Rate of Kidney Function Decline Associates with Mortality

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ABSTRACT

The effect of rate of decline of kidney function on risk for death is not well understood. Using the Department of Veterans Affairs national databases, we retrospectively studied a cohort of 4171 patients who had rheumatoid arthritis and early stage 3 chronic kidney disease (CKD; estimated GFR 45 to 60 ml/min) and followed them longitudinally to characterize predictors of disease progression and the effect of rate of kidney function decline on mortality. After a median of 2.6 years, 1604 (38%) maintained stable kidney function; 426 (10%), 1147 (28%), and 994 (24%) experienced mild, moderate, and severe progression of CKD, respectively (defined as estimated GFR decline of 0 to 1, 1 to 4, and >4 ml/min per yr). Peripheral artery disease predicted moderate progression of CKD progression. Black race, hypertension, diabetes, cardiovascular disease, and peripheral artery disease predicted severe progression of CKD. After a median of 5.7 years, patients with severe progression had a significantly increased risk for mortality (hazard ratio 1.54; 95% confidence interval 1.30 to 1.82) compared with those with mild progression; patients with moderate progression exhibited a similar trend (hazard ratio 1.10; 95% confidence interval 0.98 to 1.30). Our results demonstrate an independent and graded association between the rate of kidney function decline and mortality. Incorporating the rate of decline into the definition of CKD may transform a static definition into a dynamic one that more accurately describes the potential consequences of the disease for an individual.


Chronic kidney disease (CKD) is an important public health problem that affects more than 26 million Americans. The incidence of CKD is rising, and the number of Americans who have received a diagnosis of CKD has doubled during each of the last two decades. The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI) clinical practice guidelines established a framework for the definition and staging of CKD. Stage 3 CKD accounts for nearly 30 to 40% of all CKD, and early stage 3 CKD, defined as GFR between 45 and 60 ml/min, accounts for approximately 60 to 80% of all stage 3 CKD.

The classification of CKD into stages suggests a
chronic progressive disease with all affected patients advancing from earlier to more advanced stages of the disease; however, CKD does not progress at the same rate in all patients, and in some it does not progress at all. Very few data have described the longitudinal behavior and determinants of progression of CKD defined only as estimated GFR (eGFR) <60. It is unclear how many patients who fit the definition of stage 3 CKD actually have intrinsic kidney disease that is likely to progress and portends serious complications.

The mortality of patients with CKD is very high. It is disconcerting that the mortality of a 30-year-old patient who is on dialysis is equal to that of an 80-year-old in the general population. Evidence has suggested that CKD is an independent risk factor for cardiovascular and all-cause mortality. Although the effect of decreased kidney function on all-cause mortality has been explored, it remains largely unknown whether the rate of decline in kidney function is independently associated with increased risk for death. The notion that CKD is an independent risk factor for all-cause mortality is derived from cross-sectional studies. As a result of inherent design limitations, these studies do not take into consideration the rate of decline of kidney function and its effect on the risk for death. For example, consider the case of two patients who start with identical eGFR of 60 ml/min. One patient experiences a precipitous decline in eGFR during 2 years, and another experiences a much slower decline in eGFR during 4 years. When examined in a cross-sectional design when they both have an eGFR of 15 ml/min, their adjusted hazard ratio (HR) of death from any cause is 5.9 (compared with an HR of 1.0 for patients with eGFR >60), but do these two patients have the same risk for death? We hypothesize that the rate of decline in kidney function is associated with all-cause mortality.

The Department of Veterans Affairs (VA) operates one of the largest integrated health care systems under a single management structure in the world and maintains centralized large data repositories that provide a unique opportunity to examine longitudinal behavior of chronic disease and long-term outcomes. In this study, we used VA data sources to describe the longitudinal course of CKD in patients with rheumatoid arthritis (RA), to examine predictors of CKD progression, and to examine the effect of rate of decline of kidney function on the risk for death.

RESULTS

We built a cohort of 4171 patients with RA and early stage 3 CKD (eGFR 45 to 60 ml/min) and followed them longitudinally over time to determine the rate of kidney function change (fiscal year 2000 to 2002; median follow-up 2.6 years) and the effect of rate of decline on the risk for death (fiscal year 2003 through 2008; median follow-up: 5.7 years). We calculated the rate of change in eGFR per year for each patient and categorized patients into four groups: Those who did not experience any decline (rate of change in eGFR >0 ml/min per yr) and those who experienced mild, moderate, and severe CKD progression (rate of eGFR loss 0 to 1, 1 to 4, and >4 ml/min per yr, respectively). Among the 4171 total number of patients in the cohort, 1604 (38%) did not experience any kidney function decline, and 426 (10%), 1147 (28%), and 994 (24%) experienced mild, moderate, and severe CKD progression, respectively. Table 1 details the baseline demographic and clinical characteristics of the study cohort, categorized into these four groups. The majority of patients were of white race and male. The prevalence of comorbid conditions such as hypertension, diabetes, cardiovascular disease (CVD), and chronic lung disease (CLD) was high.

Predictors of CKD Progression

We first examined predictors of progression in the overall cohort of patients (N = 4171). The reference group consisted of patients with mild CKD progression (slope of eGFR decline between 0 and 1 ml/min per yr), which is commensurate with age-related functional decline, not disease (Table 2). Peripheral artery disease (PAD) was a significant predictor of moderate CKD progression (odds ratio [OR]: 1.512; 95% confidence interval [CI] 1.016 to 2.248). Black race, hypertension, diabetes, CVD, and PAD were predictors of severe CKD progression (Table 2). There was no significant association between intake of nonsteroidal anti-inflammatory drugs (NSAIDs) or disease-modifying antirheumatic drugs (DMARDs) and kidney function decline. None of the predictors examined showed any significant statistical association in the group of patients who experienced no decline in kidney function except for age, which showed a negative association (OR 0.983; 95% CI 0.971 to 0.995).

We then restricted the analysis to include only patients who experienced CKD progression (n = 2567), still using those who experienced mild CKD progression as the reference group, and found that the same set of predictors of moderate and severe CKD progression remained statistically significant with similar ORs (data not shown). We then tested the association between the various covariates and the rate of change in eGFR over time as a continuous variable and found that age, black race, diabetes, and PAD were associated with increased risk for decline in kidney function (P < 0.05). There was a trend that did not achieve statistical significance for the association between hypertension and CVD and kidney function decline (P = 0.0609 and P = 0.0647, respectively).

We evaluated the risk for CKD progression within subgroups of patients with one, two, or three or more modifiable risk factors. The risk for moderate CKD progression increased with each additional risk factor. The risk of severe CKD progression also increased with each additional risk factor and was substantially more pronounced across all risk levels (Table 3).

Rate of Decline in Kidney Function and the Risk for Death

During a median follow-up of 5.7 years, there were 1947 (47%) deaths in the overall cohort and 672 (42%), 174 (41%), 524
(46%), and 577 (58%) deaths among patients with no decline, mild CKD progression, moderate CKD progression, and severe CKD progression, respectively. In a Cox survival analysis using the overall cohort of patients \( N = 4171 \), we found that compared with patients who experienced mild CKD progression, patients who experienced moderate CKD progression exhibited a trend toward increased risk for death (HR 1.100; 95% CI 0.975 to 1.304), and patients who experienced severe CKD progression had significantly increased risk for death from any cause (HR 1.539; 95% CI 1.298 to 1.824; Table 4). Interestingly, compared with the reference group (patients with mild CKD progression), patients who experienced no decline in kidney function (rate of eGFR change >0 ml/min per year) also exhibited a trend toward increased risk for death (HR 1.149; 95% CI 0.988 to 1.240). In this survival model, increasing age, the presence of diabetes, CVD, PAD, CLD, hepatitis C,
dementia, and intake of DMARDS each were independently associated with increased risk for death (Table 4). Interestingly, the presence of hypertension was associated with decreased risk for death (HR 0.747; 95% CI 0.612 to 0.912). We then restricted the survival analysis only to patients who experienced a decline in kidney function (\(n = 2567\)) and found that compared with patients who experienced mild CKD progression (the reference group), patients who experienced moderate CKD progression exhibited a trend toward increased risk for death (HR 1.103; 95% CI 0.929 to 1.311), and patients who

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### Table 2. Predictors of moderate and severe CKD progression

<table>
<thead>
<tr>
<th>Parameter</th>
<th>No Decline in Kidney Function (Rate of eGFR Change &gt;0 ml/min per year) ((n = 1604))</th>
<th>Mild CKD Progression (eGFR Loss 0 to 1 ml/min per year) ((n = 426))</th>
<th>Moderate CKD Progression (eGFR Loss 1 to 4 ml/min per year) ((n = 1147))</th>
<th>Severe CKD Progression (eGFR loss &gt;4 ml/min per year) ((n = 994))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95%) CI</td>
<td>OR (95%) CI</td>
<td>OR (95%) CI</td>
<td>OR (95%) CI</td>
</tr>
<tr>
<td>Age</td>
<td>0.983* 0.971 to 0.995*</td>
<td>1.000</td>
<td>1.002 0.990 to 1.015</td>
<td>0.999 0.986 to 1.012</td>
</tr>
<tr>
<td>Black versus white</td>
<td>1.307 0.893 to 1.912</td>
<td>1.000</td>
<td>1.246 0.839 to 1.851</td>
<td>1.853* 1.257 to 2.733*</td>
</tr>
<tr>
<td>Other versus white</td>
<td>0.538 0.280 to 1.036</td>
<td>1.000</td>
<td>0.540 0.269 to 1.084</td>
<td>0.453* 0.213 to 0.964</td>
</tr>
<tr>
<td>Female versus male</td>
<td>1.030 0.662 to 1.602</td>
<td>1.000</td>
<td>1.062 0.668 to 1.688</td>
<td>1.107 0.688 to 1.781</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.054 0.712 to 1.561</td>
<td>1.000</td>
<td>1.307 0.854 to 2.000</td>
<td>1.614* 1.013 to 2.571*</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.921 0.737 to 1.152</td>
<td>1.000</td>
<td>1.193 0.947 to 1.504</td>
<td>1.387* 1.095 to 1.756*</td>
</tr>
<tr>
<td>CVD</td>
<td>1.020 0.807 to 1.289</td>
<td>1.000</td>
<td>1.047 0.820 to 1.336</td>
<td>1.392* 1.080 to 1.793*</td>
</tr>
<tr>
<td>PAD</td>
<td>1.212 0.819 to 1.794</td>
<td>1.000</td>
<td>1.512* 1.016 to 2.248*</td>
<td>1.853* 1.038 to 2.314*</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>1.361 0.600 to 3.085</td>
<td>1.000</td>
<td>0.754 0.302 to 1.883</td>
<td>1.320 0.558 to 3.124</td>
</tr>
<tr>
<td>DMARDs</td>
<td>1.019 0.801 to 1.295</td>
<td>1.000</td>
<td>1.031 0.802 to 1.325</td>
<td>1.068 0.826 to 1.381</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>0.982 0.732 to 1.317</td>
<td>1.000</td>
<td>1.010 0.743 to 1.374</td>
<td>0.939 0.685 to 1.285</td>
</tr>
</tbody>
</table>

Fully adjusted model for additional covariates including cerebrovascular disease, CLD, and dementia.

*Statistically significant.

### Table 3. Risk for moderate and severe CKD progression by number of modifiable risk factors

<table>
<thead>
<tr>
<th>No. of Risk Factors</th>
<th>No Decline in Kidney Function (Rate of eGFR Change &gt;0 ml/min per year) ((n = 1604))</th>
<th>Mild CKD Progression (eGFR Loss 0 to 1 ml/min per year) ((n = 426))</th>
<th>Moderate CKD Progression (eGFR Loss 1 to 4 ml/min per year) ((n = 1147))</th>
<th>Severe CKD Progression (eGFR loss &gt;4 ml/min per year) ((n = 994))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95%) CI</td>
<td>OR (95%) CI</td>
<td>OR (95%) CI</td>
<td>OR (95%) CI</td>
</tr>
<tr>
<td>1</td>
<td>1.449 0.872 to 2.407</td>
<td>1.000</td>
<td>1.664 0.957 to 2.892</td>
<td>2.271* 1.192 to 4.327*</td>
</tr>
<tr>
<td>2</td>
<td>1.192 0.737 to 1.928</td>
<td>1.000</td>
<td>1.794* 1.284 to 2.358*</td>
<td>2.586* 1.397 to 4.784*</td>
</tr>
<tr>
<td>≥3</td>
<td>1.291 0.788 to 2.116</td>
<td>1.000</td>
<td>1.999* 1.169 to 3.418*</td>
<td>4.233* 2.269 to 7.897*</td>
</tr>
</tbody>
</table>

Risk factors are modifiable/manageable risk factors that were significant in the multinomial model, including hypertension, diabetes, CVD, and PAD. The model is adjusted for all of the covariates including age, race, gender, cerebrovascular disease, CLD, dementia, and the intake of DMARDs or NSAIDs. The predictor variable representing the number of risk factors was treated as an ordinal variable.

*Statistically significant.

### Table 4. Rate of decline in kidney function and the risk for death

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Adjusted HR*</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>No decline in kidney function (rate of eGFR change &gt;0 ml/min per year)</td>
<td>1.149</td>
<td>0.988 to 1.240</td>
</tr>
<tr>
<td>Mild CKD progression (reference; eGFR loss 0 to 1 ml/min per year)</td>
<td>1.000</td>
<td>—</td>
</tr>
<tr>
<td>Moderate CKD progression (eGFR loss 1 to 4 ml/min per year)</td>
<td>1.100</td>
<td>0.975 to 1.304</td>
</tr>
<tr>
<td>Severe CKD progression (eGFR loss &gt;4 ml/min per year)</td>
<td>1.539</td>
<td>1.298 to 1.824</td>
</tr>
<tr>
<td>Age per year</td>
<td>1.047</td>
<td>1.041 to 1.053</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.747</td>
<td>0.612 to 0.912</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.282</td>
<td>1.169 to 1.406</td>
</tr>
<tr>
<td>CVD</td>
<td>1.670</td>
<td>1.475 to 1.891</td>
</tr>
<tr>
<td>PAD</td>
<td>1.221</td>
<td>1.092 to 1.365</td>
</tr>
<tr>
<td>CLD</td>
<td>1.611</td>
<td>1.469 to 1.767</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>1.825</td>
<td>1.426 to 2.334</td>
</tr>
<tr>
<td>Dementia</td>
<td>1.833</td>
<td>1.648 to 2.038</td>
</tr>
<tr>
<td>DMARDs</td>
<td>1.224</td>
<td>1.111 to 1.349</td>
</tr>
</tbody>
</table>

*Cox survival model that is fully adjust for all above covariates and race, gender, cerebrovascular disease, and NSAIDs.
experienced severe CKD progression had significantly increased risk for death from any cause (HR 1.535; 95% CI 1.294 to 1.820). The direction and the magnitude of effect of the different covariates on the risk for death in this model was the same as the model involving the overall cohort (data not shown). In a model fully adjusted for demographics and comorbid conditions, we separately analyzed the rate of change in eGFR as a continuous covariate in the overall cohort of patients (N=4171) and found that the slope of eGFR was independently and inversely associated with increased risk for death (parameter estimate −0.02693; HR 0.973; 95% CI 0.965 to 0.982). This association became stronger when the analysis was restricted to patients who experienced decline in kidney function (n=2567; parameter estimate −0.04838; HR 0.953; 95% CI 0.941 to 0.964).

In subgroup analysis, we found that severe CKD progression was associated with increased risk for death in almost all subgroups except patients without hypertension and without CVD (Figure 1A). We tested for interaction to determine whether the association between rate of decline and the risk for death is truly different in these subgroups and found a statistically significant interaction in subgroups on the basis of age and hypertension status (Figure 1B). Severe kidney function decline is associated with higher risk of death in patients younger than 74 years and in patients with hypertension (P = 0.0230 and P = 0.0337 for interaction, respectively).

DISCUSSION

We show in this study that among patients with early stage 3 CKD, some do not experience decline in eGFR and some experience mild, moderate, and severe progression. We also show that there is an independent and graded association between the rate of decline of kidney function and the risk for death.

Although the classification of CKD into stages suggests that CKD is a progressive disease with patients advancing from earlier to more advanced stages over time, we show in this study that 38% of patients who met the NKF KDOQI definition of stage 3 CKD did not experience any decline of kidney function over time (slope of eGFR change >0), a finding that is in agreement with the studies of Matsushita et al.30 The improvement in eGFR most likely represents a decrease in creatinine as a result of muscle loss related to coexisting comorbid illness, malnutrition, or poor overall health. The finding in our studies that these patients have a trend toward increased risk for death compared with patients with mild decline in eGFR lends further plausibility to our hypothesis.

In this well-defined cohort of patients with early stage 3 CKD, we show that there is an independent and graded association between the rate of decline in kidney function and the risk for death. Our study further extends the findings by Rifkin et al.,31 who found that rapid decline in kidney function, defined in the study as decline in eGFR that is >3 ml/min per year, was associated with increased risk for death in 4308 community-dwelling older adults with average baseline eGFR of 79 ml/min. In this study, the rates of change of kidney function were calculated using the two or three available creatinine or cystatin C measurements. In a follow-up study using the same cohort of patients, Shlipak et al.32 found that rapid decline in kidney function was associated with increased risk for heart failure, myocardial infarction, and PAD. Another study, by Khan et al.,33 with a relatively short follow-up of 34 months, found that eGFR deteriorated rapidly (>15 ml/min per year) in 12% of participants. This decline was associated with a sig-
nificant increase in mortality compared with slower decline (<5 ml/min per year). Most recently, Matsushita et al.30 examined the association between 3- and 9-year changes in eGFR and the risk for coronary heart disease or death in 13,029 participants of the Atherosclerosis Risk in Communities (ARIC) study and found that the quartile of patients with the greatest annual decline in eGFR were at significantly greater risk for coronary heart disease and death compared with the third quartile of patients, who experienced minimal annual decline in eGFR (annual decline between 0.33 and 0.47%). This percentage of annual change in eGFR was calculated using two eGFR measurements. The study included mostly patients with normal baseline kidney function (average baseline eGFR ranged from 84.0 to 105.9 ml/min). Although the investigators conducted analyses to examine the effect of rate of kidney function decline on risk for death in various eGFR categories, they had relatively few patients with eGFR 30 to 60 ml/min (n = 281), resulting in broad 95% CIs and thus highlighting the need to examine this issue further in a well-defined cohort with CKD. Our study addresses this unmet need and extends the aforementioned findings to a US veteran population with early stage 3 CKD. Furthermore, we assessed the rate of change of kidney function using on average 13 eGFR measurements per patient, which improves the accuracy of this measure; we also categorized the rates of decline of eGFR into functionally relevant categories of mild, moderate, and severe decline in kidney function that may be easier to translate into clinical practice.

The mechanisms underpinning the association between the rate of decline of kidney function and the risk for death are not clear. The rate of decline of CKD could be a marker of subclinical atherosclerosis, endothelial dysfunction, or oxidative stress.30 Other potential mechanisms include the activation of the renin-angiotensin-aldosterone system, BP dysregulation, disturbances in bone and mineral metabolism, and chronic inflammation.32

Interestingly, we also found an inverse relationship between hypertension and the risk for death in patients with early stage 3 CKD. This result is in accordance with the recent findings in both CKD and RA that suggest that traditional risk factors may behave in an opposite direction in patients with chronic disease states.34–39 The significance of this finding is not fully clear, but the absence of hypertension could be a marker of frailty and poor overall health or could be related to coexisting comorbidities such as heart failure, liver disease, ischemic cardiomyopathy, or autonomic neuropathy.

This study involved patients with RA and early stage 3 CKD; therefore, the results may not be generalizable to the larger CKD population. The imperfect nature of administrative data and the retrospective design of the study may also lead to sampling bias and inaccurate measurements of the predictor variables. To minimize such measurement bias, we used published definitions of comorbid illnesses that are validated for use in administrative data (Supplemental Appendix 1). Because of the small proportion of women in this study, we are not able to make definite conclusions regarding gender as a predictor, and our results may not be generalizable to women with CKD. Because our inclusion criteria specified the minimum number and spacing of creatinine measurements required to fulfill our inclusion criteria, and because the frequency of creatinine measurements is probably a surrogate marker of poorer overall health, we may have systematically missed those who rarely seek care within the VA and our cohort may be sicker than a broader population of veterans with RA (Supplemental Appendix 1). This would probably result in overestimation of risk for CKD progression and death; however, such inclusion criteria are needed for accurate definition of our cohort. The Modification of Diet in Renal Disease (MDRD) study equation for eGFR is an estimate of actual GFR, but it is reasonably accurate, especially in the range of early stage 3 CKD (eGFR between 45 and 60). The creatinine assays at the VA are not calibrated to the MDRD laboratory; the accuracy of the MDRD estimates for true GFR does not lessen the significance of our findings. Although we have been able to incorporate a large number of predictors (both known and putative) of CKD progression and death, we were not able to include proteinuria, and we cannot eliminate the possibility of other residual confounders.

In conclusion, our study highlights the importance of the effect of dynamic changes in eGFR on the risk for death. Furthermore, incorporating the rate of decline of kidney function in the definition of CKD may transform a static definition into a dynamic one that more accurately describes the disease state and the mortality risks associated with it in any given patient.

CONCISE METHODS

Patients

This was a longitudinal study aimed at examining predictors of CKD progression and the effect of rate of CKD decline on the risk for death. The period for the assessment of eGFR change included fiscal years 2000 through 2002. The period for the assessment of mortality included fiscal years 2003 through 2008. Patients with an International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnostic code for RA (714.xx) between October 1, 1998, and September 30, 2005, and with VA use during fiscal years 2000 through 2003 through 2008 were identified, resulting in an initial cohort of 83,305. To confine cohort entry to patients who meet the NKF KDOQI definition of early stage 3 CKD, we included patients if they had two or more outpatient eGFR measurements that were between 45 and 60 ml/min and were at least 3 months apart between October 1999 and September 2000 (fiscal year 2000). To get a measure of longitudinal disease behavior over time (CKD progression), we included patients in the analysis only when they had at least another outpatient creatinine measurement between October 2000 and September 2002. Patients were excluded when they had received a kidney transplant or when they had undergone at least one dialysis session before cohort entry (n = 231). The final number of patients in the
cohort who were available for analysis was 4171 (Figure 2). A table describing the demographic and clinical characteristics of the study cohort versus those eliminated by exclusion is available in Supplemental Appendix 1.

Data Sources
We used a number of national VA data sources to conduct the studies. Data files were merged to create a comprehensive data profile including demographic, comorbidity, laboratory, medication, and death data on each individual in the cohort:

1. Medical SAS data sets: We used the inpatient and outpatient medical SAS data sets to ascertain detailed patient demographic characteristics and comorbidity information for cohort patients, including outpatient and inpatient visits, procedures (Current Procedural Terminology [CPT] codes), and diagnoses (ICD-9-CM codes).45,46

2. Decision Support System: The VA Decision Support System Laboratory Results file was used to examine outpatient serum creatinine measurements associated with routine outpatient visits among cohort patients.45

3. Pharmacy Benefits Management: The Pharmacy Benefits Management database was used to construct a comprehensive medication profile containing all prescriptions dispensed within the VA system on each patient included in the cohort. The outpatient medications package was used to examine the effect of long-term intake of medications, including NSAIDs and DMARDs, on the risk for CKD progression and death.43

4. The VA Vital Status Database, which combines death dates from all sources currently available to VA researchers, including the VA inpatient files, the VA Beneficiary Identification and Records Locator Subsystem, Medicare Vital Status, and Social Security Administration death files was used to ascertain the occurrence and the date of death.

This study was approved by the institutional review board at the St. Louis Veterans Affairs Medical Center (St. Louis, MO).

Primary Predictors
In the multinomial regression model, we tested an array of known and putative predictors of CKD progression. The primary predictor for the survival models was CKD progression rate: The rate of change in eGFR over time. eGFR was calculated using the abbreviated four-variable MDRD study equation on the basis of age, gender, race, and serum creatinine level.44–46 eGFR = 186 × plasma creatinine$^{-1.154} \times \text{age}^{-0.203} \times 0.742$ (if female) × 1.21 (if black). When race data were missing, we made no adjustment for black race.47,48 An eGFR profile that included all outpatient eGFRs available during the eGFR assessment phase (fiscal years 2000 through 2002) was compiled for each patient. To calculate the rate of change in eGFR over time, we fitted an ordinary least-squares regression line to all of the outpatient eGFR readings for each patient. The slope of the regression line describes the rate of change in kidney function (eGFR) over time. On the basis of the rate of change in eGFR, we identified four patient groups: (1) Those who did not experience any decline (rate of change of eGFR > 0 ml/min per year); (2) Those who experienced mild decline in kidney function over time (rate of eGFR loss 0 to 1 ml/min per year); (3) Those who experienced moderate decline (rate of eGFR loss 1 to 4 ml/min per year); and (4) Those who experienced severe decline (rate of eGFR loss > 4 ml/min per year). The cutoff points in these groups is based on studies showing that an eGFR decline of 0 to 1 ml/min per year is commensurate with age-related functional decline, whereas a decline that exceeds 4 ml/min per year represents aggressive disease.1,49

The average number of eGFRs per patient was 13.39 ± 8.21 in the overall cohort and 12.69 ± 7.93, 12.85 ± 8.17, 13.44 ± 7.56, and 14.67 ± 9.18 in patients with no change, mild decline in kidney function, moderate decline in kidney function, and severe decline in kidney function, respectively.

Covariates (Independent Variables)
The regression analyses were adjusted for age; race; gender; and presence of diabetes, hypertension, CVD, PAD, cerebrovascular disease, CLD, hepatitis C, dementia, and long-term intake of DMARDs or NSAIDs. Race/ethnicity was categorized as white, black, or other (Latino, Asian, Native American, other racial/ethnic minority groups, or unknown). Comorbidities were assigned on the basis of relevant ICD-9-CM diagnostic and CPT procedure codes in the VA medical SAS data sets. Long-term use of DMARDs and NSAIDs was defined as use of medication for > 120 days (the equivalent of a 3-month prescription with at least one refill). Baseline characteristics were used to build the multinomial logistic regression model. In all of the survival models, covariates were treated as time-dependant variables when possible. The operational definitions of the covariates and a list of the ICD-9-CM and CPT codes used are presented in Supplemental Appendix 2.

Outcomes (Dependant Variables)
The primary outcome for the multinomial regression model was the rate of progression of CKD divided into four groups as described already. The primary outcome for the survival models was time from study entry to death. Death data were ascertained through September 30, 2008.

Statistical Analysis
The baseline period was defined as the time from beginning of fiscal year 1999 (October 1998) until the time of the first eGFR measurement. Baseline characteristics were ascertained during the baseline period. The rate of eGFR change was assessed from October 1999 until September 2002 (fiscal year 2000 through 2002). Time zero for the survival analysis started on October 1, 2002 (fiscal year 2003). Censorship occurred at...
death or the end of the follow-up period (September 30, 2008 [fiscal year 2008]). In the survival analysis, time in cohort was defined as the duration of time from time zero until censorship.

Predictors of mild, moderate, and severe CKD progression were examined using multinomial logistic regression models. In these models, baseline characteristics were used to define the covariates. We examined the relationship between the putative predictors and CKD decline rates as categorical (described already) and continuous outcomes in the overall cohort ($N = 4171$) and in patients who experienced decline in kidney function ($n = 2567$). The groups with CKD progression did not have a sufficiently ordinal relationship ($P < 0.0001$); therefore, a generalized logistic multinomial regression model was used. In the models in which the outcome was categorical, the group of patients with mild CKD progression (eGFR loss of 0 to 1 ml/min per year—a decline that is commensurate with age related functional decline) served as the reference group. ORs were used to estimate the relationship between the CKD progression severity and an array of predictors/independent variables. We also evaluated the odds of moderate and severe decline in kidney function within the subgroup of patients who had one, two, or three or more modifiable risk factors. The predictor variable representing the number of risk factors was treated as an ordinal variable. Those modifiable/manageable risk factors were selected among the risk factors that were significant in the general multinomial regression model and included hypertension, diabetes, CVD, and PAD at baseline.

To determine whether the rate of decline in kidney function is associated with all-cause mortality among veterans with early stage 3 CKD, we used a Cox regression model to estimate the HR for the predictor variable (i.e., rate of change of eGFR over time as a categorical variable as described already and as a continuous variable), adjusting for other covariates. In the models in which the outcome was categorical, the group of patients with mild decline in kidney function served as the reference group. These survival models were built using the overall cohort ($N = 4171$) and using a cohort that was restricted to patients who experienced CKD decline ($n = 2567$). We also examined the association between severe decline in kidney function and the risk for death in subgroups on the basis of age (above or below the median age of 74); race (black versus nonblack); and the presence of hypertension, diabetes, CVD, PAD, CLD, and dementia. We conducted formal tests for interaction to examine whether the point estimates for the various subgroups are truly different. A 95% CI of an HR that did not include unity was considered statistically significant. In these analyses, all covariates were treated as time-dependent variables. $P \leq 0.05$ was considered significant. All analyses were performed using SAS 6.12 software (SAS Institute, Cary, NC).

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DISCLOSURES

None.

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See related editorial, “Rate of Kidney Function Decline Associates with Increased Risk of Death,” on pages 1814–1816. Supplemental information for this article is available online at http://www.jasn.org/.