A Call to Action: Women and Peripheral Artery Disease
A Scientific Statement From the American Heart Association

Endorsed by the Vascular Disease Foundation and its Peripheral Artery Disease Coalition

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Lower extremity atherosclerotic peripheral artery disease (PAD) has a very high prevalence in most nations and in the United States. Lower extremity PAD is now known to be associated with equal morbidity and mortality and comparable (or higher) health economic costs as coronary heart disease (CHD) and ischemic stroke. Yet where surveyed, the public and clinicians (as well as health payers and government agencies) do not yet fully recognize the risks associated with PAD. For decades, clinicians did not recognize the impact of coronary disease in women. As such, women were not informed of their CHD risk. For any common disease, whether infectious, oncological, or traumatic, when more than half of the population at risk is not aware of this risk, and when this risk is not managed, preventable morbidity and mortality events are inevitable. Certain health facts are now evident: Women suffer the consequences of PAD at rates at least as high as those observed in men. But major knowledge gaps exist. Clinical research to evaluate gender-based differences that might underlie the delayed, postmenopausal presentation of PAD in women has not been conducted. Whether subtle but important gender-based distinctions in clinical presentations exist is unknown. The relative sensitivity and specificity of PAD diagnostic tests and pathways by gender are unclear. Although there is suggestive evidence that treatment benefits and harms are different in women and men, this cannot yet be confirmed from current clinical trial data because of the limited inclusion of women in past investigations. Other facts provide encouragement. Women with or at risk for CHD now better understand this risk. Thus, collation of accurate PAD-specific health information for women is likely to improve their own health and that of society at large.

The American Heart Association, in collaboration with the Vascular Disease Foundation (and its “Peripheral Arterial Disease Coalition”), commissioned this scientific statement to summarize the evidence that describes the epidemiological burden of PAD in women. The statement also aims to describe the associated cardiovascular risk of ischemic events, as well as the symptom classes and clinical presentations that should be known to women; to highlight the efficacy of current treatments; and to spotlight the challenges represented by the current low levels of PAD awareness among target female populations. Finally, this statement reviews the current status of PAD-
specific risk messages in current women’s cardiovascular health programs.

This statement presents a series of new evidence tables, linked to the “ACC/AHA 2005 Practice Guidelines for the Management of Patients With Peripheral Arterial Disease” and the “2011 ACCF/AHA Focused Update of the Guidelines for the Management of Patients With Peripheral Arterial Disease (updating the 2005 guideline).” Readers should refer to these guidelines as the best source of current care recommendations. This statement is designed to:

- Urge healthcare professionals to use the current vascular review of symptoms, physical examination, and diagnostic testing pathways to ensure that the PAD diagnosis is promptly established in women “at risk” for having undiagnosed PAD
- Urge individual clinicians and women’s cardiovascular health programs to incorporate PAD-specific risk messages in their current and future cardiovascular outreach efforts that are targeted to women
- Clarify the potential role of women in facilitating improved national PAD awareness, as has occurred for other cardiovascular diseases (CVDs)
- Promote the translation of the successful “Go Red for Women” and Heart Truth campaigns for coronary artery disease (CAD) awareness as models to achieve comparable success for PAD

This statement was coauthored by a writing committee composed of members of several American Heart Association councils, as well as the nonprofit Peripheral Arterial Disease Coalition of the Vascular Disease Foundation. Together, we believe that this scientific statement is a “call to action.” We hope these data and recommendations will motivate specific actions to address this challenge and thus help to improve PAD-related and global cardiovascular health.

**Epidemiology of PAD in Women**

**Prevalence of PAD**
The population-based prevalence of PAD in women has been incompletely evaluated. In contrast to the abundant data defining the gender-specific prevalence of CAD and stroke, few population surveys of PAD have been performed, and ongoing PAD surveillance is not currently conducted in any state or nation. Thus, in calculating the relative prevalence of PAD, it has been noted that many population-based studies of PAD do not report prevalence for women separately. In the published literature, the results are mixed with respect to differences in prevalence by gender. In a review by Higgins and Higgins, the prevalence of PAD in women 45 to 93 years of age was reported to range from 3% to 29% over this span of 5 decades.

To provide the most accurate gender-specific PAD prevalence estimates, this writing committee sought data from individual participant data meta-analyses. These data are adapted from Allison et al., who obtained raw data either from publicly available data sets or by contacting the original investigators. Studies were included if both men and women were studied and in which the presence of PAD was determined objectively on the basis of the measurement of an ankle-brachial index (ABI) <0.9 in participants who had no previous history of lower extremity arterial revascularization. Using individual participant data meta-analytic methods, the pooled prevalence was calculated for men and women separately (Table 1; Figure 1).

In this analysis, the prevalence of PAD increased with age for both men and women. Beyond mere definition of the prevalence of any atherosclerotic disease, there is increasing interest in the population “burden” of these syndromes (defined as the total number of individuals who have the disease). Using US census data from 2010, the burden of PAD was calculated (Figure 2) and showed that there were more women than men with PAD among US adults ≥40 years of age.

**Mortality**
Few prior studies have reviewed the gender-specific mortality of PAD. For the present scientific statement, data were adapted from the ABI Collaboration study completed by Fowkes et al. Studies were included if participants were derived from a general population, ABI was mea-
sured at baseline, and individuals were followed up for total and cardiovascular mortality. Sixteen population-based cohort studies of PAD were used, which included 480,325 person-years of follow-up of 24,955 men and 23,339 women. An individual participant data meta-analysis was conducted for studies that included subjects who had no previous history of CHD.

These results demonstrate that the associations between ABI values and total mortality, CVD mortality, and major coronary events are similar in women compared with men (Figure 3). Specifically, in women, the risks for morbidity and mortality are increased with lower ABI values and with values <1.40.

Methodological Challenges and Implications for Future PAD Research
There are several challenges in evaluating the epidemiology of PAD in women from the existing literature. First, although PAD prevalence is commonly reported from clinical series, these studies do not provide a true population-based prevalence. In a prior review by Higgins and Higgins, gender-specific values were often inferred from overall prevalence. Vavra and Kibbe reported the mean prevalence in men and women from 8 studies but did not apply appropriate meta-analytic techniques. Selection bias is likely an issue in assessment of PAD in field surveys and clinical trials, with the observation that elderly women are less prone to attend such examinations and more likely to refuse ankle blood pressure measurement.

Summary Statements
1. The gender- and age-specific prevalence of PAD has not been clearly defined from published population-based studies.
2. Although the age-dependent prevalence of PAD in adult women is lower than for men, the total population burden of PAD appears to be higher.
3. Cardiovascular mortality, all-cause mortality, and major coronary event rates by gender have not been well defined in population-based studies. A trend exists that suggests higher event rates for women than for men for individuals with an ABI <0.90.

Future studies of PAD prevalence and risk should (1) clearly define the methods by which PAD was ascertained; (2) include gender-specific, and preferably age-specific, prevalence values; (3) evaluate the possibility of study-specific selection bias; and (4) explicitly state how the blood pressure measurements for the ABI were obtained and how the ABI was calculated.

Clinical Presentation of PAD in Women
Leg Symptoms in Women
Although intermittent claudication is considered a hallmark manifestation of lower extremity PAD, it is well established that many patients with PAD do not present with classic symptoms. Many people with PAD are asymptomatic (defined as absence of exertional leg symptoms in the presence of an ABI <0.90), whereas others have atypical leg symptoms (for example, leg muscle pain).
symptoms that are present at rest and with exercise). This fact alone, not recognized until approximately 1 decade ago, has fundamentally altered perceptions of the prevalence and risk of PAD in both genders by clarifying that there is a long “latent phase” in which systemic CVD progresses and that is difficult to detect by routine clinical histories. In this regard, the presence of asymptomatic PAD and atypical exertional leg symptoms has been observed in both men and women. For example, in the Women’s Health and Aging Study (WHAS) of 933 disabled women ≥65 years of age, 328 (35%) had an ABI <0.90, which established the diagnosis of PAD. Of these 328 women with PAD, 63% had no exertional leg symptoms. Thus, asymptomatic PAD is common among older women.

Although both men and women with PAD can be either asymptomatic or present with atypical leg symptoms, gender differences in the prevalence of specific leg symptoms among patients with PAD have been reported. In a population study of 5080 Swedish men and women 60 to 90 years of age, asymptomatic PAD was more common in women than in men (12.6% versus 9.4%, P=0.03). Similarly, in the Walking and Leg Circulation Study (WALCS) cohort of 460 PAD participants without critical limb ischemia identified from Chicago (IL)-area medical centers, the 187 women were more than twice as likely as the men to report the presence of atypical exertional leg symptoms that sometimes began at rest. There were, however, no significant differences in the prevalence of asymptomatic disease between men and women with PAD in the WALCS cohort.

Natural History of Lower Extremity Outcomes in Women With PAD

People with PAD have greater lower extremity functional impairment (ie, limitations in the ability of an individual to participate in social and occupational spheres of life), faster functional decline, and greater mobility loss than those without PAD. Women with PAD have greater functional impairment than women without PAD. Furthermore, women with PAD have greater lower extremity functional impairment than men. For example, in a cohort of 560 people with confirmed PAD and intermittent claudication, including 72 women, treadmill distance to onset of intermittent claudication symptoms was 33% shorter and maximal treadmill walking distance was 23% shorter in women than in men. In the WALCS cohort, women with PAD had slower walking speed and achieved significantly shorter distances in the 6-minute walk than men. In a primary care setting of men and women ≥50 years of age, women with PAD had poorer quality-of-life scores than men with PAD. Several possible reasons have been hypothesized for the poorer functional performance among women with PAD than among men with PAD, including lower gender-based leg strength, poorer cardiopulmonary fitness, and reduced calf muscle hemoglobin oxygen saturation in women with PAD compared with men with PAD.

In prospective analyses, lower ABI values predict greater decline in walking-related disability among women. Among 847 women in the WHAS cohort, women with baseline ABI values <0.60 had a significantly higher incidence of disability for the outcomes of walking a quarter mile, walking velocity, and the number of city blocks walked during the past week than women with baseline ABI values of 0.90 to 1.50. Results of a recent longitudinal study in which PAD participants were followed for up to 4 years demonstrate that women with PAD have higher rates of mobility loss and functional decline than men with PAD.

Although women with PAD have greater functional impairment than men with PAD, women may be less likely to undergo lower extremity revascularization than men. A single-center study of 1987 women with PAD reported significantly lower rates of lower extremity revascularization compared with men with PAD after the exclusion of patients with critical limb ischemia. A more recent study from the same institution reported that lower extremity revascularization rates in 592 PAD patients with no prior history of revascularization were 22% for men and 16% for women, a difference that was not statistically significant.

Ethnic and Social Distribution of Clinical Presentation in Women With PAD

In almost all health issues, gender and ethnicity serve as factors that modify clinical presentation and societal treatment of disease. Ethnic-related differences have been documented in the prevalence and treatment of PAD. Minority women fare worse than white women in terms of health status and rates of disability and mortality, as do minority men. Diabetes mellitus is a well-known risk factor for PAD, and diabetes mellitus-specific preventive care among women is low. In some minority populations, the interaction of biology and environment results in a higher prevalence of diabetes mellitus, more advanced PAD at presentation, and a greater proportion of minority women with PAD. The preponderance of chronic diseases that are influenced by diet and physical inactivity, such as type 2 diabetes mellitus, obesity, and hypertension, rather than by factors known to have a significant heritable component suggests that the disparity in risk factors is more strongly related to social determinants of disease. In a post hoc analysis of the PREVENT III (Project of Ex Vivo Vein Graft Engineering via Transfection III) trial, a multicenter trial that evaluated the results of vein bypass surgery for chronic critical limb ischemia, the impact of gender and ethnicity was evaluated.

This study cohort included 249 black patients, including 131 men and 118 women. Graft failure rates were highest in black women, with an increased risk of graft thrombosis (hazard ratio [HR] 2.02 for secondary patency, 95% confidence interval [CI] 1.27–3.20, P=0.003) and an increased risk for major amputation (hazard ratio 2.38, 95% CI 1.18–4.83, P=0.016) at 1 year. Similarly, Hispanic ethnicity has been reported to be an independent predictor of limb loss in patients undergoing autogenous infrainguinal bypass.
summary, gender, race, and ethnicity appear to be synergistic determinants of vein graft failure and limb loss.

Previous data suggest that socioeconomic status may also represent a major factor that determines access to preventative services and the eventual outcome of treatment of PAD. Current evidence suggests that lower socioeconomic status may lead to environmental exposures that result in higher rates of obesity, physical inactivity, and increased risk of diabetes mellitus.\textsuperscript{50} In both men and women participating in the Heinz Nixdorf Recall Study (a population-based prospective cardiovascular cohort study in the Ruhr area in Germany), the ABI was lower and the prevalence of PAD was higher among participants with lower education levels.\textsuperscript{51} More specifically, study participants with a low level of education (odds ratio 2.58, 95% CI 1.53–4.34) or a medium level of education (odds ratio 1.90, 95% CI 1.27–2.85) had higher odds of having PAD than participants with a high level of education. Additional adjustment for classic atherosclerotic disease risk factors reduced the strength of this association, although it remained significant. Current smoking, diabetes mellitus, and a high body mass index were the most relevant potential mediators of the association of lower education with a higher PAD prevalence. It has been suggested that diabetes mellitus prevention, weight management, and smoking prevention and cessation programs should be specifically targeted to individuals of lower socioeconomic status.\textsuperscript{51}

Currently, women and ethnic minorities are underrepresented in essentially all PAD prospective randomized controlled trials.\textsuperscript{52} There may be a reluctance of women (and possibly also patients in some ethnic groups) to participate in cardiovascular clinical trials.\textsuperscript{53} Efforts to enroll women of diverse ethnic groups in such trials should be expanded, because further investigation is needed to determine why these subgroups have higher prevalence and worse outcomes of treatment of PAD.

Potential Role of All Caregivers in Providing Access to PAD Information

Women are more likely to obtain primary care than men.\textsuperscript{54} Regular visits by women to primary care physicians or gynecologists for primary preventive care provide a potential opportunity to screen at-risk women for PAD. Provision of educational information to physicians who provide primary care to women (including gynecologists, podiatrists, and internal medicine and family physicians, as well as nurse practitioners and physician assistants) may help improve PAD diagnosis rates and thereby effect early detection and treatment of PAD. However, as noted above, many women with PAD do not present with classic symptoms of intermittent claudication. Furthermore, the physical examination by the nonvascular specialist is known to be relatively insensitive to the diagnosis of PAD.\textsuperscript{55} Inasmuch as an accurate PAD diagnosis can therefore only be confidently established by use of objective testing, the ABI (documented to be more sensitive for the diagnosis of PAD than claudication symptoms alone in women) should be more widely used by all primary care clinicians and gynecologists. Although a large, population-based trial assessing the net benefit, harm, and cost-effectiveness of PAD screening has not been performed, it would seem prudent for the ABI to be used to provide a prompt diagnosis in “high-risk women”\textsuperscript{13} so that the known gender-based cardiovascular health disparities are not reproduced in women as occurred for CAD in decades past.

Gender-Specific Access to Cardiovascular Health Care: Current Sites of Care for Women With PAD

The evidence base has long documented that PAD is highly prevalent in women, and the data in the present report (Epidemiology of PAD in Women) now suggest that the total population burden of PAD may be higher in women than in men. Yet this burden has seemed invisible to clinicians, health systems, payers, and government agencies, because gender-based PAD health service analyses have rarely been performed. The writing committee, working with the staff of the National Heart, Lung, and Blood Institute (NHLBI), have compiled contemporary data that document rates of visits by women and men at each major site of care, including physicians’ offices, outpatient clinical departments, emergency departments, and inpatient hospital discharges (Table 2). These data demonstrate that women experience treatment for PAD in numbers similar to men. For example, in 2007, 1.1 million physician office visits by women and 1.1 million visits by men were reported to be related to PAD diagnoses (National Ambulatory Medical Care Survey, National Center for Health Statistics; http://www.cdc.gov/nchs/ahcd/about_ahcd.htm). These data also demonstrate that there are an equal number of visits by women for PAD in the outpatient office setting as for stroke and that PAD care, for women and men, is much more likely to be delivered in the outpatient setting. In contrast, 5%, 10%, and 18% of PAD, CAD, and stroke care, respectively, occurs in the inpatient setting. This new data source clarifies that at each of these points of PAD care, but especially in the outpatient office setting, women could easily be provided access to preventative information, testing, and care, as well as access to participation in future PAD clinical trials.

Summary Statements

1. Most women with PAD, like men, do not have classic symptoms of intermittent claudication.
2. Women with PAD have greater functional impairment and a more rapid functional decline than women without PAD.
3. Women (and particularly black females) are more likely than men to experience graft failure or limb loss.
4. There is a need to identify women with or at risk for PAD, especially black women, to lower cardiovascular ischemic event rates, loss of independent functional capacity, and ischemic amputation rates.
5. Women in the United States attend as many or more PAD physician visits as men, which confirms the very large burden of PAD in women.
6. Women predominantly see doctors and other clinicians for PAD in the outpatient office setting.
The diagnosis of PAD is best established in all individuals by a vascular history and physical examination, supported by targeted measurement of the ABI. For selected patients in whom incremental anatomic localization information will lead to a change in care strategy, duplex ultrasound and advanced imaging studies may be used to evaluate the location and severity of disease. These pathways, in the context of the current evidence base, are identical for women and men.

The ABI test is indicated for use in all individuals at high risk of PAD regardless of gender, as well as in individuals with exertional limb symptoms, abnormal lower extremity pulses, diabetes mellitus, or known CHD or cerebrovascular disease. A Doppler ultrasound or oscillometric device is used to locate and measure the systolic blood pressures in the arms and at both pedal pulses. Specifically, using a Doppler probe and starting at the right arm, systolic blood pressures are obtained in the right brachial, right anterior tibial, right posterior tibial, left posterior tibial, left anterior tibial, and left brachial arteries. For each leg, the ABI should be calculated by dividing the higher of the posterior and anterior tibial pressures by the higher arm blood pressure. Although there are several different methods that might be used to calculate the ABI values, clinicians and vascular laboratories should use a common method.

PAD Diagnostic Methods in Women

The diagnosis of PAD is best established in all individuals by a vascular history and physical examination, supported by targeted measurement of the ABI. For selected patients in whom incremental anatomic localization information will lead to a change in care strategy, duplex ultrasound and advanced imaging studies may be used to evaluate the location and severity of disease. These pathways, in the context of the current evidence base, are identical for women and men.

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No studies to date have examined differences in the techniques used to measure the ABI between men and women. Nevertheless, the posterior and anterior tibial systolic pressures in women and men are known to be slightly different because of gender-based height differences. For instance, when a subset of participants in the Multi-Ethnic Study of Atherosclerosis (MESA) who were free of CVD risk factors and subclinical atherosclerosis were analyzed, women had \( \sim 0.02 \) lower ABI values than men in the fully adjusted model, a result that to date is not known to be associated with any diagnostic clinical significance.

There are no known gender-based differences in the diagnostic sensitivity or accuracy of any of the physiological or classic imaging-based diagnostic PAD tests. Pulse volume recordings, toe-brachial indices, segmental pres-
sure studies, and lower extremity arterial duplex ultrasound studies may all be used to document the presence of PAD in women, as documented in the “ACC/AHA 2005 Practice Guidelines for the Management of Patients With Peripheral Arterial Disease.”

Similarly, there are no documented gender-based differences in the diagnostic sensitivity or accuracy of advanced PAD anatomic imaging techniques (eg, magnetic resonance angiography [MRA], computed tomographic angiography, or conventional catheter-based arteriography). MRA can provide a noninvasive anatomic map of the lower extremity arterial circulation after the injection of contrast, outlining luminal diameters. MRA studies do not provide clear delineation of arterial wall calcification. MRA can provide diagnostic images without exposure to ionizing radiation. However, in patients with a low glomerular filtration rate (<30 mL/min/1.73 m²), there is a low but serious risk of nephrogenic systemic fibrosis from administration of gadolinium. Also, MRA is not routinely recommended for individuals with implanted pacemakers and may not be suitable in other patients with implanted metallic devices.

Computed tomographic angiography can provide higher resolution and may provide better visualization of both the vessel lumen and arterial wall than can be demonstrated with MRA. With appropriate timing, visualization of the entire peripheral arterial tree can be obtained.

Computed tomographic angiography may also define arterial calcification, which may be of help in planning invasive treatment strategies; however, the presence of dense calcification may also limit the assessment of the magnitude of an arterial stenosis. It is a first-pass technique, and contrast volume limitations preclude multiple injections. Computed tomographic angiography requires the use of ionizing radiation and administration of iodinated contrast, which limits its safe use in individuals with renal dysfunction.

Conventional catheter-based digital subtraction arteriography is still performed as a diagnostic test for individuals with PAD, but this is now rarely required because of the availability and accuracy of the noninvasive arterial imaging techniques. As such, invasive angiography is now usually performed only at the time of endovascular treatment to confirm the noninvasive findings and to assess the immediate results of endovascular procedures.

Despite the observation that native arterial diameters for women are smaller than for men of the same age, the published evidence base does not demonstrate a differential accuracy of stenosis assessment by gender. No published studies have been designed or completed specifically to evaluate gender-based diagnostic accuracy.

**Summary Statements**

1. Although normal ABI values in women are 0.02 lower than for men, there are no gender-based differences in PAD diagnostic thresholds.
2. Arterial diameters in women are smaller than age-matched segmental diameters in men.
3. Current data suggest that women with suspected PAD may achieve identical utility from all physiological and anatomic vascular diagnostic testing strategies as men.

**Treatment of Symptomatic PAD in Women**

The principal components of symptomatic PAD treatment include pharmacological therapy, supervised exercise therapy, lower extremity revascularization, and pneumatic lower extremity compression (Table 3). Although cardiovascular risk reduction is a critical goal in the management of all patients with both symptomatic and asymptomatic PAD, this topic is beyond the scope of the present scientific statement, which focuses on symptomatic disease management from a gender-based perspective. Guidance for the primary prevention of cardiovascular events in asymptomatic populations can be found in the “AHA Guidelines for Primary Prevention of Cardiovascular Disease and Stroke: 2002 Update.”

**Pharmacological Treatment**

**Cilostazol**

Cilostazol is the only pharmacological treatment option approved by the US Food and Drug Administration that has consistently demonstrated symptomatic improvement in claudication. There have been 6 published trials with 1582 participants, including 370 women (23.4%), that support the efficacy of cilostazol over placebo and pentoxifylline for improving claudication onset and peak walking time/distance. One additional safety study with 1435 participants included 495 women (34.5%) and demonstrated no increased mortality with cilostazol versus placebo up to 3.5 years of follow-up. Meta-analyses and systematic reviews have demonstrated improvement in claudication onset distance and peak walking distance, as well as quality of life. A recent pooled analysis of 6 published and 3 unpublished trials by Pande et al included 2251 subjects with 532 women (23.6%) and demonstrated a 40-meter improvement in peak walking distance over an average of 20.4 weeks of follow-up. Gender-specific analyses demonstrated no statistical difference in estimated treatment effects between men (1.17, 95% CI 1.12–1.22) and women (1.10, 95% CI 1.02–1.19). Thus, there was no gender-by-treatment interaction for women in response to cilostazol.

**Supervised Exercise**

There is a considerable body of evidence, including 37 identified randomized trials and 7 systematic reviews or meta-analyses, demonstrating the efficacy of supervised exercise to improve symptoms of claudication and exercise performance. These studies included a total of 1814 participants, 1148 of whom performed supervised exercise. Five of the studies (14%) did not report the gender of participants. In the remaining 32 studies, there were a total of 493 female participants, averaging 27.2% of the total (range 0% to 81%).

The majority of the randomized trials (n=23), which included a total of 991 (range 12–156) participants, compared 1 or more methods of supervised exercise training (treadmill...
walking, resistance training, arm or leg cycling, StairMaster, polestriding) or control. There were a total of 234 reported female participants (mean 26%, range 0% to 48%). The duration of exercise programs ranged from 6 weeks to 6 months, and most of these studies reported significant improvement in claudication onset time/distance and peak walking time/distance in the exercise groups, particularly in those groups that performed some form of aerobic exercise training. However, none of these studies reported gender-specific analyses or outcomes.

Several studies compared supervised treadmill or walking training (ranging between 3 weeks and 15 months) to either surgical\(^\text{91}\) or endovascular revascularization,\(^\text{78,92–95}\) alone or combined. In total, there were 562 (range 36–150) participants in these studies, 307 of whom participated in supervised exercise; female participants totaled 184 (32%, range 21% to 45%). Most studies reported significant improvement in both the supervised exercise and revascularization arms of the studies. Only 1 study\(^\text{91}\) reported results of gender-specific analyses and noted that gender did not significantly influence walking performance after treatment.

Several trials compared supervised exercise with pharmacological therapy, including antiplatelet medications,\(^\text{79,97}\) pentoxifylline,\(^\text{79,97}\) prostaglandin E1,\(^\text{97}\) and iloprost.\(^\text{98}\) Seventy-seven of the 128 participants participated in supervised exercise, and 21 (16% overall; range 0% to 33%) were women. Overall, these studies reported comparable improvement in exercise versus drug therapy, with the greatest increase in walking distance observed in those who received combination therapy versus either therapy alone. However, comparisons across studies are difficult because of the variability of treatment duration (2 weeks to 6 months). One study\(^\text{79}\) described age- and gender-matched intervention groups; however, there were no gender-specific analyses or outcomes reported.

Studies comparing supervised versus home or unsupervised exercise\(^\text{108–111}\) have included 151 participants, 48 of whom (32%; range 0% to 47%) were women. Most demonstrated greater improvement in supervised versus home exercise, although 1 study\(^\text{111}\) reported similar increases in peak walking distance between groups. Finally, 1 study\(^\text{120}\) (n = 34; 7 women [20.6%]) found significant improvement in peak walking distance and claudication onset distance after 6 months of pneumatic compression or supervised treadmill training versus unsupervised exercise. Similar to previously described trials, gender-specific analyses or outcomes were not discussed. Although there is no evidence to suggest that women respond differently than men to supervised exercise training, additional studies are needed to establish whether gender-based differences exist.

### Lower Extremity Revascularization

#### Gender Representation in Lower Extremity Revascularization for Symptomatic PAD

The evidence that describes the efficacy of lower extremity revascularization for PAD is largely derived from study populations that are predominantly male. Approximately 86% of randomized clinical trials of surgical or endovascular treatment for PAD report participant gender.\(^\text{122,78,91,92,94,121–185}\) Among contemporary PAD revascularization studies that reported gender, women accounted for 32% of randomized trial participants (range 0% to 54%).\(^\text{a}\) 37% of prospective

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**Table 3. Impact of Gender on PAD Treatment Outcomes**

<table>
<thead>
<tr>
<th>Type of Intervention</th>
<th>Randomized Studies, N</th>
<th>Total Participants, N</th>
<th>Primary Outcomes Measured</th>
<th>Studies Reporting Gender of Participants, n (%)</th>
<th>Female Participants, n (%)</th>
<th>Studies Reporting Gender-Specific Results, n (%)</th>
<th>Gender-Specific Results Reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supervised exercise</td>
<td>37</td>
<td>1814</td>
<td>PWI/D; COT/D; 6-min walk test</td>
<td>31 (86)</td>
<td>493 (27; Range 0–81)</td>
<td>1 (3)</td>
<td>Insufficient data</td>
</tr>
<tr>
<td>Clofazimine</td>
<td>Pooled analysis of 9 (6 published, 3 unpublished)</td>
<td>2251</td>
<td>PWI/D; COT/D</td>
<td>9 (100)</td>
<td>532 (24; Range 16–25)</td>
<td>None individually; pooled analysis of all studies</td>
<td>No gender-by-treatment interaction</td>
</tr>
<tr>
<td>Surgical revascularization</td>
<td>40</td>
<td>16324</td>
<td>Patency, repeat operation, limb salvage, survival, amputation-free survival, adverse events, ABI, digital pressure, PWI/D, blood flow, QOL</td>
<td>34 (85)</td>
<td>4467 (Range 0–60)</td>
<td>12</td>
<td>No gender-by-treatment interaction</td>
</tr>
<tr>
<td>Endovascular revascularization</td>
<td>22</td>
<td>2665</td>
<td>Patency, technical success, repeat intervention, limb salvage, amputation-free survival, recurrent ischemia, symptoms, adverse events, ABI, ankle pressure, biomarkers, QOL, functional outcomes, PWI/D, COT/D</td>
<td>19 (86)</td>
<td>847 (Range 20–50)</td>
<td>None</td>
<td>None</td>
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<tr>
<td>Surgical and endovascular revascularization</td>
<td>7</td>
<td>1506</td>
<td>Patency, adverse events, survival, amputation-free survival, ABI</td>
<td>5 (71)</td>
<td>393 (Range 0–40)</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

PAD indicates peripheral artery disease; PWI/D, peak walking time/distance; COT/D, claudication onset time/distance; ABI, ankle-brachial index; and QOL, quality of life.

Note: Citations are detailed in “Treatment of Symptomatic PAD in Women” section.
cohort study participants (range 18% to 57%).63,175,189–217 and 37% of retrospective study participants (range 1% to 63%).39,40,218–276 Hoel et al52 similarly observed participant gender reporting in only 85% of vascular surgery clinical trials in the United States and concluded that women are underrepresented relative to their frequency of procedural intervention. Lower interest in clinical trial participation among women has been reported among patients with CHD and may account in part for enrollment disparities,53 but the relationship between gender and willingness to participate in clinical research has not been characterized in patients with PAD.

Gender and Patient Selection for Lower Extremity Revascularization

Gender-based differences in demographic, comorbidity, and anatomic characteristics among patients with PAD may reflect patient selection factors that contribute to lower revascularization rates in women. In their study of patients with abnormal vascular laboratory studies and no prior history of lower extremity revascularization, Feinglass et al19 observed that men were more than twice as likely to be selected for revascularization despite similar baseline comorbidities and prevalence of limb salvage indications. Egorova et al277 found a lower rate of procedural revascularization in women during inpatient hospitalization for PAD (46% versus 54%), although others have reported similar rates of revascularization between genders.40 Several studies have observed that women undergoing lower extremity revascularization for PAD are older,63,192,224,246,262 have more advanced disease,234,262,277 and have a lower prevalence of smoking than men. Hultgren et al224 reported a higher proportion of suprarenal procedures among women undergoing revascularization for PAD (44% versus 19%); conversely, others have reported lower rates of bypass to tibial-level outflow vessels in women.224 These contrasts in procedural management were attributed to gender-specific patient selection criteria and anatomic disease distributions.

Women with PAD have smaller tibial arteries,63 which may be perceived as a factor that increases the technical difficulty associated with distal revascularization. Higher rates of emergent hospital admission and nursing home discharge in women with PAD have also been observed277 and may reflect disparities in family or social support available to women who are considering elective revascularization. Differences in epidemiology, clinical presentation, and awareness of PAD in women are outlined elsewhere in the present statement and may also contribute to differential patient selection for lower extremity arterial revascularization.

Influence of Gender on Outcomes Associated With Revascularization for PAD

Patency

Several studies have observed inferior patency for women after surgical lower extremity revascularization.63,112,221,278 In their analysis of patients with aortoiliac occlusive disease treated with a combination of surgical and endovascular techniques, Ballard and colleagues221 found a relative risk of 4.6 for bypass or stent thrombosis in women. Green et al143 observed a gender-specific relationship between graft size and thrombosis among patients treated with prosthetic above-knee femoropopliteal bypass; 5-year cumulative patency rates in that report were 69.1% versus 37.9% for men with large versus small grafts and 45% for women in both graft-size categories. Nguyen and colleagues42 observed an interaction between race and gender as predictors of patency after lower extremity saphenous vein bypass, with black women having the greatest disadvantages in terms of graft loss (hazard ratio 2.02, 95% CI 1.27–3.20) at 1 year. Although these reports suggest inferior patency in women (particularly among those treated with surgical bypass), other studies of patency after lower extremity revascularization for PAD have not identified significant gender effects in patients treated with endovascular procedures,† surgical bypass,‡ or combinations of these revascularization techniques.251

Survival

Associations between gender and survival after lower extremity revascularization for PAD are complex and appear to be influenced by differences in age, comorbidities, and procedural factors. In their retrospective analysis of lower extremity saphenous vein bypasses, Belkin et al224 reported lower perioperative mortality in women. Magnant et al278 reported similar perioperative mortality rates among men and women undergoing infragenual bypass for lower extremity ischemia but decreased long-term survival in women (54% versus 72% 3-year survival for women versus men, respectively); these authors also observed a gender-dependent effect of diabetes mellitus, with increased mortality in diabetic women. Egorova et al277 noted an increased hospital mortality rate in women with PAD treated with procedural interventions and observed the highest mortality risk in women undergoing surgical revascularization and amputations. Hultgren et al245 identified an interaction between female gender and age as predictors of perioperative mortality among patients undergoing surgical or endovascular procedures for lower extremity ischemia; age adjustment rendered a univariate association between gender and mortality nonsignificant in their study, and female gender was actually associated with improved long-term survival in multivariable analysis. Others have reported no gender effect on survival after treatment with endovascular234 or open surgical192,197,218,280 techniques.

Reported gender effects on survival after lower extremity PAD revascularization, therefore, have been inconsistent. Gender is often a confounder for morbidity, age, and procedural factors that impact perioperative mortality and survival, and these factors should be taken into account when revascularization procedures are considered in women with PAD.

Amputation-Free Survival

Multiple studies have reported similar amputation-free survival after lower extremity revascularization for PAD in men and women.§ In their analysis of California hospital discharge data, Feinglass et al238 observed improved amputation-free survival over a mean follow-up of 61.5 months after lower extremity bypass in women versus men.

§References 63, 196, 223, 224, 254, 245, 246, 258, 280.
(male hazard ratio 1.15, 95% CI 1.12–1.18). Malmstedt et al\textsuperscript{257} noted a gender-specific effect of diabetes mellitus on amputation risk, with male diabetic patients at relatively higher risk than females. Similar or improved amputation-free survival in women is a clinically important observation given the previously discussed gender differences in age, comorbidities, and anatomic factors that otherwise might diminish enthusiasm for revascularization.

**Perioperative Adverse Events**

Female gender has been identified as a risk factor for perioperative adverse events. Several studies have reported higher rates of perioperative wound complications in women.\textsuperscript{168,224,241} Belkin et al\textsuperscript{224} observed a greater frequency of wound complications (infections, hematomas, and seromas) in women undergoing in situ lower extremity arterial bypass (13.5% versus 3.3%). Nguyen et al\textsuperscript{168} also identified female gender as an independent predictor of wound complications after lower extremity bypass (odds ratio 1.376, 95% CI 1.09–1.92) and observed associations with major wound complications, increased length of hospital stay, and lower quality of life. Mays and colleagues\textsuperscript{258} reported a significantly higher incidence of perioperative myocardial infarction in women undergoing infrainguinal vein graft bypasses (9.8% versus 2%).

Female gender has also been associated with increased risk for adverse events after endovascular treatment of PAD. In their analysis of complications associated with percutaneous lower extremity angioplasty, Matsi et al\textsuperscript{203} noted a significantly higher incidence of bleeding complications in women (15% versus 6%).

**Quality of Life and Other Outcomes**

In their prospective longitudinal study evaluating health-related quality of life among patients with intermittent claudication and critical limb ischemia, Wann-Hansson et al\textsuperscript{213} found that female gender adversely impacted durability of quality of life after revascularization. These findings differed from those of Klevsgard et al\textsuperscript{200}, who did not observe any association between gender and quality of life assessed with the same instrument. Nguyen et al\textsuperscript{251} evaluated predictors of change in quality of life after lower extremity vein graft bypass as part of the PREVENT III clinical trial and did not observe a significant gender effect. In their prospective evaluation of functional outcomes associated with surgical, endovascular, and medical treatment of patients with intermittent claudication, Feinglass et al\textsuperscript{195} did not identify significant gender associations with walking distance, physical function, ABI, pain, or symptoms.

**Lower Extremity Pneumatic Compression**

Sequential pneumatic compression has been demonstrated to increase lower extremity blood flow in patients with PAD.\textsuperscript{282–288} Women constituted 30% of participants in the studies of lower extremity pneumatic compression as treatment for symptomatic PAD that evaluated clinical outcomes and reported gender.\textsuperscript{289–291} These studies each included ≤50 patients and did not report any gender-specific analyses.

**Summary Statements**

1. There is no gender-by-treatment interaction for women in response to cilostazol.
2. The exercise training literature in PAD demonstrates a consistent and clinically meaningful response to training programs regardless of gender, although only approximately one fourth of the subjects were women and very few studies reported gender-specific outcomes.
3. Possible associations between female gender and adverse outcomes associated with PAD revascularization therapies (both endovascular and surgical) are inconsistent and may be confounded by age, comorbidities, and anatomic factors.

**Awareness and Knowledge of PAD Among Women**

**The Evidence Base of Low PAD Awareness and Knowledge**

The public continues to demonstrate a profound lack of awareness of PAD. “Awareness” is defined as the basic level of knowledge that a disease exists and/or is present in the community. Public awareness is a key step in any public cardiovascular health protective intervention. Without such awareness, the population at risk is not empowered to know how to obtain a timely diagnosis, early symptoms are not reported to clinicians, and informed treatment choices and adherence to risk reduction therapies cannot be easily achieved. Women play an important role in population-based improvements in CVD awareness because they serve a health prevention and access role in families, select personal and family healthcare providers, and engage the family unit in health interventions, as their own health is preserved.\textsuperscript{12,292}

Gender-based differences in public awareness of most cardiovascular risk factors and diseases have impeded past CVD preventative efforts.\textsuperscript{283,294} Until recently, no information has existed to document rates of public awareness of PAD, which would provide a baseline to evaluate potential gender-based knowledge gaps or to improve such awareness and knowledge. The current literature now includes 3 public awareness surveys that have been published between 2007 and 2009. In Canada and the United States, 2 identical cross-sectional population-based telephone surveys were conducted between May and July 2006. A PAD cross-sectional survey of specifically 162 women was conducted from December 2004 to March 2006 in the United States by the interdisciplinary Peripheral Artery Disease Coalition. The US survey by Hirsch et al\textsuperscript{11} was performed by use of random digit dialing on a representative sample of 2501 adults >50 years of age, with an oversampling of 250 blacks and Hispanics, to measure public awareness of PAD. The survey assessed demographics and risk factors, as well as knowledge of the causes and consequences of PAD. The study results demonstrated an overwhelming lack of awareness of PAD; 3 of 4 adult Americans surveyed have no awareness of PAD (did not recognize “PAD” or “PVD” [peripheral vascular disease] as a disease), which was much lower than for atherosclerosis risk factors or other common CVDs.
This low level of PAD awareness was starkly contrasted with the high awareness of much less common disorders such as multiple sclerosis, cystic fibrosis, or amyotrophic lateral sclerosis. Respondent cohorts at highest risk for PAD (the elderly and minorities) were the least informed. In addition, among the respondents who were aware of PAD, half or fewer were aware that smoking (44%) and diabetes mellitus (50%) could lead to PAD. Media sources ranked as the most common primary source of information (broadcast or cable television 26%, magazines 15%, and newspaper 5%). Very few respondents (19%) had heard about PAD from healthcare providers. Women were slightly more aware of PAD and its associated risk factors than men.

In the Canadian study, comparable methods were used to evaluate a sample of 501 adults who were >50 years old. This survey provided results strikingly similar to the US study, with 2 of 3 adult Canadians unaware of PAD. Results indicated that PAD awareness was lowest in males (31.8%), adults ≥70 years of age (33.3%), and those with lower education levels (28.6%) and lower income (30.9%). Younger women (50–69 years of age) with greater than high school education were more aware of risk factors for PAD than men.

A cross-sectional study by Bush et al296 that focused on 162 women from a Veterans Affairs ambulatory clinic reported that PAD knowledge and awareness were poor among women at risk for CVD (Table 4). Data were collected by use of a self-reported questionnaire that focused on symptoms, perceived risk factors, and patient preferences for knowledge. Cardiovascular risk was rated with a modified version of the Framingham risk score. Results demonstrated that this patient population had many risk factors for PAD, yet had low levels of PAD knowledge.

Summary Statements

1. Awareness of PAD in women and men is strikingly low compared with knowledge of other CVDs and general diseases.
2. Current data suggest that women may be somewhat more aware of PAD and its risk than their male counterparts.
3. Improvement or elimination of this “knowledge gap” would provide a major opportunity to improve the health of women and of the broader national population.

National Education and Research Programs Related to PAD and CVD in Women

Current Educational Materials for Patients and the Public Do Not Specifically Address PAD in Women

CVD research and education within the federal government fall primarily within the missions of the National Institutes of Health (www.nih.gov) and the Centers for Disease Control and Prevention (CDC; www.cdc.gov). Several agencies within the National Institutes of Health specifically address PAD and CVD as part of their public education responsibilities. The NHLBI (www.nhlbi.nih.gov) now oversees a well-developed CVD educational campaign directed toward women: The Heart Truth (http://www.nhlbi.nih.gov/educational/hearttruth/). This campaign now focuses only on coronary disease and stroke, the 2 most commonly recognized CVD syndromes, and their associated morbidity and mortality; the Heart Truth campaign does not cross-link with other health education programs, to minimize message dilution. The NHLBI sponsored a 3-year public awareness campaign on PAD in partnership with the PAD Coalition. Educational materials developed as part of the campaign can be found at http://www.nhlbi.nih.gov/health/public/heart/pad/stay/. PAD also is a topic in the NHLBI’s Diseases and Conditions Index, a popular Web site accessed frequently by the public (http://www.nhlbi.nih.gov/health/dci/Diseases/pad/pad_what.html).


The CDC’s Division for Heart Disease and Stroke Prevention focuses on preventing and controlling risk factors for all CVD, including PAD. CDC has a PAD fact sheet that is available on its Web site at http://www.cdc.gov/dhdsp/data_statistics/fact_sheets/fs_pad.htm. The site presents information on prevalence, risk factors, signs and symptoms, diagnosis, treatment, and prevention of PAD. A CDC state-level education campaign for low-income women (“WiseWoman”) focuses on heart disease and stroke but does not mention PAD (http://www.cdc.gov/wisewoman/index.htm).

Several broadly framed CVD planning documents, such as the national Heart Disease and Stroke Prevention Program (http://www.cdc.gov/dhdsp/) and the Public Health Action Plan to Prevent Heart Disease and Stroke (http://www.cdc.gov/dhdsp/action_plan/index.htm) mention PAD, but only as a risk factor for heart disease and stroke, not as a specific CVD with its own symptoms, clinical presentations, diagnostic pathways, and disease-specific treatments. The CDC’s National Heart Disease and Stroke Prevention Program is focused on the ABCS of heart disease and stroke prevention, including appropriate aspirin therapy, blood pressure control (including sodium reduction), cholesterol control, and smoking cessation, and this focus has the potential to prevent or modify the outcomes of PAD. The “Million Hearts” initiative, launched in September 2011, co-led by the CDC and the Centers for Medicare & Medicaid Services in partnership with the American Heart Association and other organizations, brings together programs and policies to promote the ABCS...
approach through improved clinical care and promotion of healthier lifestyles and communities. This improvement to our nation’s cardiovascular health prevention portfolio will also support improvements in PAD outcomes.

The CDC’s Division of Diabetes Translation (http://www.cdc.gov/diabetes/) addresses PAD in its public education materials on complications of diabetes mellitus. The Web site provides a diagram of the effect of diabetes mellitus on the female body, including circulatory problems in the feet and risk of amputation; however, the diagram does not use the specific term “peripheral artery disease” (“Effects of Diabetes on a Female”; http://www.cdc.gov/diabetes/consumer/problems_humanbody_female.htm). In addition, in 2005, the Division of Diabetes Translation in collabo-

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<td>NA</td>
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<td>23.0</td>
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<td>Awareness of PAD, %</td>
<td>31.8</td>
<td>38.8</td>
<td>58.5 (Enriched sampling methods)</td>
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| Perceived Causes Among Those Familiar With PAD       |                                                                            |                                                                            |                                                                                 |
|------------------------------------------------------|                                                                            |                                                                            |                                                                                 |
| Diabetes mellitus                                    | 50.9                                                                       | 49.3                                                                       | 45.9                                                                            |
| Hypertension                                         | 46.7                                                                       | 47.6                                                                       | 45.9                                                                            |
| Dyslipidemia                                         | 46.7                                                                       | 47.2                                                                       | 45.2                                                                            |
| Smoking                                              | 54.0                                                                       | 56.8                                                                       | 52.7                                                                            |
| Cardiac disease                                      | 41.6                                                                       | 44.2                                                                       | 37.8                                                                            |
| Family history                                       | 37.0                                                                       | 37.8                                                                       | 26.7                                                                            |

| Perceived Consequences Among Those Familiar With PAD |                                                                            |                                                                            |                                                                                 |

| Stroke                                               | 26.1                                                                       | 28.6                                                                       | 17.6                                                                            |
| Death                                                | 22.6                                                                       | 27.3                                                                       | 23.0                                                                            |
| Heart attack                                         | 14.4                                                                       | 14.3                                                                       | 15.1                                                                            |
| Amputation                                            | 14.6                                                                       | 12.9                                                                       | 14.9                                                                            |
rion with the CDC’s National Center for Health Statistics published an article on lower extremity PAD that highlighted the importance of PAD in patients with and without diabetes mellitus. This report can be found in the CDC journal Morbidity and Mortality Weekly Report at http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5445a4.htm.

Guidelines for Health Professionals Do Not Specifically Address PAD in Women
The National Cholesterol Education Program—Adult Treatment Panel III, the federal government entity that issues cholesterol treatment guidelines, defines the presence of PAD as a CHD risk equivalent, which supports similar goals of treatment in individuals with PAD as with CAD itself.297 (Note: Updated guidelines are anticipated to be released in early 2012; http://www.nhlbi.nih.gov/guidelines/cvd_adult/background.htm). The American Heart Association guideline on CVD prevention specifically in women is consistent with Adult Treatment Panel III in identifying women with PAD as having a CHD risk equivalent.298 In terms of diagnostic approaches to identifying individuals with PAD, Adult Treatment Panel III states that measurement of ABI is “a simple, noninvasive test to confirm the clinical suspicion of lower extremity PAD,” and it states further that ABI “can be considered a diagnostic test to identify persons at high risk for CHD.”297 These guidelines do not, however, comment on the use of ABI for screening specifically, nor do they make any gender-specific recommendations differentiating an approach for women specifically. The 2004 update of Adult Treatment Panel III makes no further mention of PAD in women.299 Similarly, the current American Heart Association guidelines for women make no mention of the use of ABI or other approaches to screen women for PAD.298 Such guideline updates increasingly recognize the ABI evidence base of efficacy for both women and men. As such, the “2010 ACCF/AHA Guideline for Assessment of Cardiovascular Risk in Asymptomatic Adults” assigns a class IIa recommendation for use of the ABI in asymptomatic adults at intermediate risk to achieve the benefit of risk reassignment and PAD diagnosis.300

There Is a Paucity of Research on PAD in Women
The National Institutes of Health has a relatively small portfolio of funded research projects on PAD (http://projectreporter.nih.gov/reporter.cfm). The research covers the scientific spectrum from basic and mechanistic research to clinical, translational, and population science. The primary institutes supporting PAD research are the NHLBI, the National Institute of Diabetes and Digestive and Kidney Diseases, and the National Institute on Aging. The National Institutes of Health Office of Research on Women’s Health (http://orwh.od.nih.gov/) has maintained an interest in PAD since 1999, and has cofunded several projects to increase enrollment of female participants or conduct gender-specific data analyses; however, virtually none of the projects are focused on women specifically or on gender differences. Many of the clinical and population science projects studying PAD barely manage to recruit their target numbers for female participants.

Public health—level data resources with information on demographic subgroups can be a great stimulus to research. These resources can include surveys, maps, and registries. The 1999 to 2004 National Health and Nutrition Examination Survey (NHANES), which was conducted by the CDC’s National Center for Health Statistics, included specific questions about PAD and provided gender-specific data. Mapping approaches such as the PAD Atlas (http://www.mappad.org) are also valuable launching tools for researchers.

Summary Statements
1. PAD is addressed in government-sponsored education programs and activities; however, it is not currently positioned as a distinct topic in women’s cardiovascular health programs.
2. Increased cross-communication between women’s heart health programs and PAD awareness programs could create a more unified and compelling risk reduction message and help identify women with symptomatic PAD so that treatments would be initiated. When possible, the information provided should reinforce that PAD is a distinct disease, not simply a “risk factor” for other CVDs.

Recommendations for Future Action and Research: A “Call to Action” for Women
Women carry a large health burden from PAD in the United States and all nations. A concerted effort, in clinical research, clinical care, and health policy, could provide opportunities to lower this burden, with benefits to women and to the community as a whole. Specific opportunities to improve the health of women with or at risk for PAD include but are not limited to the following: (1) Improvements in basic vascular biology and population-based research of PAD; (2) improvements in data collection methods to better evaluate gender-specific outcomes of diagnostic and therapeutic clinical investigations; and (3) improvements in translation of current PAD knowledge to women in clinical practice. These opportunities are detailed below, with evidence provided in each topic area above, as well as from current PAD guideline documents.13,14

Vascular Biology and Population-Based PAD Research Opportunities
The current evidence base has long demonstrated that women develop atherosclerotic arterial disease later in life, with differing anatomic presentations of stenotic and aneurysmal disease (in the aorta, first-order branches, and the lower extremity arteries) and with differing age-dependent thrombotic event rates. Nevertheless, the vascular biological underpinnings of these differences are not well defined. Additionally, the evidence base to describe the population-based gender-specific PAD incidence and prevalence remains incomplete. Clinical populations are not adequate to provide such estimates, and national PAD disease burdens can only be defined from surveillance of the full population at risk.

Recommendations
1. The potential impact of gender on the vascular biology of atherosclerosis, aneurysmal disease, and thrombosis remains an area in which new basic research contributions should be evaluated.
2. Future studies of PAD prevalence and risk should (a) clearly define the methods by which PAD was ascertained; (b) include gender-specific, and preferably age-specific, prevalence values; (c) evaluate the possibility of study-specific selection bias; and (d) explicitly state how the ankle and arm blood pressure measurements for the ABI were obtained and how the ABI was calculated.

Data Collection Methods to Better Define Gender-Specific Outcomes of Diagnostic and Therapeutic Clinical Investigations (Benefit and Harm)

Diagnosis
The current evidence base has not evaluated diagnostic physiological or advanced imaging techniques to determine whether the anthropomorphic and arterial diameter differences in women and men are associated with differences in test accuracy.

Recommendation
3. Future PAD diagnostic tool investigations should include adequate gender-based samples to prospectively evaluate the sensitivity, specificity, and accuracy of each test for women and men.

Treatment
Although the major expansion of knowledge regarding PAD treatment has provided clear benefit to both men and women, past investigation has been characterized by low rates of enrollment of women and minorities. Thus, most studies have been underpowered to detect gender-based differences in primary outcome efficacy end points or rates of treatment-related adverse events.

Recommendations
4. Clinical trials assessing the efficacy of pharmacological, exercise, and revascularization therapies to improve symptomatic PAD should recruit and enroll female participants at a rate that reflects the population prevalence of women in the symptomatic population.
5. Pooled analyses of currently available data from supervised exercise studies could help overcome limitations of small sample sizes seen in many current clinical trials and provide sufficient statistical power to conduct gender-specific analyses.
6. In addition to primary study end points, analyses related to lower extremity revascularization for PAD should consider demographic and comorbidity factors, procedure-related complications, and procedural utilization as potential outcomes for gender-specific reporting.
7. Gender should not be used as a primary selection factor for revascularization therapy in patients with PAD. Anatomic, demographic, and comorbidity factors often differ on the basis of gender, potentially influence revascularization outcomes, and should be incorporated into clinical decision making.

Translation of Current PAD Knowledge to Women in Clinical Practice
For any disease to be prevented, detected, and treated, both the public and clinicians must have access to state-of-the-art knowledge. Despite advances in population-based knowledge of PAD risk (high-prevalence target populations can be easily identified to detect PAD in its asymptomatic latent phase), populations “at high risk” include both men and women. Yet the creation and dissemination of gender-specific messages has not yet been widely used as a tool applied to the PAD pandemic.

Recommendations
8. Primary care providers, including gynecologists, should identify women with or at high risk for PAD by targeted use of the ABI test per current national guidelines.
9. Women at risk for PAD should be informed of common PAD risk factors, symptoms, and cardiovascular risk by all health professionals.
10. Women’s cardiovascular health (“heart health”) programs should include both PAD awareness campaigns and gender-relevant PAD care pathways designed to lower cardiovascular risk, prevent or decrease limb ischemic symptoms, and minimize amputation risk.
11. Women with or at risk for PAD should undergo an ABI or alternative diagnostic assessment for PAD (Table 1, ACC/AHA Guidelines for the Management of PAD).

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## Disclosures

### Writing Group Disclosures

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<th>Research Grant</th>
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<td>Spivak v LuGerfo, Plaintiff, 2008, nerve damage after resection of Schwannoma*; Johnson v Johns Hopkins, Defendant, 2008, amputation after balloon pump placement due to MI*; Coleman v Smirnov, defendant, 2008, inadequate treatment after the late diagnosis of an infected aortic bifemoral graft*; Reviewed a case as part of the Vascular Surgery Committee at the American College of Surgeons, re: compelement*.</td>
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*Modest.
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A Call to Action: Women and Peripheral Artery Disease: A Scientific Statement From the American Heart Association

Alan T. Hirsch, Matthew A. Allison, Antoinette S. Gomes, Matthew A. Corriere, Sue Duval, Abby G. Ershow, William R. Hiatt, Richard H. Karas, Marge B. Lovell, Mary M. McDermott, Donna M. Mendes, Nancy A. Nussmeier and Diane Treat-Jacobson

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