arterial events. The observed potentiation by estrogen/progestin of the adverse effects of smoking (p-value for interaction = 0.03) may parallel the increased risk of myocardial infarction among oral contraceptive users (Lewis 1996) and provides an argument against prescribing postmenopausal hormones to smokers.

In The Women's Health Initiative Estrogen Plus Progestin Trial, 16 608 generally healthy postmenopausal women with intact uterus were randomly assigned to conjugated estrogens (6.25 mg daily) with continuous medroxyprogesterone acetate (2.5 mg daily) or to placebo – the same regimen as the Heart and Estrogen/Progestin Replacement Study. During 5.6 years of follow up, the incidence of peripheral arterial events, defined as overnight hospitalization for either peripheral arterial symptoms or intervention, was low (0.14% per year), reflecting the overall healthy condition of trial participants. The hazard ratio for lower extremity events with combination estrogen/progestin was 1.07 (95% CI 0.62–1.84) (Hsia 2004). For all peripheral arterial events (including aortic and carotid disease), the hazard ratio was 0.89 (95% CI 0.63–1.25). Subgroup analysis did not identify any characteristics associated with particularly high- or low-risk of PAD with combination hormone therapy.

The Women's Health Initiative Estrogen Alone Trial randomized 10 739 women with prior hysterectomy with

conjugated estrogens (0.625 mg/daily) or to placebo (The Women's Health Initiative Steering Committee 2004). Analyses of peripheral arterial events in that trial have not yet been completed. The coronary risk with unopposed estrogen (hazard ratio 0.91, 95% CI 0.75–1.12) appears to differ from that with combination estrogen/progestin (hazard ratio 1.24, nominal 95% CI 1.00–1.54) (Manson 2003). Whether the risk of peripheral arterial events with unopposed estrogen differs from that with combination estrogen/progestin remains to be seen.

Summary

Lower extremity PAD occurs with similar frequency in men and women. Among women with abnormal ankle-brachial index, 95% will not report claudication. Consequently, non-invasive screening, such as measuring the ankle-brachial index, is appropriate in asymptomatic individuals with atherosclerotic risk factors. Clinical management of lower extremity arterial disease should include physical training, optimally with supervised exercise, and aggressive treatment of conventional atherosclerotic risk factors. The increased coronary and cerebrovascular risk in individuals with PAD appears to be attenuated by ACE inhibition and clopidogrel. Postmenopausal hormone therapy with combination estrogen/progestin provides no protection against peripheral arterial events. The role of unopposed estrogen for prevention of PAD remains to be determined.

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