In 2012, the American Heart Association published a Call to Action encouraging scientific investigation of the prevalence and significance of lower extremity peripheral artery disease (PAD) in women.1 Noting a paucity of high-quality research on PAD in women, the statement called for more population-based evidence on the sex and age-specific prevalence and incidence of PAD.

In this issue of Circulation: Cardiovascular Quality and Outcomes, Wang et al2 address this knowledge gap by studying sex differences in the incidence of PAD in chronic kidney disease. Wang et al2 report a higher incidence of PAD in women than in men participating in the Chronic Renal Insufficiency Cohort (CRIC), an observational longitudinal study of people aged 21 to 74 years with mild to moderate chronic kidney disease. Wang et al2 followed up 3174 CRIC participants (1427 [45%] women; mean age, 56.6 years) who had an ankle brachial index (ABI) ≥0.90 and no clinically evident PAD at baseline. New PAD during follow-up was defined as the occurrence of one of the following: ABI <0.90, lower extremity revascularization, or amputation. At a median follow-up of 5.9 years, the incidence of newly diagnosed PAD was 323 of 1427 (22.6%) in women versus 242 of 1747 (13.8%) in men (P <0.001). This sex difference in PAD incidence was because of a higher incidence of ABI <0.90 among women than among men (310/1427 [21.7%] versus 220/1747 [12.6%]; P <0.001). In contrast, there was no difference in the incidence of lower extremity revascularization or amputation between men and women (13/1427 [0.9%] versus 22/1747 [1.3%]; P =0.33).

Contrary to these findings, previous epidemiologic studies of people without chronic kidney disease showed no sex differences in the incidence of PAD.3–5 For example, in the Multi-Ethnic Study of Atherosclerosis (MESA), a prospective observational cohort study of men and women aged 45 to 84, there were no sex differences in PAD incidence.6 Among 5514 MESA participants free of PAD at baseline, 50 of 3601 (1.4%) women versus 39 of 1913 (2.0%) men developed new PAD at 3.2-year follow-up (P =0.56). New onset PAD in this study was defined as developing an ABI ≤0.90. Separately, in the Cardiovascular Health Study (CHS) cohort of 2289 men and women aged ≥65 years, 129 of 1398 (9.2%) women versus 81 of 891 (9.0%) men developed PAD during 6-year follow-up, a difference that was not statistically significant.4 New PAD in this study was defined as a new ABI ≤0.90 combined with an ABI drop of ≥0.15. Although CRIC reported a higher incidence of PAD only in younger participants (ie, aged ≤70 years), there was also no sex difference in the incidence of PAD among diabetic participants in the Atherosclerosis Risk in Communities (ARIC) cohort, in which the average participant was aged 56 years.5 The incidence of PAD in ARIC at 10-year follow-up was ≈14%, respectively, among 759 men and 892 women (P =0.90). New onset PAD was defined as either a new ABI <0.90, new symptoms of intermittent claudication, leg amputation, or revascularization. In summary, previous epidemiologic studies of people showed no sex differences in the incidence of PAD.

Why might results from CRIC differ from previous epidemiologic evidence on the incidence of PAD in women versus men? Interpreting results of the CRIC study requires consideration of the fact that differences in PAD incidence were observed only for the outcome of a new ABI <0.90 and not for the outcomes of lower extremity revascularization or amputation. It is conceivable that previously documented intrinsic differences in the ABI measurement between men and women6–10 may affect the ABI criterion most appropriate for defining PAD in men and women, respectively. In addition, the high prevalence of medial arterial calcinosis in lower extremity arteries of people with chronic kidney disease may make the ABI a less precise measure when evaluating sex differences in progression of lower extremity atherosclerotic disease in this population.10

Epidemiologic studies consistently document lower ABI values in women than in men in cross-sectional analyses.6–10 In the MESA cohort, mean age-adjusted ABI values overall were 1.089 and 1.14 among women and men, respectively: a highly statistically significant difference (P <0.001). Although the prevalence of ABI <0.90 was 3.7% among both men and women at baseline, women had higher prevalences of low normal ABI values (0.90–0.99; 10.3% versus 4.0%; P <0.001) and borderline ABI values (1.00–1.09; 35.5% versus 21.2%; P <0.001).6 Consistent with this phenomenon, in the ARIC study, the prevalence of PAD was higher in women than men at baseline when an ABI <0.95 was used to define PAD (8.3% versus 4.8% for black participants and 7.0% versus 4.0% for white participants).11 However, when an ABI <0.85 was used...
to define PAD, there was no sex difference in PAD prevalence (2.6% in women versus 2.9% in men and 1.3% versus 1.4% in white participants).11

On the contrary, previously epidemiologic studies document a higher prevalence of elevated ABI values in men than in women.6,12,13 Elevated ABI values may occur because of medial arterial calcinosis, which is particularly common in people with chronic kidney disease. In medial arterial calcinosis, calcium deposits in the tunica media of the arterial wall, causing a rigid, poorly compressible lower extremity pressure, increasing the ABI value, and yielding an ABI measurement that may poorly correlate with the extent of lower extremity atherosclerosis. Available evidence suggests that medial arterial calcinosis is more common in men.6,12,13 Among 5748 participants in the Cardiovascular Health Study, 167 of 2459 (6.7%) men versus 55 of 3289 (1.7%) women had an ABI >1.30 at baseline, consistent with a higher prevalence of medial arterial calcinosis in men.11 In MESA, 177 of 3112 (5.7%) men versus 60 of 3458 (1.7%) women had an ABI ≥1.30 at baseline.6 This higher prevalence of elevated ABI values in men could be accentuated in populations with chronic kidney disease because of its association with medial arterial calcinosis in the lower extremities.

Consistent with previous epidemiologic evidence, women in the CRIC study had lower baseline ABI values than men. It is conceivable that some women with baseline ABI values between 0.90 and 0.99 dropped below an ABI threshold of 0.90 during follow-up and still stayed within the typical accepted measurement error for the ABI of 0.15.14 It is important to note that the CRIC results were not substantively changed after adjusting for baseline ABI. Yet residual confounding may influence these findings. In addition, if men have a greater tendency to experience medial arterial calcinosis, men may avoid an ABI decline or may experience an increase in ABI even as lower extremity atherosclerosis progresses.

Sex differences in the ABI may be because of the fact that men on average are taller than women. Greater height leads to a higher ankle systolic pressure because arterial pressures increase with greater distance from the heart, thereby increasing the numerator in the ABI calculation. However, sex differences in height do not fully explain sex differences in the ABI value.2–11 Aboyans et al5 studied whether anatomic and physiologic differences between men and women may result in intrinsically lower ABI values in women than in men, even among those without lower extremity atherosclerosis. In a cross-sectional analysis of 1775 healthy participants in the MESA cohort who did not have clinically evident cardiovascular disease or any major PAD risk factor, the average ABI was 0.02 U lower in women than in men, even after adjusting for height and other potential confounders. The authors of this report concluded that sex differences in ABI values among individuals without cardiovascular disease, although small in magnitude, were highly statistically significant and had the potential to distort population estimates of disease burden.6

Additional factors should be considered when interpreting the CRIC results. First, the ABI has limitations as a measure of progression of lower extremity atherosclerosis. A study of 193 limbs in 114 patients with previous lower extremity revascularization reported that an ABI decline of ≥0.15 was only 41% sensitive and 84% specific for detecting progression of lower extremity atherosclerosis than the gold standard of arteriography or duplex scanning.15 The ABI may be even less sensitive to progression of lower extremity atherosclerosis in people with chronic kidney disease because of the higher prevalence of medial arterial calcinosis. Second, measurement error of the ABI is ≈0.15.14 Some studies have required a decline in ABI of ≥0.15 in combination with an ABI ≤0.90 to signify a meaningful ABI decline.3,12–14 Whether ABI declines <0.15 are clinically meaningful is unclear, particularly if the baseline ABI is already between 0.90 and 0.99.

More evidence on PAD in women is needed. Wang et al9 make an important scientific contribution, by demonstrating that among people with chronic kidney disease, women are more likely to experience a new ABI <0.90 during follow-up than men. Further study is needed to delineate the clinical significance of this finding. Additional study is also needed to delineate optimal methods of measuring progression of lower extremity atherosclerosis in men and women with and without chronic kidney disease.

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References


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