Impact of Renal Insufficiency on Mortality in Advanced Lower Extremity Peripheral Arterial Disease

Ann M. O’Hare,† Daniel Bertenthal,‡ Michael G. Shlipak,¶ Saunak Sen,‖ Mary-Margaret Chren§

*Divisions of Nephrology and †General Internal Medicine, Department of Medicine, ‡Health Services Research Enhancement Award Program, and §Department of Epidemiology and Biostatistics; and ¶Department of Medicine, University of California, San Francisco, San Francisco, California

Renal insufficiency predicts mortality among patients who are treated for myocardial infarction and congestive heart failure, but its clinical significance in advanced peripheral arterial disease has not been evaluated. A national cohort of 5787 male veterans who received an initial diagnosis of rest pain, ischemic ulceration, or gangrene between January 1, 2000, and September 30, 2002, and had at least one serum creatinine measurement within 3 mo before diagnosis were identified. Sixty-two percent (n = 3561) of cohort members had normal or mildly reduced renal function (GFR ≥60 ml/min per 1.73 m²), 30% (n = 1742) had moderate renal insufficiency (GFR 30 to 59 ml/min per 1.73 m²), and 8% (n = 484) had severe renal insufficiency or renal failure (GFR <30 ml/min per 1.73 m²) but were not on dialysis. The percentages of patients who presented with gangrene or ischemic ulceration rather than rest pain increased with declining renal function (70, 77, and 87%; P < 0.001), as did 1-yr mortality risk (17, 27, and 44%; P < 0.001). After adjustment for demographic and clinical characteristics, patients with a GFR of 30 to 59 ml/min per 1.73 m² (odds ratio, 1.32; 95% confidence interval, 1.13 to 1.53) and <30 ml/min per 1.73 m² (odds ratio, 2.97; 95% confidence interval, 2.39 to 3.69) had a significantly increased odds of death within 1 yr of cohort entry. Both moderate and severe renal insufficiency are associated with an increased odds of death in patients with critical limb ischemia. Death rates were particularly high among those with a GFR <30 ml/min per 1.73 m². This finding may be partly explained by their more frequent presentation with ischemic ulceration or gangrene rather than rest pain.


In the general population, patients with peripheral arterial disease (PAD) are at increased risk for death and for cardiovascular events (1). However, PAD often fails to elicit the same degree of concern as other forms of cardiovascular disease among both patients and clinicians. Patients with PAD are often overlooked in cardiovascular risk reduction efforts, and clinician and patient awareness and detection of this disease seem to be extremely low in the primary care setting (2).

The prevalence and incidence of PAD is high among patients with renal insufficiency (3–5). Among the select group of patients who undergo a lower extremity revascularization procedure for PAD (6,7), renal disease seems to be a risk factor for both short- and long-term mortality. However, little is known about the mortality risk associated with renal insufficiency among more broadly defined PAD cohorts. Accurate knowledge of mortality risk associated with renal insufficiency among patients who present with PAD could provide key information to guide patient and clinician decision-making and risk-reduction efforts.

We hypothesized that greater degrees of renal impairment at initial presentation with PAD would be associated with higher mortality among cohort patients, as has been demonstrated for those with other forms of cardiovascular disease such as acute myocardial infarction (MI) and congestive heart failure (CHF) (8–11). We hypothesized further that higher mortality in the group with renal impairment would be related to the presence of more advanced signs and symptoms of PAD at cohort entry. We tested these hypotheses in a national cohort of male veterans with incident critical limb ischemia defined as rest pain, ischemic ulceration, or gangrene.

Materials and Methods

Patients

Patients entered this cohort at the time of initial diagnosis of critical limb ischemia when this occurred between January 1, 2000, and September 30, 2002. Potentially eligible patients included male veterans with rest pain, ischemic ulceration, or gangrene, identified by an International Classification of Diseases, Ninth Revision (ICD-9) diagnostic code search of the Department of Veterans Affairs’ (VA) National Patient Care Database, which includes all inpatient and outpatient VA encounters (12). A recent study comparing the chart diagnosis of PAD with ICD-9 diagnostic code entries in the National Patient Care Database reported excellent specificity (95%) but only moderate sensitivity (64%).
Renal Insufficiency, and Mortality in PAD

for these codes. These authors also found that specificity could be enhanced further by requiring two diagnostic codes during a 1-yr period (13). To maximize specificity, we thus required that cohort patients have at least two diagnostic code entries for critical limb ischemia during a 1-yr period. Serum creatinine measurements for the 3-mo period before diagnosis of critical limb ischemia were obtained from the VA Decision Support System laboratory results file (14). Exclusion criteria were previous diagnosis of critical limb ischemia, amputation, or revascularization procedure within the VA; absence of at least one serum creatinine measurement within 3 mo of diagnosis of critical limb ischemia; and one or more episodes of dialysis during the year before cohort entry. The study was jointly approved by the Institutional Review Board at the University of California, San Francisco, and the Research and Development Committee at the San Francisco VA Medical Center.

We identified 7580 male veterans who received their first diagnosis of critical limb ischemia between January 1, 2000, and September 30, 2002, and had at least one subsequent diagnostic code entry for critical limb ischemia within 1 yr of cohort entry. Among these, 299 patients were excluded because they had undergone at least one episode of dialysis in the VA during the preceding year, and 1494 patients were excluded because they did not have a serum creatinine measurement within 3 mo of cohort entry. A total of 5787 patients thus were available for analysis.

Primary Predictor Variable

The primary predictor variable for the present analysis was the most recent level of renal function within 3 mo before the diagnosis of critical limb ischemia. We used the abbreviated Modification of Diet in Renal Disease (MDRD) formula to estimate GFR using serum creatinine, age, and race (15). Patients were classified by level of renal function according to National Kidney Foundation Dialysis Outcomes Quality Initiative guidelines: GFR >60 ml/min per 1.73 m² (normal or mildly reduced renal function), GFR 30 to 59 ml/min per 1.73 m² (moderate renal insufficiency or renal failure not on dialysis) (16).

Secondary Predictor Variables

Multivariate analyses were adjusted for patient age; race (black versus nonblack); and history of hypertension, diabetes, coronary artery disease (CAD), CHF, cerebrovascular disease, and chronic obstructive pulmonary disease (COPD) at the time of entry into the cohort and most recent serum glucose level within 3 mo. Data on comorbid conditions were ascertained by ICD-9 and CPT code searches of inpatient, outpatient, and fee-basis files back to 1997 and the Decision Support System laboratory results file back to 1999 (for serum glucose measurements).

Outcome Variable

The study outcome was death within 1 yr after entry into the cohort. Mortality follow-up was ascertained using the VA Beneficiary Identification and Records Locator Systems (BIRLS) database. Recent studies suggest sensitivity rates >94% for BIRLS (17–19).

Statistical Analyses

We compared baseline characteristics across renal function categories using a t test for normally distributed continuous variables, a Mann-Whitney U test for nonnormally distributed continuous variables, and a χ² test for categorical variables. Each renal insufficiency group was compared directly with the referent category with preserved renal function. We used mixed-effects logistic regression analysis to determine the odds of presenting with tissue damage (gangrene or ischemic ulceration) rather than rest pain across renal function categories. We measured the serial impact of adjustment for patient demographic and clinical characteristics and clinical presentation of limb ischemia on the overall association of renal insufficiency with mortality using staged mixed-effects logistic regression analyses in which we sequentially adjusted for these factors. To explore further the impact of clinical presentation on the association of renal insufficiency with mortality, we performed stratified analyses by clinical presentation (rest pain, ischemic ulceration, and gangrene) after adjustment for patient demographic and clinical characteristics.

We tested for interactions between diabetes and between clinical presentation and renal function in the overall model. All models were adjusted for a random effect for centers. Age was modeled as a quadratic term and serum glucose was modeled by quartile because these variables were nonlinearly associated with the outcome. Glucose measurements were missing for 74 (1%) patients, and race was either missing or unknown for 991 (17%) patients. For these variables, we introduced a separate missing category to retain in the analysis patients with missing values for any one of these variables. These analyses were conducted using STATA Statistical Software (College Station, TX).

Results

Almost 40% of sample patients had renal insufficiency defined as an estimated GFR <60 ml/min per 1.73 m²; 30% (n = 1742) had a GFR 30 to 59 ml/min per 1.73 m² and 8% (n = 484)

Table 1. Characteristics of cohort patients by level of renal function

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>GFR ≥60 (n = 3561)</th>
<th>GFR 30–60 (n = 1742)</th>
<th>GFR &lt;30 (n = 484)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (±SD)</td>
<td>67 ± 11</td>
<td>73 ± 9a</td>
<td>71 ± 10a</td>
</tr>
<tr>
<td>Black (%)</td>
<td>22%</td>
<td>18%a</td>
<td>23%</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>53%</td>
<td>68%a</td>
<td>74%a</td>
</tr>
<tr>
<td>Median serum glucose (25th–75th percentile range)</td>
<td>120 (97–174)</td>
<td>131 (100–195)a</td>
<td>135 (100–199)a</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>76%</td>
<td>89%a</td>
<td>90%a</td>
</tr>
<tr>
<td>Coronary artery disease (%)</td>
<td>48%</td>
<td>62%a</td>
<td>65%a</td>
</tr>
<tr>
<td>Congestive heart failure (%)</td>
<td>22%</td>
<td>41%a</td>
<td>48%a</td>
</tr>
<tr>
<td>Cerebrovascular disease (%)</td>
<td>24%</td>
<td>29%a</td>
<td>27%</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease (%)</td>
<td>35%</td>
<td>38%</td>
<td>33%</td>
</tr>
</tbody>
</table>

aP ≤ 0.001. Comparisons are with GFR ≥60 ml/min per 1.73 m².
had a GFR <30 ml/min per 1.73 m². The prevalence of diabetes, hypertension, CAD, CHF, and cerebrovascular disease increased with declining renal function (Table 1). When compared with patients who were missing a recent creatinine measurement, study patients had a higher prevalence of diabetes (59 versus 55%; P < 0.001), hypertension (81 versus 77%; P < 0.001), CAD (55 versus 46%; P < 0.001), and CHF (30 versus 27%; P = 0.037). They also had a higher mortality risk at 1 yr (22 versus 20%; P = 0.040). All other characteristics listed in Table 1 were not significantly different between patients with and without creatinine data.

Compared with patients with normal renal function, a higher percentage of those with renal insufficiency presented with gangrene and a lower percentage presented with rest pain (Figure 1). After adjustment for demographic characteristics and comorbid conditions, the odds of presenting with tissue damage (ischemic ulceration or gangrene) were higher for patients with a GFR <30 ml/min per 1.73 m² (odds ratio [OR], 2.21; 95% confidence interval [CI], 1.64 to 2.98) compared with those with normal renal function. Those with moderate renal insufficiency had similar odds of presenting with tissue damage as those with normal renal function (OR, 1.02; CI, 0.88 to 1.19).

As shown in the staged regression analyses (Table 2), renal insufficiency was a significant predictor of mortality in both unadjusted and adjusted analyses. Unadjusted associations were substantially attenuated after inclusion of demographic characteristics and comorbid conditions in the model. Among patients with a GFR <30 ml/min per 1.73 m², the odds of death were further attenuated after adjustment for clinical presentation of critical limb ischemia.

Overall mortality rates were 13% for patients with rest pain, 20% for those with ischemic ulceration, and 33% for those with gangrene (Table 3). The highest mortality rate (50%) was observed among patients who had a GFR <30 ml/min per 1.73 m² and presented with gangrene (Figure 2, Table 3). Patients with renal insufficiency had increased odds of death regardless of clinical presentation, and the interaction between renal insufficiency and clinical presentation of limb ischemia in the final model presented above was not statistically significant (P = 0.38). Renal insufficiency was associated with increased mortality among both those with and without diabetes (diabetes: OR for GFR 30 to 59 ml/min per 1.73 m² 1.48, CI 1.22 to 1.77, and OR for GFR <30 ml/min per 1.73 m² 2.50, CI 1.66 to 3.76; P = 0.18 for interaction).

Discussion

In a large, national cohort of male veterans who received an initial diagnosis of critical limb ischemia, the presence of renal insufficiency was a strong and independent risk factor for mortality within 1 yr regardless of whether patients initially presented with rest pain, ischemic ulceration, or gangrene. It is interesting that cohort patients with a GFR <30 ml/min per 1.73 m² were more likely than other groups to present with advanced signs and symptoms of lower extremity ischemia (ischemic ulceration or gangrene rather than rest pain). High mortality rates among patients who presented with tissue damage and attenuation of the association of GFR <30 ml/min per 1.73 m² with mortality after adjustment for clinical presentation support the possibility that high death rates among patients in this group may be related in part to how they present clinically.

Peripheral arterial disease awareness among both patients and physicians is notoriously low (2). Furthermore, the impact of renal insufficiency on mortality in this group is unknown. The present study confirms the existence of a strong association between renal insufficiency and death in an incident cohort

Table 2. Mortality within 1 year of cohort entry by level of renal function

<table>
<thead>
<tr>
<th>Estimated GFR</th>
<th>GFR ≥60 (n = 3561)</th>
<th>GFR 30–60 (n = 1742)</th>
<th>GFR &lt;30 (n = 484)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-yr mortality rate</td>
<td>17%</td>
<td>27%</td>
<td>44%</td>
</tr>
<tr>
<td>Unadjusted OR (CI)</td>
<td>1.00 (referent)</td>
<td>1.74 (1.52, 2.00)</td>
<td>3.79 (3.10, 4.64)</td>
</tr>
<tr>
<td>Adjustedb OR (CI)</td>
<td>1.00 (referent)</td>
<td>1.31 (1.13, 1.52)</td>
<td>3.24 (2.61, 4.02)</td>
</tr>
<tr>
<td>Adjustedc OR (CI)</td>
<td>1.00 (referent)</td>
<td>1.32 (1.13, 1.53)</td>
<td>2.97 (2.39, 3.69)</td>
</tr>
</tbody>
</table>

aOR, odds ratio; CI, confidence interval.
bAdjusted for age; black race; diabetes; serum glucose; and history of coronary artery disease, congestive heart failure, hypertension, chronic obstructive pulmonary disease, and cerebrovascular disease.
cFurther adjusted for severity of ischemia at presentation (rest pain, ischemic ulceration versus gangrene). All models are adjusted for a random effect for centers.
with critical limb ischemia as has been reported among patients with other forms of cardiovascular disease such as acute MI and CHF (8–11). Strikingly, the 50% 1-yr mortality rate for cohort patients who had a GFR <30 ml/min per 1.73 m² and presented with gangrene approaches rates reported for elderly patients who have renal insufficiency and are treated for CHF and acute MI (8–11). The presence of renal insufficiency in patients with critical limb ischemia thus should alert the clinician to the presence of a substantially elevated risk for mortality. High mortality in cohort patients with renal insufficiency also underlines the importance of identifying optimal PAD treatment options and of understanding the reasons for elevated mortality risk for this group.

Several previous studies have reported high rates of gangrene and ulceration among dialysis patients who undergo lower extremity revascularization (6,7,20). However, these studies focused on patient characteristics at the time of surgery rather than at the time of initial diagnosis with critical limb ischemia. The present analysis demonstrates that even at the time of initial presentation with critical limb ischemia and after adjustment for potential confounders, patients with a GFR <30 ml/min per 1.73 m² are more likely to have ischemic tissue damage (gangrene or ulceration) rather than rest pain. This does not seem to be true, however, for patients with moderate renal insufficiency. The greater tendency of patients with a GFR <30 ml/min per 1.73 m² to present with ischemic tissue damage rather than rest pain may contribute both to increased mortality risk and high overall mortality rates in this group. These findings underscore the importance of further investigation toward understanding why critical limb ischemia is more likely to be diagnosed after the development of tissue damage. One possibility is that physicians and patients may be less inclined to diagnose and intervene for early disease in this population. Alternatively, PAD may progress more rapidly or may follow a different course presenting with less typical symptoms among patients with more advanced renal insufficiency.

The major limitation of this study is that data on ischemia severity are based on ICD-9 coding. These codes do not provide detailed information on the severity of ischemic ulceration and gangrene or on the severity of comorbid conditions included in the analysis; thus, there may be residual confounding by these...
factors. Furthermore, because ICD-9 codes for PAD in the VA are highly specific but only moderately sensitive (13) and because patients with critical limb ischemia may be coded under less specific PAD codes (e.g., PAD not otherwise specified), mortality rates reported here for patients with critical limb ischemia may not be generalizable to all veterans with this condition.

Several other factors may also limit the generalizability of study findings. The slightly higher mortality rate in the study population compared with those who lack serum creatinine data suggests that our cohort may have been sicker than the group excluded. The absence of non-VA medical claims data may also have led to inclusion of patients who had experienced a previous episode of critical limb ischemia outside the VA before the study period. It is also unclear whether our findings are generalizable to women and to nonveterans. Finally, limitations related to the use of the MDRD equation in the absence of directly measured renal function include that it has not been validated in this or similar cohorts and creatinine measurements for cohort patients were not calibrated to the MDRD reference laboratory (15).

Conclusion
Renal insufficiency is a strong independent predictor of mortality in patients with incident critical limb ischemia and is associated with mortality rates in this cohort rivaling those for acute MI or CHF. Mortality risk and high overall mortality rates were most pronounced among those with a GFR <30 ml/min per 1.73 m². This finding may be partly explained by their more frequent presentation with ischemic ulceration or gangrene rather than rest pain at the time of initial diagnosis. Our findings provide a strong rationale for further studies to understand why patients in this group are more likely than both those with normal renal function and those with moderate renal insufficiency to present with tissue damage at the time of initial diagnosis with critical limb ischemia.

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