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AHA SCIENTIFIC STATEMENT

Sex Differences in Peripheral Vascular Disease: A Scientific Statement From the American Heart Association

Esther S.H. Kim, MD, MPH, FAHA, Chair; Shipra Arya, MD, SM, Vice Chair; Yolanda Bryce, MD; Heather L. Gornik, MD, MHS, FAHA; Chandler A. Long, MD; Mary M. McDermott, MD, FAHA; Amy West Pollak, MD, MSc, FAHA; Vincent Lopez Rowe, MD; Alexander E. Sullivan, MD, MSCI; Mary O. Whipple, PhD, RN, PHN; on behalf of the American Heart Association Council on Peripheral Vascular Disease; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology; Council on Genomic and Precision Medicine; Council on Quality of Care and Outcomes Research; and Stroke Council

ABSTRACT: Sex differences in the risk factors, diagnosis, treatment, and outcomes of patients with cardiovascular disease have been well described; however, the bulk of the literature has focused on heart disease in women. Data on sex differences in peripheral vascular disease are ill defined, and there is a need to report and understand those sex-related differences to mitigate adverse outcomes related to those disparities. Although peripheral vascular disease is a highly diverse group of disorders affecting the arteries, veins, and lymphatics, this scientific statement focuses on disorders affecting the peripheral arteries to include the aorta and its branch vessels. The purpose of this scientific statement is to report the current status of sex-based differences and disparities in peripheral vascular disease and to provide research priorities to achieve health equity for women with peripheral vascular disease.

Key Words: AHA Scientific Statements ■ aneurysm ■ carotid artery diseases ■ peripheral arterial disease ■ peripheral vascular diseases ■ sex characteristics ■ vasculitis ■ women

Since the publication of "Women's Health: Report of the Public Health Service Task Force on Women's Health Issues" in 1985, important advances have been made to better understand the impact of cardiovascular disease (CVD) on women's health.[1,2] Dedicated research investigating sex differences in CVD has highlighted significant differences in the presentation, diagnosis, treatment, and outcomes of patients affected by CVD. These important findings have led to the recent publication of scientific statements dedicated to CVD in women and have also led some to call for the development of sex-specific guidelines for CVD.[3,4] Although the term CVD encompasses the range of diseases affecting the heart and blood vessels, the primary focus in investigations of sex differences in CVD has been on investigating sex differences in cardiac diseases (eg, heart failure, coronary artery disease, and arrhythmias). It is known that cardiac disease and peripheral vascular disease (PVD) often coexist, given their common risk factors (as in the case of atherosclerotic CVD), but there are unique considerations in vascular disease that also warrant exploration. Thus, although many advances have been made in our understanding of the sex differences in heart disease, less is known about sex differences in PVD. To improve the quality of life and to prolong the lives of women with PVD with or without heart disease, sex-based disparities must be identified and addressed.

This purpose of this scientific statement is to summarize the sex-based differences in epidemiology, risk factors, screening, diagnosis, treatment, and outcomes in PVD and to provide research priorities to mitigate sex-based disparities and prevent the underdiagnosis and undertreatment of women with PVD. PVD encompasses vascular disease of the arteries, veins, and lymphatics, but this document focuses solely on peripheral arterial disease, including aortic disease. It is well recognized that significant interactions exist between sex and race, and when available, we have incorporated sex differences in

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PVD by race to highlight any additional barriers to achieving equitability in care for PVD.

AORTIC DISEASE

Epidemiology, Risk Factors, and Screening

Aortopathy refers to a group of conditions that weaken the aortic wall, leading to aortic aneurysm (thoracic ascending, descending, and abdominal), aortic dissection, or both (in addition to other acute aortic syndromes: intramural hematoma and penetrating aortic ulcer). Aortopathy can be a sporadic/degenerative, nonsyndromic heritable thoracic aortic disease or familial disease, including Marfan syndrome or Loeys-Dietz syndrome. The estimated composite death rate of aortopathies globally has increased from 2.49 per 100 000 in 1990 to 2.78 per 100 000 in 2010.[5]

Within the spectrum of aortopathies, sex-based differences exist along the care-axis continuum from prediagnosis screening through postintervention outcomes.[6] Women have a lower incidence of aortopathies in general but a higher risk of rupture than men for all pathologies (Table 1).

Women affected by aortopathy tend to be diagnosed at a significantly older age and to have a greater likelihood of presenting with more severe or symptomatic disease compared with men (Table 1).[33] Aortic disease screening is recommended only for abdominal aortic aneurysms (AAAs) on the basis of disease incidence and prevalence. Thus, sex differences exist in formal screening guidelines with some variation in recommendations, depending on the recommending society. The American College of Cardiology/American Heart Association guidelines recommend AAA screening for men ≥65 years of age with a history of smoking but list screening as reasonable in women ≥65 years of age with a history of smoking.[13] Screening is recommended in both men and women ≥65 years of age who have first-degree relatives with AAA. The Society for Vascular Surgery guidelines recommend AAA screening in men or women 65 to 75 years of age with a history of tobacco use and suggest screening in men or women ≥65 years of age who have first-degree relatives with AAA.[14] The US Preventive Services Task Force does not make a recommendation for or against AAA screening in women 65 to 75 years of age with a history of smoking or a family history of AAA, citing insufficient evidence to assess benefit versus harm of screening.[34] Medicare policy currently offers a 1-time AAA screening duplex ultrasound examination for women beneficiaries with a family history of AAA.[35] The lack of comprehensive, evidence-based screening guidelines for women is influenced by the low prevalence of disease and underrepresentation in scientific trials. This may contribute to their more severe and delayed presentation state at the time of diagnosis.

The risk factors for the development of aortopathy are similar between men and women and include smoking, hypertension, age, CVD, and family history.[36] There is a higher risk of AAA development in women who had a relative with an AAA compared with men with a relative with an AAA. Furthermore, the prevalence of AAAs was higher in relatives of women patients with a diagnosis of an AAA compared with the relatives of men with a diagnosis of an AAA.[37] For syndromic aortopathies such as Marfan syndrome (autosomal dominant, caused by a mutation in *FBN1*), men are more likely than women to have aortic root dilation, aortic regurgitation, and thoracic aortic aneurysms, whereas mitral valve prolapse, arachnodactyly, and scoliosis are more common in women.[38] Sex differences exist in dilatation severity (more severe in men), but there is no difference in progression rates by age or sex.[39] In Loeys-Dietz syndrome (autosomal dominant, caused by a mutation in *SMAD2*, *SMAD3*, *TGFB2*, *TGFB3*, *TGFBR1*, or *TGFBR2*), there is evidence of sex differences in outcomes based on mutation. For *TGFBR1* mutations, 90% of men had an aortic event by 60 years of age compared with 50% of women, and the proportion of men presenting with aortic dissection was higher than in women.[40] No sex differences exist in outcomes in patients with *TGFBR2* or in clinical presentation, screening, or treatment recommendations. However, counseling and aortic imaging are recommended before pregnancy in patients with syndromic aortopathy, nonsyndromic heritable thoracic aortic disease, Turner syndrome, bicuspid aortic valve with aortic dilation, or another aortopathy.

The presentation of aortic pathology in women at more advanced ages is likely multifactorial but due in part to growing evidence of the protective effect of estrogen hormones on AAA formation and growth.[41] The biochemical pathway is affected by modulation of matrix metalloproteinase activity, downregulation of cytokines, immune cell migration, and other immune mediators at key points in the pathophysiological process in AAA development.[42] Moreover, larger AAAs in women have been associated with earlier onset of menopause, further supporting the protective effect of estrogen exposure on aneurysmal progression.[41] Biomechanical studies have revealed decreased uniaxial tensile strength in female aortas compared with male aortas, which may contribute to the increased rupture risk observed in women.[43] It is unclear whether the growth rate of aortic aneurysms differs according to sex; limited evidence exists, and available data are conflicting. What remains clear is that women have a significantly higher risk of rupture; in the UK Small Aneurysm Trial, women were 3 times as likely to rupture as men at equivalent sizes. Furthermore, women experience rupture at smaller sizes, and up to 30% occur at diameters <5.5 cm compared with 8% in men at the same size threshold.[44] Given the differences in normal aortic size, being 2 to 6 mm smaller in women, it has been postulated that aortic size index or

Table 1. Aortic Disease: Sex-Specific Epidemiology, Risk Factors, and Clinical Outcomes

	Epidemiology	Sex-specific differences	Clinical outcomes
TAA	TAA and dissection combined[7] Women 9.1 per 100 000 per y Men 16.3 per 100 000 per y 40% dissection, 40% nonruptured aneurysms, 20% aortic rupture overall, including patients of both sexes Olmsted County, Minnesota: TAA 10.4/100 000 person-y[8] Mean age: Women 76–77 y[8,9] Men 63–65 y Rupture risk Cumulative risk 20% Age-, sex-adjusted incidence 3.5 per 100 000 person-y 79% of ruptures are in women[8] Growth rate Women 0.9–1.2 mm/y Men 0.4–0.6 mm/y[10,11]	Aortic root reconstruction (root replacement, Ross, or valve-sparing root operations; $P<0.001$)[12] Women 29% Men 45% Repair criteria or thresholds[13,14] Sporadic or degenerative aortic disease: Aortic root or ascending aorta aneurysm 5.5 cm or rapid growth; with aortic valve replacement 5.0 cm Descending thoracic aorta: repair threshold in 5.5 cm (endovascular) and 6 cm (open) Nonsyndromic heritable thoracic aortic disease 5.0 in absence of high-risk features; 4.5 cm with high-risk features (family history of dissection, rapid growth, diffuse aortic root and ascending aorta dilation, or marked vertebral artery tortuosity or aortic root area: height ≥10 cm^2/m) Marfan syndrome: 5.0 cm aortic root/ascending; 4.5 cm with high-risk features and experienced surgeon Loeys-Dietz syndrome: repair based on genetic variant, aortic diameter, growth rate, extra-aortic features, family history, age, sex, and shared decision-making Bicuspid aortic valve: 5.5 cm aortic root/ascending; 5.0 cm with high-risk features and experienced surgeon; 4.5 cm with aortic valve replacement/repair	After TEVAR[12,15]: Postoperative mortality Women 11% Men 7.4% 30-d mortality ($P<0.01$) Women 5.4% Men 3.3% ($P<0.01$) 1-y mortality ($P<0.01$) Women 9.8% Men 6.3% ($P<0.01$) Postoperative stroke[12] Women 8.8% Men 5.5%
Acute aortic syndrome (dissection, penetrating aortic ulcer, intramural hematoma)	Meta-analysis: 4.8/100 000 person/y[16] Hungary: 2.9/100 000 person/y, male:female ratio 1.55:1[17] Olmsted County, Minnesota: 3.5 per 100 000 person/y; 5.2 and 2.2 per 100 000 person-y for men and women, respectively[18] Women present 7 y older than men[19] Equal male:female prevalence at age ≈75 y[20]	Extent of dissection similar 2:1 ratio type A to type B in women and men Imaging findings (impending rupture, pericardial effusion, and coronary compromise) worse in women[21] High-risk features in uncomplicated TBAD higher in women (refractory hypertension and pain)[22] Complicated TBAD (malperfusion or rupture) presentation higher in men (32%–40%) vs women (18%–19%)[19,22] Medical management of type A dissection[21] Women 28% Men 13% Medical management of TBAD[21,23] Women 79%–87% Men 70%–82% Repair criteria or thresholds Type A: immediate operative repair with renal, mesenteric, or lower-extremity perfusion Type B: initial medical therapy; repair recommended for rupture, branch artery occlusion and malperfusion, dissection extension, progressive aortic enlargement, intractable pain, or uncontrolled hypertension. IMH: Urgent repair with acute type A or type B IMH and complications (malperfusion, periaortic hematoma, pericardial effusion with tamponade, refractory or recurrent pain, or rupture); prompt surgical repair in uncomplicated acute type A IMH; medical therapy in uncomplicated acute type B IMH. PAU: Urgent repair with PAU and rupture; urgent repair for ascending aorta PAU with associated IMH; repair with uncomplicated PAU and persistent pain	Mortality ($P=0.001$)[21] Women 30.1% Men 21.0% In-hospital complications (hypotension, cardiac tamponade) more common in women Trend toward greater frequency of coma/altered mental status in women Limb ischemia observed less frequently in women[21]

(*Continued*)

Table 1. Continued

	Epidemiology	Sex-specific differences	Clinical outcomes
AAA	174/100 000 per y in women 354/100 000 per y in men[24,25] Women present 5–10 y older than men[26,27]	Rupture risk (Sweden Malmo[28]): 5.6/100 000 person-y Women 3/100 000 Men 8.4/100 000 Growth rate Women 2.0–3.5 mm/y Men 1.6–2.4 mm/y[29–31] Repair criteria or threshold Women 5.0 cm Men 5.5 cm Both sexes: symptomatic or rapid growth Surveillance should be done in patients with AAA diameters as follows: 3.0–3.9 cm: every 3 y Women 4.0–4.4 cm: annually Men 4.0–4.9 cm: annually Women ≥4.5 cm: every 6 mo Men ≥5.0 cm: every 6 mo	After open repair for intact and ruptured AAA, women have a higher mortality rate.[26] Elective EVAR was used more commonly for men compared with women (82.1% vs 74.1%; *P*=0.01).[32] EVAR: women have a higher access arterial injury rate, more frequent returns to operating room, longer ICU stays, and longer hospital LOS. Open: women have higher intraoperative morbidity and longer ICU stays.[26]

AAA indicates abdominal aortic aneurysm; EVAR, endovascular aortic aneurysm repair; ICU, intensive care unit; IMH, intramural hematoma; LOS, length of stay; PAU, penetrating aortic ulcer; TAA, thoracic aortic aorta; TBAD, type B aortic dissection; and TEVAR, thoracic endovascular aortic aneurysm repair.

aortic height index be used to index for these body size differences instead of using aortic diameters for repair thresholds.[45–50]

Treatment Choices and Outcomes

The natural history and outcomes after treatment for aortopathies tend to yield less favorable results in women compared with men.[51] Unfortunately, this is not confined to distinct locations of the aorta or the means of intervention. Treatment threshold and criteria for repair for the 3 broad categories of aortopathies and their subgroups are outlined in Table 1. There are sex-specific treatment thresholds only for AAA (5.5 cm for men, 5.0 cm for women) as shown by large population-based studies, but women have been underrepresented in randomized controlled trials (RCTs; <4% for small aneurysm trials); thus, the recommendations are based on weak evidence.

In women, repair of aortopathies also becomes important in the context of pregnancy. Women with Marfan or Loeys-Dietz syndrome are at high risk for arterial dissection and uterine rupture during pregnancy and the postpartum period.[52] This is hypothesized to be related to the hyperdynamic state and effect of sex hormones on the vasculature.[53] Surgery before pregnancy is recommended in patients with Marfan syndrome or nonsyndromic heritable thoracic aortic disease for aortic diameters >4.5 cm, bicuspid aortic valve and sporadic aortic diameter ≥5.0 cm, and Turner syndrome and aortic size index ≥2.5 cm/m^2.[13] Surgery before pregnancy is reasonable in patients with Loeys-Dietz syndrome with *TGFB2* or *TGFB3* and aortic diameter ≥4.5 cm.[13] A multidisciplinary team–based approach with a maternal-fetal medicine specialist and cardiologist is recommended. Surveillance imaging (transthoracic echocardiography or magnetic resonance imaging) is recommended during each trimester and for several weeks postpartum. Delivery by cesarean section is recommended in patients with chronic aortic dissection and is reasonable in patients with aortic root or ascending aorta aneurysm diameter ≥4.5 cm; if otherwise appropriate, vaginal delivery is recommended in patients with aortopathy and aortic diameter <4.0 cm.[13]

Endovascular thoracic and AAA repair (thoracic endovascular aortic aneurysm repair/endovascular aortic aneurysm repair) is the most common modality currently used for aortic aneurysmal disease repair. Women are more likely to undergo open surgery for an elective AAA repair compared with men.[32] This imbalance in the use of endovascular repair in women is heavily influenced by anatomical features more commonly found in women that disqualify them on the basis of the instructions-for-use criteria for endovascular aortic aneurysm repair devices (ie, vessel size, inadequate proximal neck).[54]

The Canadian Thoracic Aortic Collaborative performed an analysis that revealed that despite comparable rates of aortic arch repair between the sexes, women were significantly less likely to receive an aortic root reconstruction compared with men.[12] Furthermore, they identified that the mortality and stroke rate in women after thoracic aortic surgery with hypothermic circulatory arrest was significantly higher than in their male counterparts. This is significant because higher morbidity and mortality rates have consistently been reported in women after open AAA surgery as well.[55]

Aortic dissections confer significant morbidity and mortality risk to all patients affected by this disease process. A large retrospective analysis of patients with type B dissections demonstrated that women were more

frequently managed medically compared with men, but the adjusted, propensity-weighted regression demonstrated no significant effects on in-hospital mortality according to sex.[23] Women are less likely to present with complicated type B aortic dissection (malperfusion or rupture) but more likely to present with high-risk features (refractory hypertension and pain).[22,56,57] The results after endovascular treatment of aortic dissection have varied, and further inquiry is needed. With regard to thoracic endovascular aortic aneurysm repairs, women have been found to have higher mortality rates at 30 days and 1 year after repair.[15]

Other adverse postoperative outcomes have been disproportionately reported in women.[58] For example, higher type II endoleak rates have been described after thoracic endovascular aortic aneurysm repair for complicated type B dissections, as well as higher overall endoleak rates after endovascular aortic aneurysm repair.[59] An increasing body of literature highlights the importance of frailty and its influence on postoperative outcomes and quality of life. A retrospective analysis of patients with thoracoabdominal aortic aneurysm found that women had significantly higher frailty metrics compared with their male counterparts at the time of diagnosis and, as a result, are less likely to be offered intervention/surgery.[60] Sex differences have been identified in other outcomes, including length of stay, discharge, and readmission after aortic intervention. A large analysis of patients from the American College of Surgeons National Surgical Quality Improvement Program database who underwent aortic aneurysm (AAA, thoracic aortic aneurysm, and thoracoabdominal aortic aneurysm) surgery illustrated that women had a higher unplanned readmission rate after aortic aneurysm surgery and were twice as likely to be discharged to a care facility instead of their home.[61]

Underrepresentation Within Trials/Potential Sources and Solutions for Disparities

Women were significantly underrepresented in many of the seminal RCTs comparing endovascular with open repair of AAAs and in industry-sponsored trials testing new devices; the participation-to-prevalence ratio is consistently <0.8.[62–65] Thus, the conclusions drawn from these studies may offer limited applicability to the female population and may explain the poor performance of endovascular devices in women. Although women make up the minority of patients affected by aortic aneurysm and dissection, they present with more severe and complicated disease and have worse natural history and postprocedural outcomes compared with men. RCTs centered on defining sex-specific thresholds for repair of aortopathies are needed in women such as the planned multinational WARRIORS trial (Women's Abdominal Aortic Aneurysm Research: Repair Immediately or Routine Surveillance).[66] Moving forward, given the sex-based disparities within CVDs, women need to be meaningfully represented in research trials (participation-to-prevalence ratio goal, 0.8–1.2) and specific primary or secondary analyses powered to answer sex-specific research questions to ensure that the disparity gap is closed. Ongoing study of access to care, early diagnosis/detection, preventive interventions, and equitable inclusion in trials is required to address this sex-based disparity in medicine and to optimize the course of care for women affected by this pathology.[6] Table 1 summarizes sex-specific epidemiology, risk factors, and clinical outcomes for aortic disease.

PERIPHERAL ANEURYSMS AND DISSECTING ARTERIOPATHIES

Peripheral aneurysms and dissecting arteriopathies comprise a wide range of familial and acquired systemic and localized vascular conditions, including fibromuscular dysplasia (FMD), vascular Ehlers-Danlos syndrome, visceral and peripheral aneurysms, and cervical and visceral artery dissections. A summary of each of the conditions and the known epidemiology, risk factors, sex-specific differences, and current research are summarized in Table 2.

Previous studies have demonstrated a female predominance of FMD (between 5:1 and 9:1) and vascular Ehlers-Danlos syndrome (7:3).[68,69,81] Among patients with FMD, the female predominance is most apparent for the multifocal type of FMD, with more balanced sex distribution for the focal type of FMD, which has been postulated to be a distinct disease process.[81,82] Popliteal artery aneurysms and visceral dissections, however, are significantly more common in men, with a male:female prevalence of 20:1 and 7:3, respectively. A female predominance for splenic artery aneurysms has been reported.[83]

Despite sex differences in the prevalence of these conditions, no sex-specific risk factors have been consistently identified. In cervical artery dissections, previous work has consistently demonstrated a slight male predominance (≈57% male); however, it has been hypothesized that this may be more a result of sex differences in risk factors (eg, smoking, cervical trauma resulting from heavy lifting) than underlying hormonal or genetic differences.[79] Women who are diagnosed with cervical artery dissection tend to be younger (mean age, 41.0 years) than their male counterparts (46.4 years).[79]

Popliteal artery aneurysms are common in men with AAA and screening-detected aortic dilatation.[84] Some differences in outcomes by sex have been reported. For example, among patients with FMD, although male patients represent a minority of those diagnosed, they have 2-fold rates of aneurysm and dissection compared with women.[85] In vascular Ehlers-Danlos syndrome, the life expectancy for men is lower than for women (46 and

Table 2. Peripheral Aneurysms and Dissecting Arteriopathies: Sex-Specific Epidemiology, Risk Factors, and Clinical Outcomes

	Epidemiology	Risk factors	Sex-specific differences	Representation of women in research
FMD	Age: Mean age of diagnosis 46–53 y[67] Race and ethnicity: No racial or ethnic propensity but more common in White individuals than Black individuals[68] Sex: Female predominance (5:1–9:1 female:male)[68,69] Female predominance more pronounced among patients with multifocal vs focal type of FMD	Known associations: Female sex Mechanical trauma due to increased kidney mobility[70] Age (highest prevalence among women in 70–79 y age group; among men in ≥80 y age group)[68] Genetic susceptibility[71] Sex-specific risk factors: Unknown, although potential influence of sex hormones has been suggested[53]	Screening: Screening for renal FMD recommended in women with hypertension 20–50 y of age and in all ages/sexes in cases of severe or resistant hypertension[68] Clinical presentation: No known difference Treatment: No known difference Outcomes: Women less likely to have aortic and renal dissection (OR, 0.52 and 0.26, respectively) Women more likely to have vertebral and coronary artery dissection (OR, 1.90 and 8.55, respectively) Intracranial and renal artery aneurysm more common in women	Clinical trials: None identified Registries: European/International FMD Registry and Initiative, North American Registry for FMD
vEDS	Age: Mean age at diagnosis 28 y[52] Race and ethnicity: All racial and ethnic groups Sex: Female predominance (7:3 female:male) Accounts for <5% of EDS cases	Known associations: Autosomal dominant, caused by pathological variant in *COL3A1*, leads to decreased type III collagen Sex-specific risk factors: None identified	Screening: No known difference Clinical presentation: No known difference Treatment: No known difference Outcomes: Median life span 48 y Life expectancy for men lower than women (46 y vs 54 y)[72,73]	Clinical trials: Comparison of celiprolol with placebo in vEDS (DiSCOVER, NCT05432466) Registries: Vascular Low Frequency Disease Consortium, Registry of Vascular Ehlers-Danlos
PAAs	Age: Risk increases with age, peaks in 60–70 y of age Race and ethnicity: More common in White individuals Sex: Male predominance (1:20 female:male)[74] Most common peripheral aneurysm (85%)[74]	Known associations: Age, male sex, smoking, connective tissue disorder, White race, family history of aneurysmal disease, history of AAA[75] Sex-specific risk factors: None identified	Screening: No known difference Common in men with AAA and screening-detected aortic dilatation Clinical presentation: Women tend to be younger and less likely to have CAD[76] Treatment: No known difference Outcomes: After open repair for symptomatic PAAs, risk of major amputation was 3 times higher for women (3.09 [95% CI, 1.05–9.06])[76]	Clinical Trials: None identified Registries: Vascular Quality Initiative, Vascunet

(*Continued*)

Table 2. Continued

	Epidemiology	Risk factors	Sex-specific differences	Representation of women in research
Other peripheral aneurysms	Age: Median age 59 y[77] Race and ethnicity: All racial and ethnic groups Sex: Location related to sex; overall, most common site is splenic artery (≈60%), next is hepatic artery (≈20%)[77] Common iliac artery (28.7% vs 8.9%), internal iliac artery (6.6% vs 1.3%), and popliteal artery (11.1% vs 2.5%) more common in men compared with women[74] Splenic artery (0.9% vs 5.1%) and renal artery (0.8% vs 6.0%) more common in women compared with men[74] No sex difference in visceral artery/renal artery aneurysm in 1 cohort[78] Female sex predominance for splenic artery aneurysm	Known associations: Increasing age, hypertension, smoking, EDS, FMD[77] Sex-specific risk factors: Increased risk of rupture during pregnancy and postnatal period[78]	Screening: No known difference Clinical presentation: No known difference Treatment: No known difference Outcomes: No known difference	Clinical trials: None identified Registries: EmboCoh Visceral Aneurysm Registry
Cervical artery dissection	Age at diagnosis: Women 41.0 y Men 46.4 y[79] Race and ethnicity: All racial and ethnic groups Sex: Slight male predominance (≈57% of cases), although this may be related in part to sex differences in risk factors[79,80]	Known associations: Smoking, hypercholesterolemia, diabetes, hypertension, cervical trauma (heavy lifting, chiropractic manipulation)[79] Sex-specific risk factors: None identified	Screening: No known difference Clinical presentation: No known difference Men more likely to have hypertension, women more likely to have migraine and pulsatile tinnitus[80] Treatment: No known difference Outcomes: No known difference	Clinical trials: Risk of recurrence of cervical artery dissection during pregnancy/puerperium (NCT04253535) Registries: Cervical Artery Dissection and Ischemic Stroke Patients Cohort

AAA indicates abdominal aortic aneurysm; CAD, coronary artery disease; EDS, Ehlers-Danlos syndrome; FMD, fibromuscular dysplasia; OR, odds ratio; PAA, popliteal aneurysm; and vEDS, vascular Ehlers Danlos Syndrome.

54 years, respectively).[72,73] Patterns of dissection also vary by sex.[68,76] Additional research is needed to understand the physiological mechanisms for these differences in presentation and outcomes.

Few clinical trials are currently targeting these conditions, and the male:female distribution tends to reflect the population, with limited racial and ethnic diversity. The DiSCOVER trial (Clinical Trial to Compare the Efficacy of Celiprolol to Placebo in Patients With Vascular Ehlers-Danlos Syndrome; NCT05432466) compares celiprolol with placebo in vascular Ehlers-Danlos syndrome. Preclinical work in murine models of Marfan syndrome has shown promise in slowing aortic root dilatation, but clinical translation has been challenging.[86] Numerous registries, however, are enrolling participants to better understand the pathogenesis, treatment, and outcomes of patients with these rare vascular diseases. Ongoing registries targeting these arteriopathies include the North American Registry for FMD; European/International FMD Registry and Initiative; Registry of Vascular Ehlers-Danlos; and National Heart, Lung, and Blood Institute GenTAC Registry.[38,87] These registries, which enable clinicians and researchers to identify larger populations of patients with these conditions, are critical to identifying and implementing effective screening given clinical characteristics and reducing the risk of aneurysm and dissection, which are common outcomes of these conditions. Additional work is needed to understand sex-specific risk factors that explain the female predominance of many arteriopathies, as well as additional guidelines for screening and management.

PERIPHERAL ARTERY DISEASE

Epidemiology

Prevalence of Peripheral Artery Disease in Women

Lower-extremity peripheral artery disease (PAD) affects ≈8.5 million people in the United States and 230 million people worldwide.[88,89] When an ankle-brachial index (ABI) <0.90 is used to define PAD, the prevalence is similar in men and women.[88–91] In the CHS (Cardiovascular Health Study), a population-based study of people ≥65 years of age in the United States, PAD prevalence was 13.8% in men and 11.4% in women (P=0.49). Men with

PAD had higher prevalences of other coexistent CVDs than women with PAD (56% versus 40%; $P<0.001$).[90] In MESA (Multi-Ethnic Study of Atherosclerosis), a population-based study of people without clinically evident CVD at baseline, the prevalence of ABI <0.90 was 3.7% in women and 3.7% in men.[91]

Among 3174 participants in the observational longitudinal CRIC (Chronic Renal Insufficiency Cohort) with mild to moderate chronic kidney disease followed up for a median of 5.9 years, the incidence of new PAD during follow-up was 21.7% in women compared with 12.6% in men.[92] This finding differed meaningfully from the CHS, which reported PAD incidence rates of 9.2% in 1389 women and 9.0% in 2289 men during a 6-year follow-up. CRIC results also differed from those of the ARIC longitudinal study (Atherosclerosis Risk in Communities), in which the incidence of PAD was ≈14% in 759 men and ≈14% in 892 women over 10 years of follow-up. Reasons for the higher incidence of PAD among women compared with men in the CRIC study are unclear but may be due to intrinsic differences in ABI measurement between men and women (described later) and to the fact that men may be more susceptible to medial arterial calcinosis than women, which is common in chronic kidney disease.[93]

In MESA, the prevalence of ABI 0.90 to 0.99, consistent with mild PAD, was more than twice as high in women compared with men (10.3% versus 4.0%; $P<0.001$), and the prevalence of ABI 1.00 to 1.09, just below the normal ABI range of 1.10 to 1.40, was significantly higher in women (35.5% versus 21.1%; $P<0.01$).[91] These data suggest that ABI values may be intrinsically lower in women compared with men even in the absence of PAD. Consistent with this, in the MESA cohort without any CVD or risk factors, the ABI in women was 0.02 lower than in men.[94] This phenomenon should not affect PAD diagnosis in individual patients but could result in an overestimation of the prevalence of mild PAD in women in large population studies.[95]

Race, Female Sex, and PAD

The prevalence of PAD is higher among Black women compared with White women.[89–91,95] In a Markov chain Monte Carlo analysis, the estimated lifetime risk of PAD was 27.6% in Black women and 19% in White women.[96] In a study from the late 20th century that combined data from 7 community-based studies, the prevalence of PAD was approximately twice as high in Black women and American Indian women compared with White women.[88] However, data on the prevalence of PAD in American Indian women are limited.

Risk Factors for PAD

Risk factors for PAD include cigarette smoking, diabetes, hypertension, dyslipidemia, and inflammation.[95,97,98] People with PAD have lower socioeconomic status and lower education levels than people without PAD; data on the association of air pollution with PAD have been mixed.[99–102] In a systematic review, compared with not currently smoking cigarettes, current cigarette smoking was more strongly associated with PAD among women than among men.[103] There were no significant sex differences in the risk of former versus never smoking or the risk of current versus never smoking in women compared with men.[103] In the UK Biobank study (94% White) of 500 207 people (54.5% women), smoking was more strongly associated with risk of hospitalization for PAD among women compared with men.[104] However, it is unclear whether these associations apply to more diverse populations or to other outcomes in people with PAD who are not hospitalized for PAD. In a population-based study from Sweden, men with PAD were significantly more likely to have a history of cigarette smoking than women with PAD.[105] Two epidemiological studies reported that low alcohol intake was associated with a lower prevalence of PAD in men but not in women.[95] However, in a study from Edinburgh, this sex difference was no longer observed after adjustment for social class. Overall, data on sex differences in associations of alcohol with PAD are mixed.[95] Table 3 summarizes sex-specific epidemiology, risk factors, and clinical outcomes for PAD.

Sex Differences in PAD Symptoms

Intermittent claudication, consisting of exertional calf pain that does not begin at rest and that resolves within 10 minutes of rest, is the most classic symptom of PAD.[124] However, most people with PAD do not report classic intermittent claudication symptoms, and many report no exertional leg symptoms (ie, are asymptomatic).[107] Among people with PAD, rates of atypical leg symptoms and asymptomatic PAD are higher in women than men.[105,108,125,126] In the WALCS study (Walking and Leg Circulation Study) of 460 patients with PAD, women had a higher prevalence of spinal stenosis, peripheral neuropathy, and knee arthritis than men, and these comorbidities were associated with a higher prevalence of atypical leg symptoms.[108] The higher prevalence of atypical leg symptoms and asymptomatic PAD in women compared with men, perhaps due to a higher prevalence of comorbidities that contribute to atypical leg symptoms or lower physical activity in women, respectively, could result in higher rates of underdiagnosis of PAD in women than men. A study of Australian primary care practices performed ABI testing in 2489 patients (34.7% women) without a prior diagnosis of PAD who had established CVD or multiple CVD risk factors.[127] Rates of previously undiagnosed PAD were 31.8% in women and 25.7% in men.[127]

Functional Impairment, Functional Decline, and Quality of Life in Women With PAD

In people without PAD, men have larger muscles, greater strength, and faster walking speeds than women.[110,128]

Table 3. Sex-Specific Differences in Prevalence, Characteristics, Outcomes, and Treatment of PAD

	What is known	Sex-specific differences	Additional considerations
Epidemiology	The prevalence of PAD is ≈10%–15% in epidemiological studies of people ≥65 y of age. In clinical settings, 20%–30% of people ≥65 y of age and 50–64 y of age with a history of diabetes or smoking have PAD.[106] Older age, cigarette smoking, diabetes, hypertension, dyslipidemia, Black race, high levels of inflammation, and chronic kidney disease are associated with higher rates of PAD.[106]	In the CHS of community-dwelling men and women ≥65 y of age, the prevalence of ABI <0.90 was 13.8% in men and 11.4% in women (*P*=0.49). In the MESA study of community-dwelling men and women 45–84 y of age without clinically manifest cardiovascular disease, women had a higher prevalence of ABI 0.91–1.09 compared with men. Black women and American Indian women have a significantly higher prevalence of PAD than White women.[89,91]	Systematic differences in risk factors for PAD have not been consistently documented between men and women. However, some evidence suggests that smoking may be more strongly associated with PAD in women than men.[103] Future study should better define the prevalence and significance of PAD in women from all racial and ethnic groups.
PAD symptoms	Intermittent claudication is the most classic symptom of PAD, but ≈30%–60% of people with PAD report that they have no leg discomfort with walking.[107] Most people with PAD report leg pain or discomfort on walking that is atypical for claudication symptoms.[107]	Asymptomatic PAD is more common in women than men. Among people with PAD, atypical exertional leg symptoms are more common in women than men.[108]	Compared with men with PAD, women with PAD have a higher prevalence of lower-extremity arthritis, spinal stenosis, and peripheral neuropathy, which could contribute to sex differences in leg symptoms.
Functional impairment	People with PAD have significantly poorer walking endurance, walking speed, and physical activity levels compared with age-matched people without PAD. People with PAD have smaller calf muscles and poorer leg strength than people without PAD.	Compared with men with PAD, women with PAD have significantly poorer walking endurance and walking velocity.[108,109] Women with PAD have faster rates of mobility loss than men with PAD.[109] Women with PAD have smaller calf muscles and poorer leg strength than men with PAD.[109]	Differences in walking endurance and walking speed are explained at least in part by lower leg strength in women compared with men.[108,109] Sex differences in walking speed, walking endurance, strength, and muscle mass also exist in people without PAD.[110]
Exercise therapy for PAD	Supervised walking exercise and structured community-based walking exercise are both first-line therapies for PAD.[111] CMS covers 12 wk of supervised walking exercise for PAD.[106]	Women and men with PAD have similar benefits from supervised treadmill exercise.[112] Women and men with PAD have similar benefits from structured community-based walking exercise.[113] Women with PAD were significantly less likely than men with PAD to participate in CMS-covered supervised exercise.[114]	Future research should identify reasons for sex differences in participation rates in supervised exercise therapy.
Treatment to prevent cardiovascular events	Because of increased rates of cardiovascular events, all patients with PAD should be treated with high-intensity statin therapy and guideline-recommended antiplatelet or antithrombotic therapy.[111] Guidelines recommend that people with PAD should be treated to attain blood pressure <130/80 mm Hg and recommend selective use of angiotensin receptor blockers or ACE inhibitors to treat hypertension in PAD.[111] Guideline-recommended therapy is underprescribed in men and women.[111]	Some but not all studies reported that women with PAD were less likely to receive guideline-recommended therapies to prevent cardiovascular events than men with PAD. Some evidence suggested that women were less adherent to or less likely to agree to cardiovascular preventive therapy than men.	Future research should identify methods to maximize the use of guideline-recommended medications to prevent cardiovascular events in women with PAD.

(*Continued*)

Table 3. Continued

	What is known	Sex-specific differences	Additional considerations
Lower-extremity revascularization	Lower-extremity revascularization is recommended by guidelines to improve walking performance and quality of life in patients with disabling ischemic leg symptoms who do not respond to guideline-recommended medical therapy or exercise.[111] Lower-extremity revascularization is recommended by guidelines to prevent limb loss in patients with CLTI.[111]	Compared with men, women undergo lower-extremity revascularization at an older age and more commonly for CLTI than for claudication symptoms.[115–118] In some studies of lower-extremity revascularization, men were more likely to be treated with surgical intervention, whereas women were more likely to be treated with endovascular procedures.[115,117] Data are mixed on sex differences in lower-extremity outcomes and patency after lower-extremity revascularization.[116,119–122] In 1 study from the VQI registry (N=7332, ≈45% female), there were no sex differences in rates of reintervention or major adverse limb events after endovascular treatment for claudication. However, among 8100 individuals (45% female) undergoing endovascular treatment for CLTI, women had lower mortality and lower amputation rates compared with men.[122] In a meta-analysis of 40 studies, after lower-extremity revascularization, women had higher mortality, amputation, early graft thrombosis, and other adverse outcomes at 30-d follow-up. However, after 30 d of follow-up, there were no sex differences in outcomes.[123]	Women have smaller arteries than men, which could affect response to revascularization procedures. Future studies of endovascular devices for lower-extremity revascularization should include sufficient proportions of women and study sex differences in outcomes.

ABI indicates ankle-brachial index; ACE, angiotensin-converting enzyme; CHS, Cardiovascular Health Study; CLTI, chronic limb-threatening ischemia; CMS, Centers for Medicare & Medicaid Services; MESA, Multi-Ethnic Study of Atherosclerosis; PAD, peripheral artery disease; and VQI, Vascular Quality Initiative.

Similarly, among people with PAD, women have less leg strength, smaller calf muscle area, slower walking speed, and shorter 6-minute walk than men.[109,126] In the WALCS cohort of 460 people with PAD, sex differences in the distance achieved during the 6-minute walk test were attenuated but remained statistically significant after adjustment for sex differences in strength.[108] In WALCS participants with PAD followed up for 47 months, compared with men, women had significantly higher rates of becoming unable to walk for 6 minutes without stopping, greater declines in walking velocity, and greater declines in 6-minute walk distance and were more likely to report becoming newly unable to walk up and down a flight of stairs or walk one-quarter of a mile without assistance.[109] These sex differences were no longer statistically significant after adjustment for sex differences in calf muscle area.[109] Sex differences in cardiopulmonary fitness and calf muscle hemoglobin oxygen saturation have also been documented in people with PAD.[129,130]

Sex Differences in PAD Treatment

In both men and women, PAD is associated with significantly increased rates of all-cause mortality and cardiovascular events compared with people without PAD.[131] In both men and women, compared with a reference (normal) ABI value of 1.1 to 1.20, lower ABI values are associated significantly with higher rates of all-cause mortality, cardiovascular mortality, and major coronary events.[131] To prevent cardiovascular events, all people with PAD should be treated with high-intensity statin therapy, with the goal of attaining at least a 50% reduction in low-density lipoprotein cholesterol, and with guideline-recommended antiplatelet or antithrombotic drugs.[111] However, guideline-recommended therapies are underused in both men and women with PAD.[132,133] In a systematic review of sex differences in the management of atherosclerotic CVD, multiple but not all studies from the United States, Europe, and the United Kingdom reported that women with PAD were less likely than men with PAD to receive statin medications, antiplatelet drugs, and angiotensin-converting enzyme inhibitors or angiotensin II receptor blocker medications.[118,134–137] Some studies reported lower adherence rates to statin or antiplatelet therapy in women compared with men.[137] In 1 study, women were less likely than men to be prescribed a statin after lower-extremity revascularization but were more likely than men to report that a clinician recommended a statin.[118] The Women's Health Initiative showed no statistically significant effects of estrogen plus progesterone or estrogen alone on the incidence of PAD.[138,139]

Sex Differences in Exercise Therapy and PAD

Supervised and structured home-based exercise are first-line therapies for PAD-related walking disability.[111] Supervised exercise is covered by the Centers for Medicare & Medicaid Services and typically consists of walking exercise 3 times weekly at a center in the presence of an exercise physiologist or nurse.[106] Structured home-based

walking exercise also significantly improves walking impairment in PAD and is recommended by American Heart Association/American College of Cardiology guidelines as first-line therapy for PAD.[106,140] According to statistical tests for interaction, effects of supervised and structured home-based exercise have not differed significantly between men and women.[112,113,141] For example, in an individual participant-level meta-analysis of 309 patients with PAD, 132 (42.7%) were female, and the effects of supervised treadmill exercise did not significantly differ between women and men.[112] Similarly, in a randomized clinical trial of 194 participants with PAD (50% women), the effects of a structured home-based walking exercise program significantly improved 6-minute walk distance by 53 m, and results did not differ significantly between men and women.[113] However, among patients with symptomatic PAD and Medicare insurance, women were significantly less likely than men to be enrolled in supervised exercise.[142] Reasons for this sex difference were not reported.[142] In 2 clinical trials, adherence to supervised exercise sessions was similar between men and women.[141,143]

Female Sex and Lower-Extremity Revascularization

Compared with men, women undergo lower-extremity revascularization at an older age and more commonly undergo revascularization for chronic limb-threatening ischemia than for intermittent claudication.[115–118] In some studies of lower-extremity revascularization, women were more likely than men to be treated with endovascular procedures, whereas men were more likely to be treated with open surgery.[115,144] In a study of 58 247 patients (41% women) who underwent endovascular revascularization of 106 073 arteries, there were no sex differences in rates of iliac artery stenting compared with percutaneous transluminal angioplasty alone. However, women were significantly less likely than men to receive stenting of the femoropopliteal arteries and more likely to receive angioplasty alone.[116] Women were significantly more likely to undergo reintervention in the femoropopliteal arteries (hazard ratio, 1.28) and more likely to develop occlusions in the iliac (hazard ratio, 1.42) or femoropopliteal (hazard ratio, 1.19) arteries than men.[116] Other studies showed no sex differences in patency or showed improved lower-extremity outcomes after lower-extremity revascularization in women compared with men.[119,120] Among 7332 patients (≈47% female) in the Vascular Quality Initiative registry undergoing endovascular treatment for claudication between 2010 and 2015, there were no sex differences in rates of reintervention or rates of major adverse limb events at the 5-year follow-up.[122] In contrast, among 8100 individuals (45% female) undergoing endovascular treatment for chronic limb-threatening ischemia, women had significantly lower rates of major amputation or mortality compared with men.[122] The IN.PACT superficial femoral artery randomized clinical trial demonstrated that paclitaxel-coated balloon angioplasty was superior to percutaneous angioplasty for treating superficial femoral artery atherosclerosis associated with intermittent claudication, and no sex differences in primary patency, safety, rates of clinically driven target lesion revascularization, or mortality rates were identified in post hoc analyses.[121] In a meta-analysis of 40 studies that compared sex differences in adverse events after lower-extremity revascularization, women had higher mortality, amputation, early graft thrombosis, embolization, and cardiac, stroke, and pulmonary complications at the 30-day follow-up, but there were no sex differences in survival, primary or secondary patency of the revascularized limb, or limb salvage at time points >30 days after revascularization.[123] In the early 21st century, women undergoing femoropopliteal bypass graft procedures who were taking hormone replacement therapy had significantly reduced primary graft patency and higher rates of graft failure when prosthetic bypass materials were used.[145]

Future Research on Sex Differences in PAD

Future research should define the degree to which PAD is underdiagnosed in women and identify reasons for the higher prevalence of PAD in Black women and American Indian women in the United States compared with White women in the United States. Future research should establish the incidence and prevalence of PAD in women from racial and ethnic groups that are traditionally underrepresented in scientific investigation in the United States. Sex differences in associations of atherosclerotic disease risk factors with PAD, when they exist, should be defined. Optimal methods to improve prescription rates and adherence to guideline-recommended therapy in women should be identified.[146] Future studies of devices for lower-extremity revascularization should be sure to include adequate numbers of women, including women from all ethnic and racial groups, because optimal devices may differ according to sex differences in artery size or compliance.[146]

ATHEROSCLEROTIC EXTRACRANIAL CAROTID ARTERY DISEASE

Epidemiology and Risk Factors

Stroke remains the third leading cause for death and disability in the United States, with 62% of strokes of ischemic type.[114] From 1990 to 2019, the number of incident strokes increased by 70% overall, with a smaller increase (15%) in incident strokes for individuals <70 years of age. The 5 greatest risk factors for stroke are systolic hypertension, high body mass index, high fasting glucose, smoking, and ambient particulate matter pollution, which is the least appreciated.[114] In 2019, 56% of strokes occurred in women.[147] Young women (<45 years

of age) have a higher or similar stroke incidence compared with men of a similar age.[148] In middle age, men have a higher incidence of stroke, which then changes for postmenopausal women: Women >80 years of age have a higher stroke risk.[114,149] There are sex-related unique risk factors for stroke related to pregnancy, with an increase in long-term risk after preeclampsia, at older age at menopause, and with the use of exogenous estrogen therapy.[148] As with CVD in general, there are health disparities with risk of stroke. Even after adjustment for age, insurance status, and education, Black women and Hispanic women ≥70 years of age had a 76% to 77% higher risk of stroke.[150]

Up to 15% of ischemic strokes are related to atherosclerotic carotid artery disease.[151] Traditional cardiovascular risk factors of age, hypertension, hyperlipidemia, tobacco use, diabetes, and elevated body mass index are also associated with carotid artery disease.[152] On a macrovascular level, women have relatively larger areas of the internal and external carotid arteries (outflow) compared with common carotid arteries (inflow) relative to men, who have the opposite (larger inflow compared with outflow), which may affect the development of carotid atherosclerotic plaque.[153] Changes in endothelial vascular function and arterial stiffness with age are ultimately linked to the development of systolic hypertension.[154]

Sex Differences in Carotid Atherosclerotic Plaque

A recent systematic review and meta-analysis of sex differences in carotid atherosclerosis for carotid plaque composition, morphology, and size revealed important insights into sex-related differences[155] in patients with both symptomatic and asymptomatic carotid artery disease. There was heterogeneity among the studies in the meta-analysis related to plaque size and carotid calcifications, likely related to differences in study populations.[155] Women had smaller plaque size, whether measured as maximum wall thickness in a 1-dimensional size, wall area as a 2-dimensional size, or wall volume as a 3-dimensional size. However, there was no sex-related difference in the normalized wall index, which accounts for the total vessel size. There was no sex difference in the amount of calcification relative to the total plaque volume. Atherosclerotic plaques in men are more likely to have a lipid-rich necrotic core (odds ratio, 1.87 [95% CI, 1.36–2.57]) compared with women, and this difference is amplified in symptomatic patients, in whom the odds ratio increased to 3.27 (95% CI, 2.38–4.50) versus 1.79 (95% CI, 1.16–2.76) for asymptomatic patients (*P* for subgroup differences=0.03). Intraplaque hemorrhage (IPH) is seen more commonly in men (odds ratio, 2.52 [95% CI, 1.74–3.66]). Therefore, overall plaque composition for women has less lipid-rich necrotic core and IPH compared with men. From this meta-analysis, it appears that men with carotid atherosclerotic plaques have a greater volume of IPH and lipid-rich necrotic core with relatively less calcification compared with women, who have a greater relative degree of calcification compared with IPH and lipid-rich necrotic core.[155] The differences in plaque composition are related to stroke risk. Independently of maximum plaque thickness and cardiovascular risk factors, IPH is independently associated with stroke.[156,157] Although women overall have a lower burden of IPH in carotid plaque compared with men, a recent study showed a significant increase in risk of stroke for asymptomatic women with IPH (hazard ratio, 3.37 [95% CI, 1.81–6.25] for women versus 1.67 [95% CI, 0.98–2.79] for men).[157]

Evaluation for Carotid Artery Disease

The US Preventive Services Task Force recommended against screening for asymptomatic carotid artery disease in the general population again in 2021.[158] However, it is important to consider that this recommendation does not apply to individuals with a history of stroke or any signs or symptoms of transient ischemic attack. There are missed opportunities to talk with patients about symptoms that may be consistent with prior transient ischemic attack even if they are currently asymptomatic in the clinic. For symptomatic patients, carotid ultrasound and computed tomography angiography are the traditional first-line tests for carotid artery disease, depending on the timing of the clinical presentation. However, these imaging studies are unable to adequately assess for the presence of IPH. IPH is best evaluated by magnetic resonance imaging. Overall, there are limited data about sex-specific risks for stroke based on carotid plaque composition, and this remains an important opportunity for future research.

Treatment Options for Carotid Artery Stenosis and Outcomes

All patients with carotid artery stenosis should be recommended to follow a lifestyle approach with Mediterranean diet, exercise, and smoking cessation, in addition to being started on guideline-directed medical therapy with antiplatelets, lipid-lowering agents, blood pressure reduction, and glycemic control.[159–164] The use of guideline-directed medical therapy is indicated for both reduction in cerebrovascular events and other systemic complications of CVD. There is no uniform use of guideline-directed medical therapy for primary and secondary prevention of stroke in the setting of carotid artery disease among diverse populations.[165] Access to medications and comprehensive medical treatment approaches can vary significantly according to the social determinants of health.[166] There are limited sex-related data on the gaps in the use of guideline-directed medical therapy for asymptomatic carotid artery stenosis.

There is an opportunity for future research to understand differences in aspirin benefit depending on degree of carotid artery stenosis for women compared with men. A recent analysis used a carotid plaque score from a subset of the MESA study (with 57% women) to demonstrate an overall net benefit using a 5-year number needed to treat with an increasing amount of carotid atherosclerosis (carotid plaque score ≥2) in the setting of an atherosclerotic CVD risk of 5% to 20%. In comparison, with high atherosclerotic CVD risk of >20%, there was a favorable risk-benefit ratio with any degree of carotid plaque.[167] Future research should further investigate the degree of asymptomatic carotid artery stenosis and associated imaging characteristics that are associated with the greatest benefit in the use of aspirin for primary prevention of stroke in women.

Women have historically been underrepresented in clinical trials for treatment of carotid artery stenosis with either transfemoral carotid artery stenting or carotid endarterectomy (CEA), with even more striking disparity noted with inadequate racial and ethnic representation in clinical trials.[168] Contemporary large institutional and population studies no longer demonstrate the higher perioperative risk of stroke after CEA seen in the ACAS trial (Asymptomatic Carotid Atherosclerosis Study)[169] for asymptomatic disease or NASCET trial (North American Symptomatic Carotid Endarterectomy Trial)[170] and ESCT trial (European Carotid Surgery Trial)[171] for symptomatic disease, which were all limited by underrepresentation of women in these historical landmark trials.[172] For both asymptomatic and symptomatic patients undergoing CEA in CREST (Carotid Revascularization Endarterectomy Versus Stenting Trial), no significant differences were seen in the risk of perioperative stroke or death between female and male patients.[173] In CREST-2, there remained limited participation from women and people of underrepresented races and ethnicities in the clinical trial of treatment of carotid artery stenosis.[174] For symptomatic patients undergoing CEA, there was no significant difference in overall risk of stroke with CEA between women and men in 99 495 participants from 30 studies.[175] Innovative strategies are needed to improve the participation of diverse participants in studies of carotid artery revascularization. For individuals at high surgical risk for CEA, trans–carotid artery revascularization has a lower stroke and death rate for women and men compared with transfemoral carotid artery stenting.[176] The Society for Vascular Surgery guidelines on the management of extracranial cerebrovascular disease do not provide specific recommendations on the treatment of carotid artery stenosis according to sex. However, Rockman et al[172] illustrate a thoughtful approach to considering options for revascularization for women with carotid artery disease in a recent systematic review. A recent trans–carotid artery revascularization database review noted similar outcomes between men and women after trans–carotid artery revascularization but with the significant limitation that there was inadequate representation of women in the study to determine whether there is a true difference in outcomes between men and women.[177] Future studies will need a large cohort of women after trans–carotid artery revascularization.

Future Research on Sex Differences in Extracranial Carotid Artery Disease

Future work in extracranial carotid artery disease should include diverse cohorts of women to explore the relationship between race and ethnicity and health disparities on outcomes after carotid artery revascularization, risk of stroke, and carotid plaque composition. In particular, there is an opportunity to understand whether there are sex-related differences in carotid artery intervention for asymptomatic disease. Table 4 summarizes sex-specific epidemiology, risk factors, and clinical outcomes for atherosclerotic extracranial carotid artery disease.

ATHEROSCLEROTIC RENAL ARTERY DISEASE

Epidemiology

Renal artery stenosis is due predominantly to atherosclerotic plaque in adults (>90%) compared with FMD, which is a more common cause in younger patients.[182] The CHS found that atherosclerotic renal artery stenosis (ARAS), defined as ≥60% diameter stenosis, was present in 6.8% of adults >65 years of age, with Black Americans making up 23% of the study population.[183] ARAS was independently associated with increasing age, elevated low-density lipoprotein cholesterol, and systolic hypertension.

Treatment Choices/Outcomes

Overall, RCTs (STAR [The Benefit of Stent Placement and Blood Pressure and Lipid-Lowering for the Prevention of Progression of Renal Dysfunction Caused by Atherosclerotic Ostial Stenosis of the Renal Artery],[184] ASTRAL [Angioplasty and Stenting for Renal Artery Lesions],[185] and CORAL [Cardiovascular Outcomes in Renal Atherosclerotic Lesions][180]) have failed to show convincing benefit of renal artery stenting for changes in blood pressure, renal function, or pulmonary edema. Enrollment of women in these RCTs ranged from 27% to 50%. Only the CORAL trial reported outcomes according to sex. In this trial, no differences were found in the main outcome based on sex.

Given the lack of clear clinical benefit for revascularization (stenting) for ARAS, there are inadequate data to fully understand the sex-related differences or disparities

Table 4. Extracranial Carotid Artery, Mesenteric Artery, and Renal Artery Atherosclerosis: Sex-Specific Epidemiology, Risk Factors, and Clinical Outcomes

	Epidemiology	Risk factors	Clinical outcomes
Atherosclerotic extracranial carotid artery disease	Young women (age <45 y) have a higher or similar stroke incidence compared with men of similar age.[148] Women >80 y of age have higher stroke risk than men.[149] Women have a greater relative degree of calcification compared with IPH and LRNC in carotid artery plaque composition.[155]	Women: Increased long-term risk for stroke after preeclampsia, older age at menopause, and use of exogenous estrogen therapy[148]	CREST-2: Limited participation from women and people of underrepresented races and ethnicities[174] CEA: No significant difference in overall risk of stroke with CEA between women and men in 99 495 participants from 30 studies[175] Women underrepresented in clinical trials of TF-CAS and CEA[168]
Atherosclerotic renal artery stenosis	27%–50% enrollment of women in RCTs[178] Among Black patients with ARAS, a significantly greater proportion are women compared with White patients (65% vs 44.9%; *P*=0.01).[179]	No data on sex-based differences	CORAL: no difference in outcome by sex[180]
Atherosclerotic mesenteric artery disease	Women are 3 times as likely to be affected with CMI as men.[181]	No significant differences in risk factors based on sex have been identified.	There are inadequate data for differences in outcomes after revascularization for AMI and CMI related to patient sex and diverse cohorts.

AMI indicates acute mesenteric ischemia; ARAS, atherosclerotic renal artery stenosis; CEA, carotid endarterectomy; CMI, chronic mesenteric ischemia; CORAL, Cardiovascular Outcomes in Renal Atherosclerotic Lesions; CREST, Carotid Revascularization Endarterectomy Versus Stenting Trial; IPH, intraplaque hemorrhage; LRNC, lipid-rich necrotic core; RCT, randomized controlled trial; and TF-CAS transfemoral carotid artery stenting.

seen for different ethnic and racial groups. A small exploratory study found that despite the same severity of renal artery stenosis, Black patients had higher rates of severe or refractory hypertension.[179] In a cohort of older Black patients referred for coronary angiography, 19% had >70% diameter renal artery stenosis refractory hypertension or history of flash pulmonary edema, with bilateral renal artery stenosis in 26% of the patients with ARAS.[186] Black Americans overall are at increased risk of chronic kidney disease and end-stage renal disease requiring hemodialysis. Further study is needed to better understand contemporary rates of ARAS in Black Americans with refractory hypertension and symptoms of pulmonary edema or progressive kidney dysfunction. Further studies are also needed to explore sex-related differences in outcomes for renal artery stenting in the setting of hemodynamically significant ARAS for patients with resistant hypertension or a history of congestive heart failure.

ATHEROSCLEROTIC MESENTERIC ARTERY DISEASE

Epidemiology and Clinical Presentation

Atherosclerotic mesenteric artery disease involves the celiac artery, superior mesenteric artery, or inferior mesenteric artery. The spectrum of clinical presentations with mesenteric ischemia ranges from acute to chronic or acute on chronic.

Table 4 summarizes sex-specific epidemiology, risk factors, and clinical outcomes for atherosclerotic mesenteric artery disease.

Women and Mesenteric Ischemia

Sex-related factors influencing acute mesenteric artery ischemia include thrombotic events that occur acutely in the setting of underlying vascular atherosclerosis. These events can be influenced by the use of exogenous hormones related to either oral contraceptives or hormone replacement therapy. In addition, women are historically undertreated with statin and aspirin in the setting of known vascular disease, which could lead to silent progression of mesenteric artery atherosclerosis.[187]

The development of chronic mesenteric ischemia (CMI) typically involves significant atherosclerosis of at least 2 of the mesenteric arteries, with 1 vessel being the superior mesenteric artery. Although less common, nonatherosclerotic causes such as malignancy, vasculitis, radiation injury, and other autoimmune disorders can lead to CMI.[188] The classic presentation of CMI occurs beginning in the fifth or sixth decade and involves abdominal discomfort, which occurs 15 to 30 minutes after eating as a result of the postprandial increase in mesenteric blood flow that gradually resolves over the next few hours. Women are 3 times as likely to be affected by CMI than men.[181] CMI commonly occurs in elderly patients with underlying vascular disease. One study of patients with PAD undergoing angiography found that 25% had significant stenosis of >50% in either the celiac or superior mesenteric artery.[189] The incidence of symptomatic CMI is rare and represents <2% of atheromatous revascularization procedures.[190] A meta-analysis from 2012 encompassing almost 1800 patients from 43 studies reported mortality rates of 3.5% after endovascular treatment versus 7.2% of those treated with open

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Table 5. Vasculitis: Sex-Specific Epidemiology, Risk Factors, and Clinical Outcomes

	Epidemiology	Risk factors	Sex-specific differences	Representation of women in research
Large-vessel vasculitis				
GCA	Age: >50 y Incidence greatest in those 70–80 y of age Race and ethnicity: Predominantly White Sex: 2-3:1 female:male	Known associations: *HLA-DRB1*04* allele *PTPN22, VEGF, NOS2, ERAP1, REL,* and *PRKQC* gene polymorphisms Sex-specific risk factors: Unknown	Clinical presentation: Men: >2-fold risk of aortic aneurysm[194] Women: Axillary involvement more common[195] Treatment: Treatment failure 5-fold higher in women with prednisone-only regimens[196,197] Outcomes: Similar rates of mortality between men and women[198]	Clinical trials: Appropriate sex representation in clinical trials[199,200] Ongoing registries: VCRC: Giant Cell Arteritis Longitudinal Study
Takayasu arteritis	Age: Women: 15–30 y of age Men: 25–34 and 50–74 y of age Sex: 5:1 female:male Race and ethnicity: Geographic predominance: Asia, Northern Europe, Mediterranean, North America[201]	Known association: *HLA-B*52*[202] Sex-specific risk factors: Unknown	Clinical presentation[203]: Similar severity between sexes Women: Aortic arch branch vessel involvement (Numano type I) Men: Renal artery stenosis, extensive aortic lesions and abdominal aortic aneurysms (Numano type V), hypertension Treatment: No known differences Outcome: Mortality 2 times higher in women vs men[204]	Clinical trials: Appropriate sex representation in clinical trials[205] Ongoing registries: VCRC: Longitudinal Study for Takayasu's Arteritis
Medium-vessel vasculitis				
PAN	Age: 5th and 6th decades[206] Sex: 1.5:1 male:female[201] Race and ethnicity: Any background	Known association: Associated with hepatitis B and C infection *CECR1* loss-of-function mutation, presents in childhood[207] Sex-specific risk factors: Unknown	Clinical presentation: Women more commonly present with cutaneous polyarteritis nodosa Treatment: No known differences Outcome: No difference in mortality between sexes[208]	Clinical trials: Appropriate sex representation in clinical trials[209] Ongoing registries: VCRC: Longitudinal Protocol for Polyarteritis Nodosa
Kawasaki disease	Age: <5 y of age Sex: 1.5:1 male:female Race and ethnicity: Predominantly East Asian descent (Japanese)	Known association: ITPKC, CASP3, FCGR2A, BLK, CD40, and HLA class II Sex-specific risk factors: Unknown	Clinical presentation: No known differences[210] Treatment: No known differences Outcome: No known differences[211]	Clinical trials: Appropriate sex representation in clinical trials[212] Ongoing Registries: International Kawasaki Disease Registry
Variable-vessel vasculitis				
Behçet disease	Age: 3rd and 4th decades Sex: Equally affected Race and ethnicity: Eastern Mediterranean, Central Asian, and Far East Asian countries	Known association: *HLA-B51/B5* allele associated with a 6-fold increase in disease risk Sex-specific risk factors: Unknown	Clinical presentation: Young men have more aggressive disease with >2-fold risk of vascular involvement[213,214] Treatment: Differential treatment response by sex for genital ulcers, erythema nodosum, and arthritis but no known difference for vascular disease[215] Outcome: Vascular involvement is associated with the greatest morbidity and mortality[216]	Clinical trials: Appropriate sex representation in clinical trials[215,217] Ongoing registries: RISE registry AIDA registry (NCT05200715)
Cogan syndrome	Age: 3rd and 4th decades Sex: Equally affected[218,219] Race and ethnicity: Any background	Known association: Possibly molecular mimicry after reovirus type III infection[220] Sex-specific risk factors: Unknown	Clinical presentation: Men more commonly present with scleritis and episcleritis[218] Treatment: No known differences Outcome: No known differences[218]	Clinical trials: None Ongoing registries: VPPRN

(*Continued*)

Table 5. Continued

	Epidemiology	Risk factors	Sex-specific differences	Representation of women in research
VEXAS syndrome*	Age: >50 y Sex: Nearly exclusively affects men[221,222] Race and ethnicity: Not known	Known association: Missense mutations in codon 41 of *UBA1*[221] Sex-specific risk factors: X-linked gene, women protected by unmutated allele[223]	Clinical presentation: May cause GCA or PAN[223] Treatment: No known differences Outcome: No known differences	Clinical trials: None Ongoing registries: AIDA registry (NCT05200715)
Single-organ vasculitis				
Isolated aortitis	Age: ≈40–71 y Sex: ≈70% female[224] Race and ethnicity: Any background	Known association: Spectrum of disease with GCA, Takayasu arteritis, and IgG4-related aortitis Sex-specific risk factors: Unknown	Clinical presentation: High rates of aortic aneurysm No known sex differences[224,225] Treatment: No known differences Outcome: No known differences	Clinical trials: None Ongoing registries: VPPRN

AIDA indicates AutoInflammatory Disease Alliance International; GCA, giant cell arteritis; IgG4, immunoglobulin G4; PAN, polyarteritis nodosa; RISE, Rheumatology Informatics System for Effectiveness; VCRC, Vasculitis Clinical Research Consortium; VEXAS, vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic; and VPPRN, Vasculitis Patient-Powered Research Network.

*Recently described large- and medium-vessel vasculitis. Not currently included in the 2012 International Chapel Hill Consensus Conference Nomenclature of Vasculitides.[226]

Classifications adapted from the 2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides.[226]

revascularization. Furthermore, perioperative complication was reported in roughly one-third of patients undergoing open revascularization compared with only 13% after endovascular intervention.[191] Although open revascularization for CMI amassed higher morbidity and mortality, fewer patients had return of ischemic symptoms, and graft patency/durability was significantly higher at the 5-year follow-up. Because of the low diagnosis frequency of symptomatic CMI, a paucity of data exist affording further insights based on sex. A small ex vivo study of human small intestines found that the female small intestines demonstrated better protection against ischemia/reperfusion injury with an ameliorated inflammatory response.[192] Further research into cellular and molecular mechanisms may prove useful in understanding sex-based differences surrounding ischemic insults to the intestines.

Future Research on Sex Differences in Mesenteric Atherosclerotic Disease

There are inadequate data on differences in outcomes after revascularization for acute myocardial infarction and CMI related to patient sex and diverse cohorts. It is important to note that 80% of patients with CMI ischemia symptoms were initially misdiagnosed with gastroesophageal reflux disease or as needing alternative medical therapies instead of having CMI. It will be important to understand differences in time to diagnosis for CMI in diverse patient populations because groups affected by health disparities may have a longer time to diagnosis.[193] The presence of atherosclerosis in other vascular territories such as lower-extremity PAD, coronary artery disease, or cerebrovascular disease helps to identify individuals at increased risk for mesenteric artery ischemia. Future work could be done with artificial intelligence to assess the presence of atherosclerosis on imaging to help predict risk of future ischemic events such as CMI.

VASCULITIS

Vasculitides are a collection of rare diseases characterized by vascular inflammation, which results in a wide range of clinical presentations both across and within disease entities. The International Chapel Hill Consensus Conference of 2012 standardized the classifications of systemic vasculitides by the type of vessel most often affected (Table 5), although it is common for involvement to extend to arteries outside of the traditional spectrum.[226] Large-vessel vasculitides (those that affect the aorta and its major branches) and medium-vessel vasculitides (those that affect visceral arteries and veins) most often lead to manifestations of PVD. Patients may present with claudication of the upper or lower extremities, stroke or transient ischemic attack symptoms, and vascular aneurysms, dissections, or stenoses. Small-vessel vasculitides affect arterioles, capillaries, and venules and have a wide spectrum of presentations ranging from glomerular nephritis to palpable purpura. These syndromes rarely cause medium- or large-vessel stenotic or aneurysmal lesions and therefore are not discussed as part of this scientific statement. Systemic lupus erythematosus, rheumatoid arthritis, and sarcoidosis can have a vasculitic component but are also not discussed because small-vessel involvement predominates.

Epidemiology and sex predilection vary by vasculitis type. Giant cell arteritis is the most common vasculitis in the United States, with an age- and sex-adjusted prevalence rate of 204 per 100 000 individuals ≥50 years of age.[227] Giant cell arteritis and Takayasu arteritis have a strong female predominance, whereas medium- and variable-vessel vasculitides and immunoglobulin G4–related aortitis either have a slight male predilection or affect men and women equally.[227,228] Clinical features of each vasculitis often vary by sex (Table 5). For example, the aortic arch branch vessels are more commonly affected in women with Takayasu arteritis, whereas abdominal aortic and renal artery involvement is more common in men.[202] The mechanism for sex-specific clinical phenotypes is unknown. One notable exception is VEXAS syndrome (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic), a recently discovered, X-linked, male-predominant condition that has been linked to hematologic and systemic inflammatory conditions, including giant cell arteritis and polyarteritis nodosa. This syndrome is caused by acquired missense mutations in the *UBA1* gene that encodes the E1 enzyme, which is the main mediator of cellular ubiquitylation.[223]

High-quality investigations into the diagnosis, treatment, and prognosis of these vasculitides are needed, with special attention to the effect of sex (Table 5). There is often a delay of weeks to months between symptom onset and vasculitis diagnosis, which has been associated with later treatment initiation and worse clinical outcomes.[229] These delays are multifactorial and related to nonspecific symptoms at disease onset, lack of specific serological markers, and need for multispecialty consultation to synthesize clinical, imaging, and histopathological features to reach a diagnosis. Data evaluating the role of sex and access to care on diagnostic delay are limited and inconclusive.[230] Similarly, sex-based treatment disparities are unknown. Long-term follow-up data from a national registry in Korea found a 2-fold increased mortality in women with Takayasu arteritis compared with men, but these data did not account for the different prevalence of the disease between sexes. Mortality in Behçet disease, however, is significantly higher among men despite similar sex prevalence, an observation reflective of the greater severity of disease in this population.[213] It is incompletely understood whether there is a sex-based difference in timing of diagnosis and treatment initiation and how this affects long-term prognosis.

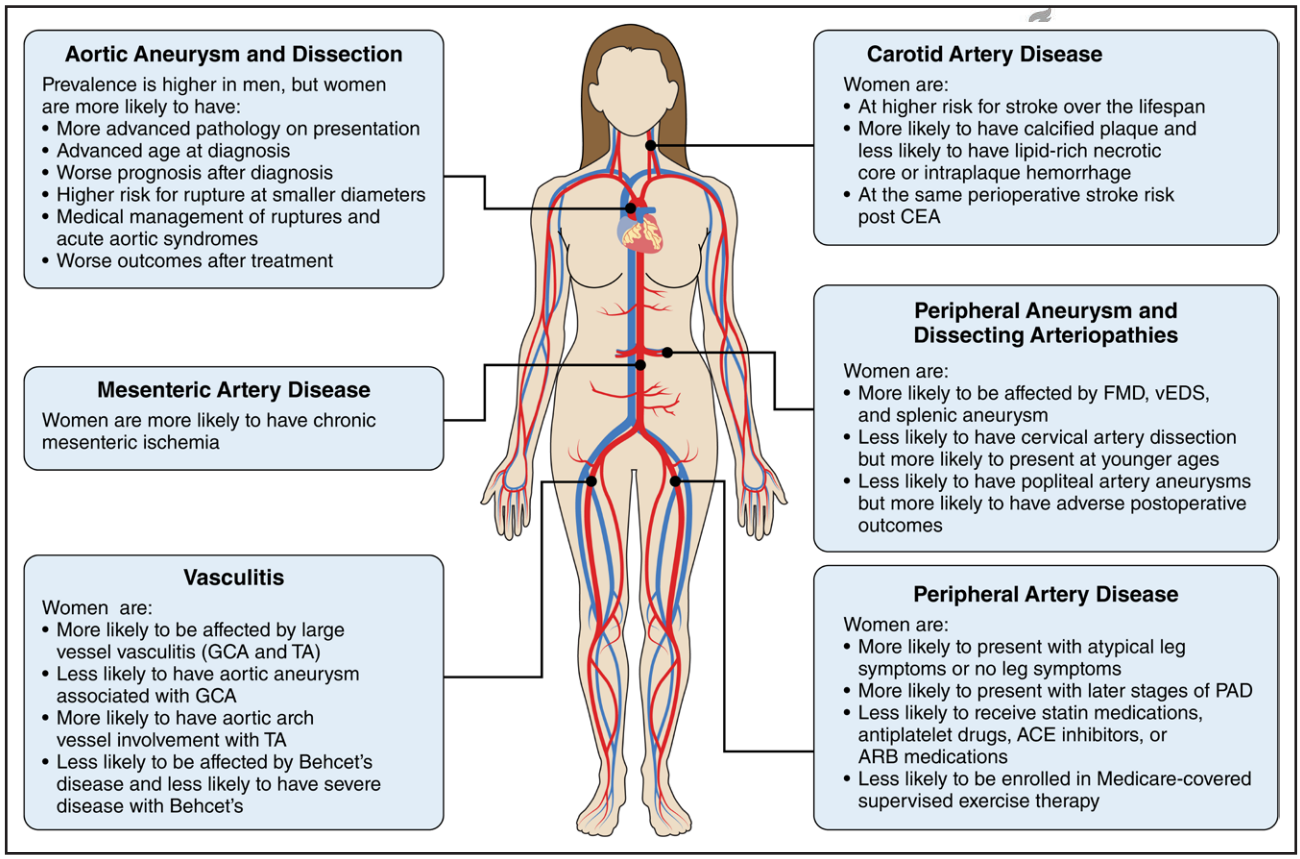

Figure. Sex differences in PVD.
There are significant sex-based differences and disparities in epidemiology, risk factors, diagnosis, treatment, and outcomes of peripheral vascular disease (PVD). ACE indicates angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; CEA, carotid endarterectomy; FMD, fibromuscular dysplasia; GCA, giant cell arteritis; PAD, peripheral artery disease; TA, Takayasu arteritis; and vEDS, vascular Ehlers Danlos syndrome.

Table 6. Summary Table: Peripheral Vascular Disease in Women: Current State, Gaps, and Proposed Research Priorities to Achieve Health Equity

	Current state	Gaps	Research priorities to achieve health equity
Aortic disease (TAA, AAA, and acute aortic syndromes, including aortic dissection, penetrating aortic ulcer, intramural hematoma)	Incidence of aortopathy higher in men compared with women Women present with more advanced age and pathology. No dedicated literature on racial and ethnic differences in outcomes by sex	Sex-specific risk factors aortopathy occurrence and growth not well established Consensus screening guidelines for women	Further understand sex-specific natural history of disease Sex-specific screening and surveillance protocols Further research on intersectionality of race and ethnicity and sex for aortic disease
	Lack of consistent size thresholds for repair in women vs men Women tend to have a higher growth rate of aneurysm size/diameter Women have higher risk for rupture at smaller aortic diameters	Consensus on sex-specific size threshold for treatment	Further research for repair thresholds for women with aortopathy
	Women have worse prognosis compared with men after diagnosis with aortopathy (higher mortality, more complications, less likely to be offered repair)	Adequate representation in device RCTs Equity in outcomes after diagnosis and intervention	Development of endovascular stent grafts with smaller diameter delivery systems to accommodate smaller access vessels Improved representation in RCTs for aortic disease trials Research to decrease bias in treatment selection for women and improve patient-centered care
PAD	PAD is twice as common in Black women compared with White women. PAD is approximately twice as common in American Indian women compared with White women	Few data exist on the prevalence of PAD in women who are American Indian. Reasons for the difference in PAD prevalence among Black women, American Indian women, and White women in the United States are not defined. More data are needed to better define the prevalence of PAD in women from ethnic groups that are traditionally underrepresented in research in the United States.	Develop interventions to eliminate the higher prevalence of PAD in women who are Black or American Indian Collect data to establish the prevalence of PAD among women from multiple racial and ethnic groups in the United States
	Women with PAD are more likely than men to be asymptomatic or to present with atypical leg symptoms	Reasons for sex differences in the prevalence of asymptomatic PAD and PAD associated with atypical leg symptoms are unknown	Delineate the cause of sex differences in PAD symptoms Develop interventions to reduce rates of undiagnosed PAD in women
	In some studies, women were less likely to be taking a statin medication to prevent cardiovascular events	Reasons for lower rates of statin use in women with PAD compared with men with PAD are unknown	Develop interventions to improve rates of statin use by women with PAD
	In randomized clinical trials, women attain similar benefit from supervised exercise therapy as men. During the first 18 mo of CMS coverage of supervised exercise, women were significantly less likely than men to have started a supervised exercise program. Among women who received a referral for exercise therapy, women were more likely than men to participate.	Data are needed to understand why women with PAD were less likely to participate in supervised exercise programs than men with PAD.	Identify methods to help all women with PAD gain access to exercise therapy Identify methods to maximize exercise adherence, either at home or in a supervised setting, among women with PAD
	Women have smaller arteries than men. Women typically present for revascularization with later stages of PAD than men. After lower-extremity revascularization for claudication, outcomes may be similar between men and women, but data are mixed. After lower-extremity revascularization for CLTI, women may have lower rates of revascularization and lower rates of mortality, but data are inconsistent.	Little is known about whether optimal methods and endovascular devices for lower-extremity revascularization differ between men and women.	Identify the most optimal types of revascularization procedures for women according to disease location and severity

(*Continued*)

Table 6. Continued

	Current state	Gaps	Research priorities to achieve health equity
Atherosclerotic extracranial carotid artery disease	Black women and Hispanic women ≥70 y of age had a 76%–77% higher risk of stroke than White women	Reasons for racial and ethnic disparities in outcomes in stroke among women are ill described	Further research to limit racial and ethnic disparities among women with carotid disease
	Women with carotid disease are prescribed GDMT less frequently than men with carotid disease	Understanding reasons for low prescription and use of GDMT	Explore the systems-based changes to improve GDMT use for primary and secondary prevention of stroke due to carotid artery disease among diverse populations
	Low representation of women in RCTs despite population-based screening efforts and equal prevalence of carotid disease as men	Understanding reasons for lower representation of women in carotid treatment RCTs	Innovative patient, community, and systems-based strategies to increase enrollment of women in RCTs
	Overall, carotid plaque composition for women has less LRNC and IPH compared with men	Reasons for differences in plaque composition are unknown.	Basic and translational studies to understand the underlying causes for sex differences in plaque composition
Atherosclerotic renal artery disease	Sex-based differences were not routinely reported in natural history studies and RCTs of ARAS	Sex-based differences are unknown given the lack of clear clinical benefit for revascularization (stenting) for ARAS in both sexes	Sex-based studies are needed to determine clear benefit for renal artery stenting and appropriate clinical circumstances
Atherosclerotic mesenteric artery disease	Higher prevalence of CMI in women compared with men	Understand contributors to higher risk for CMI in women compared with men Improve GDMT for secondary prevention of vascular events for women with PAD and mesenteric atherosclerosis	Enroll more women in research studies of CMI Understand the vascular biology underlying AMI and CMI in women to determine the sex-related plaque characteristics to guide medical treatment
Arteriopathies	Significant differences in male:female predominance for many arteriopathies	Sex-specific risk factors that explain striking male and female predominance in different arteriopathies are not well understood. Treatments to prevent/delay complications and data on how these may differ by sex are limited.	Expanding and diversifying registries Translation of treatments evaluated in preclinical murine models to clinical testing Development of novel methodologies and collaborative strategies to facilitate treatment studies in rare disease
Vasculitis	Limited high-quality evidence overall with even less investigation of sex-based differences and disparities	Many vasculitides are poorly understood and treated according to expert consensus and historical regimens	Prioritize patient enrollment in ongoing registries to better understand these disease entities

AAA indicates abdominal aortic aneurysm; AMI, acute mesenteric ischemia; ARAS, atherosclerotic renal artery stenosis; CLTI, chronic limb-threatening ischemia; CMI, chronic mesenteric ischemia; CMS, Centers for Medicare & Medicaid Services; GDMT, guideline-directed medical therapy; IPH, intraplaque hemorrhage; LRNC, lipid-rich necrotic core; PAD, peripheral artery disease; RCT, randomized clinical trial; and TAA, thoracic aortic aorta.

Few clinical trials have assessed treatment strategies, but the participants enrolled in these trials reflect the sex predilection of the disease.[199,205] For vasculitides that have other systemic manifestations such as Behçet disease, patients with aggressive vascular involvement have been excluded from landmark trials.[231] Vascular manifestations are a leading cause of death in patients with vasculitis, which highlights the importance of including this high-risk population in future scientific endeavors.[216] However, it is important to remember that the rarity of these vasculitides and the broad spectrum of disease without strict diagnostic criteria make clinical trials and dedicated investigations into sex-related disparities challenging. Most data to date have emerged from small local or regional cohorts. Collaborations such as the Vasculitis Foundation's Vasculitis Patient-Powered Research Network, UK and Ireland Vasculitis Rare Disease Group Vasculitis Registry, and Joint Vasculitis Registry in German-speaking countries bring clinicians, researchers, and patients together around the common goal of advancing care and engaging patients in research endeavors. The Vasculitis Foundation offers resources for patients to learn about opportunities to engage in >25 potential clinical trials and multiple different registries, including the Vasculitis Patient-Powered Research Network, which is a partnership between the Vasculitis Foundation and the Vasculitis Clinical Research Consortium. Patients can enroll in the Vasculitis Pregnancy Registry, which seeks to improve the understanding of pregnancy characteristics and outcomes among women with vasculitis. These initiatives offer promise to better understand sex differences in short- and long-term outcomes in patients with vasculitis outside of the limitations of traditional study design.[205,232] As the care of patients with vasculitis advances, it is important for frontline clinicians to provide patients with resources of different modalities to learn about their disease. Although both men and women most often turn to health care professionals for medication information, women are more likely to use online resources, support groups, and package inserts, whereas men are more likely to use their partner as a secondary source of information.[233] Understanding how

each patient receives information and providing them with those appropriate resources can help strengthen the therapeutic alliance, enhance health literacy, and improve clinical outcomes.

CONCLUSIONS

There are significant sex-based differences and disparities in epidemiology, risk factors, diagnosis, treatment, and outcomes of PVD (Figure). Particularly noteworthy are the delayed presentation and higher mortality of women from acute aortic syndromes, worse outcomes after aortic repair, and higher likelihood of being offered medical treatment for type A aortic dissection. Women are strikingly disproportionately represented in arteriopathies such as FMD and CMI. Among Medicare beneficiaries with PAD, women were less likely to participate in supervised exercise therapy compared with men.[142] Women are underrepresented in RCTs of PVD. These numerous disparities provide opportunities to pursue health equity for women with PVD, and it is imperative that future research, including basic and translational research, incorporates sex-based variables in their design and reporting (Table 6). Within the inequities for women exist other racial and sociodemographic disparities that further exacerbate sex-based differences. We applaud policies for inclusion such as those mandated by the Executive Order in Advancing Women's Health Research and Innovation and the National Institutes of Health, which obligate inclusion of sex-, race-, and ethnicity-based enrollment and reporting as appropriate to the research question under study.[234–236] The impact of such inclusion policies on mitigating sex-based disparities in PVD is unknown but should be assessed in future research.

Sex is a biologic variable determined by chromosomal composition, and gender is a "multidimensional social construct related to norms and societal expectations that exist within a historical and cultural context."[237] Both sex and gender affect human health and disease, and it is recommended that both sex and gender be included in CVD research and reporting.[238] These terms are often used interchangeably in the literature, and it was not possible to strictly divide the 2 terms in this document to adequately describe their influence on PVD. Certainly, the study of PVD going forward will benefit from the distinction between sex and gender and the inclusion of both constructs in research design and reporting.

ARTICLE INFORMATION

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

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Disclosures

Writing Group Disclosures

Writing group member	Employment	Research grant	Other research support	Speakers' bureau/ honoraria	Expert witness	Ownership interest	Consultant/ advisory board	Other
Esther S.H. Kim	Atrium Health, Sanger Heart and Vascular Institute	None	None	None	None	None	None	None
Shipra Arya	Stanford University School of Medicine	VA HSR&D (VA merit I01HX003215)†	None	None	None	None	Gore Medical*	None
Yolanda Bryce	Memorial Sloan Kettering Cancer Center	None	None	Boston Scientific†; ShockWave Medical, Inc†	None	None	None	None
Heather L. Gornik	University Hospitals, Harrington Heart & Vascular Institute	None	None	None	None	None	None	None
Chandler A. Long	Duke University Medical Center	None	None	None	None	None	None	None

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Writing Group Disclosures Continued

Writing group member	Employment	Research grant	Other research support	Speakers' bureau/ honoraria	Expert witness	Ownership interest	Consultant/ advisory board	Other
Mary M. McDermott	Northwestern University, Feinberg School of Medicine	NHLBI†; National Institute on Aging†	ACI Medical†; Mars†	None	None	None	None	None
Amy West Pollak	Mayo Clinic	None	None	None	None	None	J&J Innovative Medicine (unpaid)*	None
Vincent Lopez Rowe	Geffen School of Medicine at UCLA	None	None	None	None	None	None	None
Alexander E. Sullivan	Vanderbilt University Medical Center	None	None	None	None	None	None	None
Mary O. Whipple	University of Minnesota School of Nursing	None	None	None	None	None	None	None

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*Modest.

†Significant.

Reviewer Disclosures

Reviewer	Employment	Research grant	Other research support	Speakers' bureau/honoraria	Expert witness	Ownership interest	Consultant/ advisory board	Other
Daniel Joseph Bertges	University of Vermont Medical Center	None	None	None	None	None	None	None
Julie Brittenden	University of Aberdeen (United Kingdom)	None	None	None	None	None	None	None
Leslie Cho	Cleveland Clinic	None	None	None	None	None	None	None
Timothy William Ingraham Clark	Penn Presbyterian Medical Center	None	None	None	None	None	None	None

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