Sex Differences in the Incidence of Peripheral Artery Disease in the Chronic Renal Insufficiency Cohort

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Background—To define how the incidence of peripheral artery disease (PAD) in chronic kidney disease differs according to sex and age.

Methods and Results—The Chronic Renal Insufficiency Cohort (CRIC) is a multicenter, prospective cohort study of chronic kidney disease participants. Fine and Gray methods were used to determine the cumulative incidence of PAD, defined by an ankle brachial index <0.90 or a confirmed PAD event, with death as a competing event. Adjusted subdistribution hazard ratios from the Fine and Gray model determined the risk of PAD according to sex. A priori, we hypothesized that the relationship between sex and cumulative incidence of PAD differed according to age. The mean age of the 3174 participants in this study was 56.6 years and consisted of 55% males. During a median follow-up of 5.9 years, 17.8% developed PAD, 13.0% were lost to follow-up and 11.1% died. Females had a 1.53-fold greater adjusted PAD risk compared with males (95% confidence interval, 1.27–1.84; \(P<0.001\)). These sex-related differences in PAD risk also differed by age ( \(P=0.013\)). Women, compared with men were at a markedly increased risk for PAD at younger ages; however, at ages >70 years, the risk was similar across both the sexes. Older men had a substantially greater PAD risk compared with younger men. In women, PAD risk did not vary with age.

Conclusions—Females with chronic kidney disease have a higher PAD risk compared with males at younger ages. There is an important need to improve our understanding of the biological and clinical basis for these differences.

Key Words: ankle brachial index ■ epidemiology ■ mortality ■ peripheral artery disease ■ sex

The American Heart Association estimates that peripheral artery disease (PAD) affects 8 million people >40 years of age in the United States, and 12% to 20% of Americans aged >65 years.1,2 PAD is a major source of morbidity and mortality resulting in functional impairment, limb loss, as well as death.3 Despite epidemiological studies that have contributed to our understanding of PAD prevalence and its association with traditional atherosclerotic risk factors, there have been conflicting studies published on the incidence of PAD and differences in treatment outcomes in women versus men.1-7 Much of the uncertainty surrounding this topic stems from the fact that because PAD surveillance is not conducted in any state or nation, the prevalence of PAD by sex remains incompletely evaluated.8 In addition, the majority of clinical trials published in PAD have enrolled primarily men9-11 and did not evaluate for effect modification by sex, thus widening this knowledge gap.

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There is a growing concern, however, that PAD outcomes are worse in women. In a recent study of the Nationwide Inpatient Sample between 1998 and 2009 of patients undergoing a revascularization procedure, women were likely to have advanced disease at presentation and have a higher in-hospital mortality.7 In addition, studies have reported that women with PAD have a greater functional impairment,12 a worse quality of life,13 and more depressive symptoms compared with men.14 US census data from 2010 also suggest that more women than men >40 years of age have PAD.8

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Peripheral artery disease (PAD) is a national and worldwide health burden and is a major source of morbidity and mortality. Sex differences in PAD incidence are not well understood due in part to underrepresentation of females in previous clinical trials. Previous studies suggest that PAD outcomes may be worse in women compared with men. PAD is common in patients with chronic kidney disease.

WHAT THE STUDY ADDS

• This study used the Chronic Renal Insufficiency Cohort, which is well-balanced with regard to sex, includes participants of various ages, and has detailed vascular function data obtained at standardized intervals to study sex differences in PAD incidence.
• Females had a significantly higher incidence of PAD as defined by an ABI <0.90 or revascularization or amputation procedure, compared with men.
• The sex effect on PAD incidence was modified by age. There was a markedly increased risk of PAD in women compared with men at younger ages. By the age of 70 years, however, the incidence was similar between males and females.
• There is an important need to improve our understanding of the biological and clinical basis for these differences.

And yet, how risk factors for PAD may affect this possible sex-based difference is unknown. For example, age is an established PAD risk factor, but the incidence of PAD according to sex across a broad spectrum of ages remains incompletely defined. Patients who are at particularly high risk for PAD also include those with chronic kidney disease (CKD). Data from the National Health and Nutrition Examination Survey demonstrated that 24% of persons with CKD stage ≥3 had PAD as defined by an ankle brachial index (ABI) <0.9, which was significantly >4% prevalence in the group with normal renal function. Indeed, the National Kidney Foundation Task Force issued a statement suggesting that patients with CKD be considered in the highest risk category for subsequent cardiovascular events, such as myocardial infarction, stable and unstable angina, and cardiac death.

The Chronic Renal Insufficiency Cohort (CRIC) is well-balanced with regard to sex, has participants throughout a wide age range, and has detailed vascular function data obtained at standardized intervals. As such, it is an ideal population to study sex-based differences in PAD incidence. The objective of this study is to leverage the strengths of a uniquely phenotyped cohort of individuals with CKD to determine the differences in PAD incidence between men and women and to define how this relationship differs by age.

Methods

Study Design

The CRIC study design and methods have been described in detail previously. Briefly, CRIC is a prospective cohort study of 3939 participants enrolled from June 2003 to August 2008 through 7 clinical centers in the United States (Ann Arbor and Detroit, MI; Baltimore, MD; Chicago, IL; Cleveland, OH; New Orleans, LA; Philadelphia, PA; and Oakland, CA) who were followed for ≤8.7 years. Participants included men and women 21 to 74 years of age at study entry with mild to moderate CKD as defined by glomerular filtration rate (GFR). Age-based GFR was used as an inclusion criterion for the study and included the following: for age 21 to 44, GFR 20 to 70 mL/min per 1.73 m²; age 45 to 64, GFR 20 to 60 mL/min per 1.73 m²; and age 65 to 74, GFR 20 to 50 mL/min per 1.73 m². Exclusion criteria included New York Heart Association class 3 and 4 heart failure, cancer, and immunosuppressive therapies during the previous 6 months. The initial protocol called for each of the 7 clinical centers to enroll 450 participants during a 33-month period (May 2003 through March 2006). In August 2005 after Hurricane Katrina, enrollment at Tulane was halted after enrollment of 405 patients and recruitment targets at the other 6 clinical centers were increased. Recruitment strategies varied from center to center and consisted of computerized searches of laboratory databases as well as medical record searches and referrals from healthcare providers. Participants underwent detailed baseline examinations and annual in-person follow-up examinations. The study was approved by the Institutional Review Board of each participating clinical center. Written informed consent was obtained from all participants.

For the purposes of this study, participants were excluded from this analysis if they had an ABI <0.90 at their baseline visit or had a previous history of an amputation or revascularization procedure for PAD. Therefore, we focused on a subset of participants (n=3174) in this analysis.

Ascertainment of PAD

The ABI is the standard test used to diagnose PAD. After lying supine for 5 minutes, systolic blood pressure was measured in both arms using appropriately sized cuffs. The systolic blood pressure for the dorsalis pedis artery and posterior tibial artery was measured for each leg using a Doppler probe. The leg-specific ABI was determined by dividing the higher systolic blood pressure for the dorsalis pedis artery or posterior tibial artery by the higher systolic blood pressure of the brachial artery. In participants with functioning fistulae or arteriovenous grafts, the available contralateral brachial artery blood pressure was used. The patient-specific ABI was defined as the lower leg-specific ABI. In CRIC, the ABI is measured at the baseline visit and annually. Clinical PAD events defined as revascularization (angioplasty or surgical bypass) or major amputation (below the knee or above the knee) were captured by hospital chart review at the annual clinic visit or 6-month telephone visit when specific International Classification of Diseases-Ninth Revision codes suggested that an amputation or revascularization procedure was performed. These events were then adjudicated by a specially trained research nurse. Aortic aneurysm treatment was not considered an event in this study. Incident PAD was thus defined by the first-occurring event among the following: (1) ABI <0.90, (2) revascularization procedure, or (3) major amputation. Subjects were censored at the time of withdrawal or at completion of the study.

Death was treated as a competing event. Deaths were captured from medical records, death certificates, next of kin, and linkage to the Social Security Death Master File. Dates of death were determined from the death certificate or medical records whenever possible. Participants were contacted at least every 6 months and next of kin were questioned about the ascertainment of death.

Statistical Analysis

Summary statistics stratified by sex were calculated for basic demographic and clinical characteristics. The χ² test was used to compare categorical variables, and t-tests were used for continuous variables. Poisson regression was first used to describe annualized incidence rates (number of cases per 100 person-years) for PAD as defined by an ABI <0.90, annualized incidence rates for death, as well as annualized incidence rates for the composite end point of PAD and death.
in men and women. Survival analysis end points included PAD-free survival and overall survival. Both the outcomes were analyzed by sex using the Kaplan–Meier method, and statistical comparison was performed via the log-rank test.

Because of the high prevalence of mortality in this cohort of participants, competing risks regression analyses were implemented. We used Fine and Gray methods to determine cumulative incidence of PAD over time and explore the relationship between sex and PAD, accounting for death as a competing event.\(^{22}\) Gray’s test was used to compare the cumulative incidence curves of PAD between men and women in the presence of death as the competing risk.\(^{21,22}\) Univariable analysis using the Fine and Gray proportional hazard model for the subdistribution of competing risks was performed and from these models, the subdistribution hazard ratio (SHR) was derived. All variables from the univariate model which had a \(P\) value of <0.05 were considered for inclusion into the multivariable model, which was built using forward stepwise selection. Because of the increased risk of incident PAD and death with age, the effect of age on the relationship between sex and PAD cumulative incidence was also explored. On the basis of the pooled prevalence data derived from a meta-analysis of 7 US population studies,\(^{23}\) we hypothesized a priori that age would affect the cumulative incidence of PAD in women differently than in men. All analyses were performed using STATA version 12 (College Station, TX).

**Results**

**Study Population**

The overall mean age of the cohort of 3174 participants at time of study entry was 56.6 years and consisted of 55.0% males and 44.0% with diabetes mellitus. There were 12 individuals who were excluded after their baseline visit, and they were omitted from time to event analysis. A total of 61 participants either had no follow-up or had missing covariates, leaving 3113 for complete case analysis. The mean ABI in males was 1.13±0.15 and that in females was 1.08±0.13. The mean GFR was 46.7 mL/min per 1.73 m\(^2\) and the mean body mass index was 31.9 kg/m\(^2\). Males had more hypertension (86.1% versus 82.2%, \(P=0.003\)), coronary artery disease (20.6% versus 13.0%, \(P<0.001\)), history of tobacco use (58.1% versus 41.9%, \(P<0.001\)) as well as hypercholesterolemia (85.2% versus 73.5%, \(P<0.001\)) compared with females. However, the prevalence of diabetes mellitus, congestive heart failure, and chronic obstructive pulmonary disease was no different between men and women. All demographic data and clinical characteristics are summarized in Table 1.

With a median follow-up of 5.9 years (range, 12.0 days–8.7 years), 17.8% of the cohort developed PAD, 11.1% died, 13.0% were censored at the time of withdrawal, and 58.1% censored at the end of the study. Overall, females had a higher PAD incidence (PAD combined) compared with males (22.6% versus 13.8%, \(P<0.001\); Table 2). This translated to an incidence of 13.10 per 100 person-years for women and 19.93 per 100 person-years for men. For the combined end point of PAD or death, women had an overall higher rate when compared with men (31.2% versus 27.0%, \(P=0.025\)).

**PAD and Survival in Females and Males**

Kaplan–Meier curves for PAD-free survival showed a steady decline during the period of observation for both the sexes as shown in Figure 1A. Initially, the curves approximated each other initially, but they separated by 2 years (88.0% for females versus 90.1% males, \(P=0.057\)). Overall, men had greater PAD-free survival compared with women (log-rank test \(P=0.0034\)). Kaplan–Meier curves for overall survival separated at \(\pm 4\) years (93.8% for females versus 91.9% males, \(P=0.056\)). Females experienced greater overall survival compared with males (log-rank test, \(P=0.0010\); Figure 1B).

**PAD Risk in Females and Males**

Females had a statistically significantly higher risk of PAD in the unadjusted Fine and Gray model, with subdistribution hazard ratio (SHR, 1.73; 95% confidence interval [CI], 1.47–2.05; \(P<0.001\)). This risk was relatively unchanged and remained significant after adjusting for age, baseline ABI, diabetes mellitus, coronary artery disease, smoking, hypertension, body mass index, race, and estimated GFR (SHR, 1.53; 95% CI, 1.27–1.84; \(P<0.001\)). Figure 2 demonstrates the predicted risk

| Table 1. Summary Statistics of Demographics and Clinical Characteristics by Sex (n=3174) |
|-----------------------------|-----------------------------|-----------------------------|
| Variable                    | Males, n=1747               | Females, n=1427              | \(P\) Value |
| Age, mean±SD                | 56.8±11.1                   | 56.5±11.4                   | 0.474       |
| ABI, mean±SD                | 1.13±0.15                   | 1.08±0.13                   | <0.001      |
| Race                        |                             |                             |             |
| White                       | 50.9%                       | 43.9%                       | <0.001      |
| Black                       | 35.7%                       | 45.1%                       |             |
| Other                       | 13.4%                       | 11.1%                       |             |
| Diabetes mellitus           | 44.5%                       | 43.4%                       | 0.535       |
| eGFR                        | 47.3±16.6                   | 46.0±17.8                   | 0.040       |
| BMI                         | 31.1±6.3                    | 32.9±9.1                    | <0.001      |
| CHF                         | 8.9%                        | 7.2%                        | 0.076       |
| Hypertension                | 86.1%                       | 82.2%                       | 0.003       |
| CAD                         | 20.6%                       | 13.0%                       | <0.001      |
| Smoking                     |                             |                             |             |
| Never                       | 41.9%                       | 58.1%                       | <0.001      |
| Former                      | 45.7%                       | 31.0%                       |             |
| Current                     | 12.4%                       | 10.9%                       |             |
| Hypercholesterolemia        | 85.2%                       | 73.5%                       | <0.001      |
| COPD                        | 2.2%                        | 3.0%                        | 0.147       |
| ACE inhibitor               | 53.7%                       | 40.6%                       | <0.001      |
| ARB                         | 26.1%                       | 24.4%                       | 0.277       |
| \(\beta\)-blocker           | 47.7%                       | 44.4%                       | 0.066       |
| Statin                      | 53.1%                       | 49.2%                       | 0.027       |
| Aspirin                     | 41.6%                       | 36.6%                       | 0.004       |

\(P\) value represents the comparison of continuous and categorical variables by sex. ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blockers; BMI, body mass index; CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; and eGFR, estimated glomerular filtration rate.
of PAD in females, assuming a mean age of 57 years, estimated GFR of 46.7 mL/min per m², baseline ABI of 1.10, and body mass index of 31.9 kg/m².

However, the increased risk of PAD in females compared with males was modified by age (P < 0.001). Specifically, women had a 2.57-fold increased risk compared with men in those <40 years of age (SHR, 2.57; 95% CI, 1.27–5.20, P = 0.009; Table 3). The magnitude of this increased risk gradually decreased with age, such that the risk was similar in women and men during past the 7th decade (SHR 1.05; 95% CI, 0.66–1.67, P = 0.821).

However, among men alone, PAD risk clearly worsened with age, such that for a 10-year increase in age, the SHR was significantly greater in men (SHR, 1.06; 95% CI, 1.14–1.52; P < 0.001). In women alone, this relationship was not significant (SHR, 1.00; 95% CI, 0.94–1.19; P = 0.310). This effect of age on the subdistribution hazard ratio for PAD for males and females is reflected in Table 4; Figures 3A and 3B. In Figure 3A, the age-stratified cumulative incidence for males is clearly separated according to age. In contrast, in Figure 3B, the age-specific curves for females are largely overlapping. Similarly, the SHR for males increased with each age group, whereas the SHR for females did not change with increasing in age.

Discussion

In this study, we demonstrate that the cumulative incidence of PAD is higher in women compared with men in this cohort of participants with CKD, with an important interaction by age. Using the Fine and Gray model, the overall risk of PAD in this cohort was 1.53-fold greater in women compared with men. However, by the age of 70 years, these risks were similar between the 2 sexes. Furthermore, the risk of PAD increased with age in men but not in women. Women in this cohort developed PAD at an earlier age, and this risk remained relatively constant over time. Women did not experience an increase in the cumulative incidence of PAD later in life, as observed in men.

Although epidemiological studies have reported PAD prevalence in defined populations and its association with traditional atherosclerotic risk factors, incomplete and contradictory data have been published on the prevalence and differences in outcome of PAD in women versus men. Population-based prevalence is difficult to discern because PAD screening is not currently uniformly conducted at a national level. Furthermore, the few population-based studies that do exist do not report prevalence by sex.8 Guidelines from the American College of Cardiology/American Heart Association 2005 refer to male sex as a risk factor for PAD24 but this was later refuted as the rates of PAD in women have been suggested to be as high as those in men.8 More contemporary data from cohort studies25,26 suggest that women are older, present with more severe disease, and have inferior rates of limb salvage compared with men.8,27,28 Other studies suggest comparable outcomes between men and women.25

![Figure 1](https://example.com/fig1.png)

**Figure 1.** Kaplan–Meier curves for (A) peripheral artery disease–free survival (log-rank P value=0.0034) and (B) overall survival (log-rank P value=0.0010).
However, our results shed insight into an important interaction by age in these sex-related differences in the cumulative incidence of PAD, which may, in part, explain these conflicting findings. Women are at a particularly increased risk for PAD at younger ages; but at ages >70 years, the PAD risk becomes more similar between sexes. Moreover, older men compared with younger men have a substantially greater predilection for developing PAD. In women, this relationship is relatively constant over a broad spectrum of ages.

Because these data suggest that incident PAD is more common in females with CKD at younger ages, current screening methods may not be adequate for targeting women for primary prevention of cardiovascular outcomes. From the 2011 American College of Cardiology Foundation/American Heart Association Task Force Focused Update of the Guideline for the Management of Patients With Peripheral Artery Disease,29 the ABI should be used as a diagnostic study in individuals with ≥1 of the following: exertional leg symptoms, nonhealing wounds, age ≥65 years, or ≥50 years with a history of smoking or diabetes mellitus. Our data indicate that this age-related screening window is likely too late for women. Although it has previously been suggested that women are protected from cardiovascular events at younger ages because of the effect of estrogens and other sex hormones, data on hormone replacement therapy from the Women's Health Initiative30 and the Heart and Estrogen/progestin Replacement Study (HERS)31 did not support this notion. Indeed, the data from our study indicate that women are protected from cardiovascular events at younger ages because of the effect of estrogens and other sex hormones, data on hormone replacement therapy from the Women's Health Initiative30 and the Heart and Estrogen/progestin Replacement Study (HERS)31 did not support this notion. Moreover, older men compared with younger men have a substantially greater predilection for developing PAD. In women, this relationship is relatively constant over a broad spectrum of ages.

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Figure 2. Cumulative incidence of peripheral artery disease (PAD) by sex. Using Fine and Gray model at the mean age of the cohort (57 years) as well as the mean for other variables in the model, adjusted for diabetes mellitus, smoking, body mass index, glomerular filtration rate, coronary artery disease, race, hypertension, baseline ankle brachial index, and allows for effect modification of age by sex.

Table 3. Effect of Age on the SHR of Peripheral Arterial Disease Comparing Females With Males

<table>
<thead>
<tr>
<th>Age, Y (n)</th>
<th>SHR (95% CI) Females vs Males</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40 (302)</td>
<td>2.57 (1.27–5.20)</td>
<td>0.009</td>
</tr>
<tr>
<td>40–49 (439)</td>
<td>2.12 (1.22–3.68)</td>
<td>0.008</td>
</tr>
<tr>
<td>50–59 (972)</td>
<td>1.54 (1.12–2.11)</td>
<td>0.007</td>
</tr>
<tr>
<td>60–69 (1098)</td>
<td>1.49 (1.12–1.98)</td>
<td>0.006</td>
</tr>
<tr>
<td>&gt;70 (363)</td>
<td>1.05 (0.66–1.67)</td>
<td>0.821</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; and SHR, subdistribution hazard ratio. Estimated by the multivariable Fine and Gray competing risk regression adjusted for diabetes mellitus, smoking, body mass index, glomerular filtration rate, coronary artery disease, race, hypertension, and baseline ankle brachial index.
this event interval censored. Nonetheless, annual ABI measurement has been recommended as the frequency with which to surveil patients with known PAD.40 Loss to follow-up is a limitation of all cohort studies, but this is estimated to be only 2% per year in this cohort. Finally, the cohort is designed to study participants with CKD, and thus may not be generalizable to the population at large. However, this is a rich data set that lends important insight into a highly relevant population commonly afflicted by PAD.

We also note important strengths of this study. These include the rigorous exploration of competing risks, including the use of Fine and Gray modeling approaches, which comprehensively accounts for death as a competing risk. The near equal representation of the sexes and the clear definition of incident PAD given the thorough baseline and follow-up assessment of the cohort via ABI also represent key strengths. These circumvent the pitfalls of earlier studies, which likely led to under recognition of PAD in women, and thus, uniquely leverage a rich database to address this important knowledge gap.

In summary, in our cohort of 3174 participants with CKD, women had a 1.53-fold higher risk of PAD compared with men before the age of 70 years. Future studies should be devoted to understanding the impact of earlier detection of PAD in women and improving our understanding of the biological and clinical basis for these sex-based differences.

### Appendix

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### Table 4. Effect of Age on the SHR of Peripheral Arterial Disease, Stratified by Sex

<table>
<thead>
<tr>
<th>Age, Y (n)</th>
<th>Males SHR (95% CI) vs Baseline</th>
<th>Age, Y (n)</th>
<th>Females SHR (95% CI) vs Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40 (169)</td>
<td>1.00 (0.49–2.04)</td>
<td>&lt;40 (133)</td>
<td>1.02 (0.58, 1.76)</td>
</tr>
<tr>
<td>40–49 (236)</td>
<td>1.53 (0.84–2.80)</td>
<td>50–59 (440)</td>
<td>1.02 (0.63, 1.63)</td>
</tr>
<tr>
<td>50–69 (605)</td>
<td>1.75 (0.96–3.20)</td>
<td>&gt;70 (205)</td>
<td>2.47 (1.29–4.71)</td>
</tr>
<tr>
<td>&gt;70 (205)</td>
<td>2.47 (1.29–4.71)</td>
<td>&gt;70 (158)</td>
<td>1.01 (0.58, 1.76)</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; and SHR, subdistribution hazard ratio.

Estimated by the multivariable Fine and Gray competing risk model, adjusted for diabetes, smoking, body mass index, glomerular filtration rate, coronary artery disease, race, hypertension, and baseline ankle brachial index.

#### Figure 3

Adjusted cumulative incidence of peripheral artery disease (PAD) using the multivariable Fine and Gray model by age category adjusted for the mean of other variables in the model in (A) males and (B) females.

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"This is a sample page from a scientific paper discussing the impact of age on the risk of peripheral artery disease (PAD) in males and females. The study highlights the importance of ABI measurement for surveillance in patients with known PAD and notes the strengths of this study, including the use of Fine and Gray modeling approaches. The paper also acknowledges important sources of funding and contributors to the study. The table and figure supplement the main text with data and visualizations, respectively."
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Disclosures

None.

References


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for the CRIC Study Investigators

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