Kidney Function and Mortality among Patients with Left Ventricular Systolic Dysfunction

Nadia A. Khan,* Irene Ma,* Christopher R. Thompson,† Karin Humphries,‡
Deeb N. Salem,‡ Mark J. Sarnak,§ and Adeera Levin‖

Divisions of *Internal Medicine, †Cardiology, and ‡Nephrology, University of British Columbia, Vancouver, British Columbia, Canada; and Divisions of †Cardiology and §Nephrology, Tufts-New England Medical Center, Boston, Massachusetts

Kidney disease has emerged as a risk factor for mortality in heart failure populations. The objective of this study was to determine the impact of different stages of kidney dysfunction (defined using the Kidney Disease Outcomes Quality Initiative [K/DOQI] classification system) and changes in kidney function on mortality in a cohort of patients with heart failure. A retrospective analysis was conducted of data from the randomized controlled trials Studies of Left Ventricular Dysfunction. A total of 6640 participants with asymptomatic and symptomatic heart failure were studied. Estimated GFR (eGFR) were calculated and then categorized according to the K/DOQI classification system into the following categories: ≥90, 60 to 89, 30 to 59, and 15 to 29 ml/min per 1.73 m². Reduction in eGFR from baseline was calculated and subsequently categorized according to rate of decline (<5, 5 to 10, 11 to 15, and >15 ml/min per 1.73 m² per year). Independent of baseline differences, lower levels of eGFR were associated with a higher total mortality compared with those with eGFR ≥90 ml/min (30 to 59 ml/min per 1.73 m²); hazard ratio [HR] 1.32, 95% confidence interval [CI] 1.10 to 1.59, \( P = 0.004 \); 15 to 29 ml/min per 1.73 m²; HR 2.54, 95% CI 1.54 to 4.19, \( P < 0.001 \). eGFR deteriorated rapidly (>15 ml/min per 1.73 m² per year) in 12% of participants. This decline was associated with a significant increase in mortality compared with slower decline (<5 ml/min per 1.73 m² per year), despite adjustments for baseline kidney function, baseline heart failure, or change in heart failure (HR 5.63; 95% CI 4.90 to 6.46; \( P < 0.0001 \)). The levels of eGFR from the K/DOQI classification system are associated with mortality in a well-characterized heart failure population. Rate of decline in kidney function is a strong predictor of increased mortality in this population, independent of worsening heart failure and baseline kidney function.


The presence of chronic kidney disease (CKD) is associated with worse outcomes among those with acute coronary syndromes (1–4) and chronic heart failure (5–7). The classification of kidney disease recently established by the National Kidney Foundation (Kidney Disease Outcomes Quality Initiative [K/DOQI]) has become the new standard for staging severity of CKD (8). The utility of this staging system to predict outcomes in patients with heart failure is unknown despite the recognition that patients with heart failure often have kidney disease. In addition, the rate of decline in kidney function at each of the K/DOQI stages of kidney disease is unknown. Although slow rates of decline in kidney function can occur in normally aging populations, small studies have shown that acute worsening of kidney function is associated with increased mortality in hospitalized patients with decompensated heart failure (7,9–12). Therefore, we hypothesized that progressive kidney dysfunction would be independently associated with mortality in a large ambulatory heart failure population.

We sought to assess the value of the K/DOQI staging system using estimates of baseline GFR (eGFR) (13) by examining the prevalence of abnormalities associated with CKD at each eGFR level and the associated mortality rates at each of these levels of eGFR. We studied the rate of decline in kidney function according to these baseline levels of eGFR, factors associated with rapid decline in kidney function, and the impact of this decline on mortality. In addition, we determined the effect of angiotensin-converting enzyme (ACE) inhibition on rate of decline in kidney function and mortality according to severity of baseline renal function. To study these objectives, we used data from two randomized, controlled trials (the Studies of Left Ventricular Dysfunction [SOLVD]) that contain serial serum creatinine levels for a large cohort of patients who had ambulatory heart failure and were followed over a long period of time.

Materials and Methods

The SOLVD studies included two large, double-blind, randomized trials that evaluated the effect of the ACE inhibitor enalapril *versus* placebo among patients with left ventricular ejection fractions of 0.35 or less. Patients were included when they had asymptomatic heart failure (in the prevention trial) or symptomatic heart failure (in the treatment trial). Patients were excluded from entering the study if they had...
recognizable kidney disease (i.e., a serum creatinine >2.5 mg/dl [177 mmol/L]). For study participants, serum creatinine was obtained at baseline and during regularly scheduled follow-up every 4 mo. The primary end point of the SOLVD trials and this analysis was death from any cause. The details of the rationale, design, and methods have been described previously (14).

Patients with incomplete creatinine data (157 patients, or 2% of SOLVD participants) were excluded from this analysis. The following variables were treated as continuous: age, left ventricular ejection fraction, pulse pressure, serum creatinine level, and serum hematocrit. Dichotomous variables based on their presence or absence included current smoking, previous myocardial infarction, left ventricular hypertrophy, history of angina, previous stroke or transient ischemic attack (cerebrovascular accident), ischemic (versus nonischemic) origin of left ventricular dysfunction, history of hypertension, and history of diabetes. Categorical variables included ethnicity (black, white, Hispanic, or other) and New York Heart Association (NYHA) functional class (I, II, III, or IV). Change in NYHA functional class was defined as any increase by one or more functional class. GFR were estimated using a validated prediction formula (15): eGFR (ml/min per 1.73 m²) = 186 × (serum creatinine)^-1.154 × (age in years)^-0.203 × (0.742 if female) × (1.210 if black). eGFR then was categorized according to the K/DOQI classification of CKD established by the National Kidney Foundation (8) into the following five categories: ≥90, 60 to 89, 30 to 59, 15 to 29, or <15 ml/min per 1.73 m². According to the K/DOQI guideline, patients with decreased eGFR between 60 and 89 ml/min per 1.73 m² can be considered as having CKD only when they also have albuminuria or abnormalities on kidney biopsy or imaging studies. However, as there was a paucity of data on albuminuria, we studied the effects of the eGFR cut points as per the K/DOQI guideline and used ≥60 ml/min per 1.73 m² to describe conservatively “normal” kidney function. eGFR loss per year was calculated using the difference between the last reported eGFR and the baseline eGFR per year of follow-up. Reduction in eGFR from baseline was categorized as <5, 5 to 10, 11 to 15, and >15 ml/min per 1.73 m² per year. Because eGFR may normally decline 1 to 2 ml/min per 1.73 m² per year in aging populations (16), we conservatively estimated <5 ml/min per 1.73 m² per year as normal loss. To account further for variations in eGFR as a function of time (i.e., length of follow-up), we analyzed change in each measurement of eGFR from baseline as a time-dependent covariate.

**Statistical Analyses**

We used ANOVA or Kruskal-Wallis test to compare continuous data among the different eGFR categories and the χ² statistic to compare dichotomous data. Rates of overall survival were estimated according to the Kaplan-Meier method, and differences between groups were assessed by means of the log-rank statistic. We used logistic regression to assess the univariate and multivariate association of independent variables with development of rapid decline in kidney function (defined as >15 ml/min per 1.73 m² per year) and Cox proportional hazard models for the outcome of total mortality. Variables that were significantly associated with mortality from the univariate analyses (P < 0.10) were included in multivariate models. Proportionality of hazards over time for eGFR categories was assessed with no violations of assumption detected. We also tested separate models for the presence of statistical interaction between level of eGFR and either the presence of diabetes or assignment to enalapril versus placebo. To account for differing number of eGFR measurements over time, we also used a time-varying covariate to describe the change in eGFR from baseline in the multivariate Cox proportional hazard model. The hazard ratios (HR) are reported with 95% confidence intervals (CI). A two-sided P ≤ 0.05 was considered to indicate statistical significance. Statistical analyses were conducted with the Statistical Analysis System software, version 8.02 (SAS Institute, Cary, NC).

**Results**

A total of 6640 participants were available for this analysis and followed for an average (± SD) of 34.2 ± 14 mo in the prevention trial and 32.3 ± 15 mo in the treatment trial. Of these, 86% were male, and the mean age was 60 ± 10 yr. Despite the exclusion of patients into the original trials with serum creatinine of >2.5 mg/dl (177 mmol/L), the majority (86%) of participants in the cohort had an eGFR <90 ml/min per 1.73 m², and 33% would be classified as having CKD (eGFR <60 ml/min per 1.73 m²), according to current guidelines. It is difficult to comment conclusively on the group of patients with eGFR between 60 and 89 ml/min per 1.73 m², as there was a lack of albuminuria or other data to confirm the diagnosis of CKD.

**Baseline Characteristics**

Tables 1 and 2 describe the baseline demographics, heart function, and comorbid conditions as a function of eGFR level. The prevalence of cardiovascular risk factors and comorbid conditions increased with worsening level of eGFR. Patients with lower eGFR were older and more often white and female. The prevalence of diabetes, stroke, hypertension, and angina was higher among those with lower levels of eGFR, and the mean pulse pressure, a surrogate marker for arterial stiffness, was higher in those with lower eGFR. Lower levels of eGFR were also associated with lower hematocrit levels.

**Mortality According to Baseline Kidney Function**

There were a total of 1566 deaths during follow-up. Among those with baseline eGFR ≥90 ml/min per 1.73 m², 18% who died, 20% in 60 to 89 ml/min per 1.73 m², 31% in 30 to 59 ml/min per 1.73 m², and 50% in the 15 to 29 ml/min per 1.73 m² groups. The Kaplan-Meier survival curves in Figure 1 show that survival decreased sharply once eGFR levels fell below 60 ml/min per 1.73 m². There was no difference in total mortality between those with mildly depressed eGFR (60 to 89 ml/min per 1.73 m²) and those with normal-range eGFR (≥90 ml/min per 1.73 m²). Further subdivision of the GFR level 30 to 59 ml/min per 1.73 m² to 45 to 59 and 30 to 44 ml/min per 1.73 m² yielded similar risks for increased mortality. Table 3 demonstrates the adjusted mortality rates for each level of eGFR. Both moderate and severe reductions in baseline eGFR were independently associated with increased mortality when compared with eGFR ≥90 ml/min per 1.73 m², even after adjustment for age, race, ejection fraction, baseline NYHA functional class, history of diabetes, history of hypertension, prevention versus treatment trial, and enalapril assignment.

**Effect of Enalapril and Diabetes on Outcomes after Adjustment for eGFR**

Two subgroup analyses were performed to determine whether the effect of eGFR on mortality was modified by randomization to enalapril or diabetic status. Although there was no statistical interaction between eGFR level and random-
Worsening Kidney Function

Serial eGFR measurements were available for 98% (6535 of 6640) of patients. Loss in eGFR was common, as demonstrated in Figure 2. Of the participants, 30% had no decline in renal function, 34% had a decline of <5 ml/min per 1.73 m² per year, 19% had a decline of 5 to 10 ml/min per 1.73 m² per year, 5%...
had a decline of 11 to 15 ml/min per 1.73 m² per year, and 12% had a decline of >15 ml/min per 1.73 m² per year. The significant decline in kidney function was evident across the baseline levels of eGFR. Even when analyzed as a percentage decrease, 22% of the cohort had a reduction in eGFR of at least 20% from baseline (1453 of 6535), and this percentage reduction was seen across all levels of baseline eGFR (data not shown).

Factors Associated with Decline in eGFR
Factors that were independently associated with development of a rapid decline in kidney function (i.e., >15 ml/min per 1.73 m² decline per year) included age, female gender, nonwhite race, lower ejection fraction, poor NYHA functional class (III or IV versus I or II), and lower hematocrit. As discerned from multivariable analysis in Table 4, diuretic and antiplatelet use was not associated with rapid decline in renal function. Enalapril assignment was also not associated with rapid decline in renal function regardless of baseline eGFR level ($P > 0.05$ for interaction).

Rate of Decline in Kidney Function and Mortality
Table 5 shows that rate of decline in kidney function was associated with mortality. Among those with rapid decline, >15 ml/min per 1.73 m² per year, mortality rates were considerably elevated compared with those with slower decline, <5 ml/min per 1.73 m² per year (369 of 756 [49%] versus 879 of 4475

Table 3. Adjusted HR for total mortality according to baseline eGFRa

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<thead>
<tr>
<th>Risk Factors</th>
<th>HR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per 10-yr increase)</td>
<td>1.19</td>
<td>1.12 to 1.27</td>
<td>&lt;0.0001</td>
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<td>Female</td>
<td>0.77</td>
<td>0.66 to 0.89</td>
<td>0.0004</td>
</tr>
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<td>White</td>
<td>0.78</td>
<td>0.69 to 0.90</td>
<td>0.0004</td>
</tr>
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<td>EF per 10% increase</td>
<td>0.69</td>
<td>0.63 to 0.75</td>
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<td>Antiplatelet use</td>
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<td>0.77 to 0.96</td>
<td>0.007</td>
</tr>
<tr>
<td>Diuretic use</td>
<td>1.33</td>
<td>1.15 to 1.53</td>
<td>0.0002</td>
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<td>NYHA III/IV (versus I/II)</td>
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<td>1.33 to 1.75</td>
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<td>Enalapril assignment</td>
<td>0.86</td>
<td>0.77 to 0.95</td>
<td>0.003</td>
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<td>Hypertension</td>
<td>1.00</td>
<td>0.90 to 1.12</td>
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<td>Diabetes</td>
<td>1.23</td>
<td>1.09 to 1.39</td>
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<td>Hematocrit (per 10 increase)</td>
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<td>0.73 to 0.92</td>
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<td>Pulse pressure (mmHg)</td>
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<td>eGFR (ml/min per 1.73 m²)</td>
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<tr>
<td>≥90</td>
<td>1.0</td>
<td>—</td>
<td>—</td>
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<tr>
<td>60 to 89</td>
<td>1.02</td>
<td>0.85 to 1.22</td>
<td>0.84</td>
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<tr>
<td>30 to 59</td>
<td>1.32</td>
<td>1.10 to 1.59</td>
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<tr>
<td>15 to 29</td>
<td>2.54</td>
<td>1.54 to 4.12</td>
<td>0.0003</td>
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aHR, hazard ratio; CI, confidence interval.

Figure 1. Kaplan-Meier analysis of event-free survival according to baseline estimated GFR (eGFR; ml/min per 1.73 m²).
Given the above predictors of decline in eGFR, we adjusted for baseline kidney function, baseline heart function, worsening heart function (any increase in NYHA functional class), and other cardiovascular risk predictors. Table 5 demonstrates that rapid decline in renal function was independently associated with a substantially increased mortality. When change in eGFR was analyzed as a continuous and time-varying covariate, reduction in eGFR from baseline remained independently associated with a higher rate of death \( (P < 0.0001) \). The survival curves in Figures 3 and 4 demonstrate that rapid decline in kidney function are associated with increased mortality even among those with relatively preserved baseline eGFR \( (\geq 60 \text{ ml/min per } 1.73 \text{ m}^2) \). In those with less residual kidney function at baseline \( (<60 \text{ ml/min per } 1.73 \text{ m}^2) \), however, mortality begins to increase at slower rates of decline \( (>5 \text{ ml/min per } 1.73 \text{ m}^2 \text{ per year}) \). Furthermore as shown in Table 5, enalapril conferred a survival benefit independent of these other factors as well.

**Discussion**

There are several important findings in this study. There is a high prevalence (32%) of CKD \( (<60 \text{ ml/min per } 1.73 \text{ m}^2) \) in this group of patients with heart failure, originally selected for lack of “severe” kidney disease. This finding is consistent with studies of hospitalized patients and outpatients with heart failure (5-11) and in this cohort of patients in an earlier publication by Al Ahmed et al. (17). This study extends the findings of Al Ahmed et al. (17) by using the more refined K/DOQI classification system, instead of analyzing the cohort into tertiles. In conjunction with previous studies, this analysis high-
lights the lack of sensitivity of serum creatinine alone to identify impaired kidney function and the potential importance of estimating eGFR to detect more accurately impaired kidney function.

The K/DOQI classification system, developed using general population data from the Third National Health and Nutrition Examination Survey, is the new standard for staging severity of CKD. The utility of this staging system to predict outcomes has not been validated in an independent, high-risk patient population, despite the recognition that patients with heart failure commonly have kidney dysfunction. Our analysis demonstrated an increasing prevalence of comorbid conditions by level of eGFR in a cohort of patients with systolic dysfunction. Our analysis supports and extends the findings from the earlier general population study, showing similar stepwise increases in the prevalence of comorbid conditions such as anemia and hypertension as well as other cardiovascular risk factors with decline in level of eGFR but in an independent, high-risk heart failure population (18–20).

The use of eGFR and subsequent classification of kidney function using the K/DOQI system may provide a reasonable graded risk predictor for total mortality in heart failure populations. This study determined that eGFR values below a threshold of 60 ml/min per 1.73 m² defined an increasing risk for death. Few studies have examined the impact of mild reductions of eGFR on mortality despite the high prevalence of

<table>
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<th>HR</th>
<th>95% CI</th>
<th>P</th>
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<tr>
<td>Age (per 10 yr)</td>
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<td>Female</td>
<td>0.69</td>
<td>0.59 to 0.80</td>
<td>&lt;0.0001</td>
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<td>White</td>
<td>0.81</td>
<td>0.71 to 0.92</td>
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<td>EF per 10% increase</td>
<td>0.72</td>
<td>0.67 to 0.78</td>
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<td>Antiplatelet use</td>
<td>0.85</td>
<td>0.76 to 0.95</td>
<td>0.004</td>
</tr>
<tr>
<td>Diuretic use</td>
<td>1.47</td>
<td>1.31 to 1.67</td>
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<td>NYHA III/IV (versus I/II)</td>
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<td>Change in NYHA class</td>
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<td>0.76</td>
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<td>0.0007</td>
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<td>Hematocrit (per 10 increase)</td>
<td>0.86</td>
<td>0.76 to 0.96</td>
<td>0.006</td>
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<td>Baseline eGFR (per 1-ml/min per 1.73 m² increase)</td>
<td>0.98</td>
<td>0.98 to 0.99</td>
<td>&lt;0.0001</td>
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<td>Rate of decline in eGFR (ml/min per 1.73 m² per yr)</td>
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<tr>
<td>&lt;5</td>
<td>1.0</td>
<td>—</td>
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<tr>
<td>5 to 10</td>
<td>1.01</td>
<td>0.85 to 1.20</td>
<td>0.89</td>
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<tr>
<td>11 to 15</td>
<td>2.20</td>
<td>1.76 to 2.76</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>&gt;15</td>
<td>5.63</td>
<td>4.90 to 6.46</td>
<td>&lt;0.0001</td>
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Figure 3. Kaplan-Meier survival curve for participants with baseline eGFR ≥60 ml/min per 1.73 m², according to rate of decline in eGFR (by log rank test, P < 0.0001).
patients with eGFR between 60 and 89 ml/min per 1.73 m². We found no difference in mortality between those with mild reductions in baseline eGFR (60 to 89 ml/min per 1.73 m²) and those with normal eGFR (≥90 ml/min per 1.73 m²). These findings suggest a J-shaped curve for mortality risk starting at a level <60 ml/min per 1.73 m².

Although CKD accompanies traditional cardiac risk factors as well as kidney-associated comorbid conditions, we adjusted for these factors to determine the independent effect of level of GFR on mortality. Previous analyses that demonstrated associations between increased mortality and kidney function in heart failure populations (5,17) were limited by using data-dependent tertile or dichotomous divisions rather than using predetermined cut points for eGFR and by controlling for a number of other variables that affect outcome, such as change in kidney function over time. The findings of an independent, graded association between reduced eGFR and risk for death is concordant with findings from large community-based cohorts and other cardiovascular populations, such as patients after myocardial infarction (17,21–23).

Enalapril assignment was associated with a reduced risk for all-cause mortality, even at moderate and severely depressed levels of baseline eGFR, and did not seem to have an adverse impact on kidney function. This finding is important for clinicians, as there may be a tendency not to initiate ACE inhibitors (6,24–26) because of potential for worsening renal function. The mortality benefit of enalapril remains regardless of degree of baseline kidney dysfunction or change in kidney function. These findings are corroborated by earlier studies that demonstrate that ACE inhibitors reduce risk for cardiovascular disease and delay the progression of CKD (6,27–35).

The natural course of kidney disease in patients with heart failure was largely unknown, as most studies were cross-sectional or limited in follow up data. In this ambulatory heart failure population, kidney function deteriorated significantly in more than one third of all patients and occurred across all levels of baseline eGFR. Rapid decline in kidney function was associated with a significant increase in mortality compared with slower decline (<5 ml/min per 1.73 m² per year), despite adjustments for baseline kidney function, baseline heart failure, or change in heart failure (HR 5.63; 95% CI 4.90 to 6.46; P < 0.0001). As discerned from Figures 3 and 4, mortality increased with rapid decline in renal function for those with CKD and among those with preserved renal function (≥60 ml/min per 1.73 m²). Previous studies that evaluated change in kidney function were limited by evaluating only in-hospital patients who were followed for short periods of time (9,11) or used proxies for declining kidney function, such as change in serum creatinine, which are less sensitive than eGFR (29). This study provides novel information on the “natural” course of kidney disease in a large ambulatory population who had systolic dysfunction and were followed for a mean of 2.6 yr. These findings suggest that rate of change in kidney function may provide a new powerful tool for risk stratifying patients with heart failure beyond baseline kidney function.

Given the strong association with rapid deterioration in eGFR and mortality, understanding the reasons for this high prevalence of deterioration is important. In heart failure, low cardiac output, neurohumoral stimulation, aggressive diuresis, and ACE inhibitor use may contribute to a higher rate of decline in eGFR (5,29,36–38). Prolonged renal vasoconstriction mediated by both anemia and heart failure may also contribute to rapid decline in kidney function (39). Several recent studies identified that anemia can worsen kidney function and cause a more rapid progression to dialysis compared with those without anemia (40,41). Our study demonstrated that poor heart function and anemia were associated with development of rapid decline in kidney function. Anemia is a modifiable risk factor that is currently being studied in a number of populations with and without heart disease. Possible explanations for the association between higher mortality and rapid deterioration in kidney function include that deterioration in kidney function merely reflects severity of baseline heart disease or worsening heart failure, i.e., kidney function declines with...
overly aggressive diuresis or low cardiac output. Consistent with this, Dries et al. (5) also found that moderate reductions in eGFR (<60 ml/min per 1.73 m²) were associated with increased hospitalization for heart failure and death as a result of pump failure. However, kidney disease itself is associated with other novel factors that may increase mortality: proinflammatory markers, arterial stiffness, dyslipidemia, hyperhomocysteinemia, and anemia (17,23,42–46). We attempted to understand better, using multivariate modeling, whether worsening kidney function was a reflection of heart failure or due to other mechanisms. We adjusted for baseline heart failure severity and decline in NYHA functional class (defined as any increase in functional class level), and despite these adjustments and adjustments for traditional cardiac risk factors, rapid decline in kidney function remained independently associated with a marked increase in all-cause mortality. These data support the hypothesis that other mechanisms beyond worsening heart failure should be explored as contributing to higher mortality.

There are several limitations to our analysis. Because this is a post hoc re-analysis of a large, randomized, controlled trial, there may be residual confounding by unmeasured factors despite adjustment for known risk factors with the multivariate modeling. In particular, we were unable to account for adjustments in dosages of enalapril, early discontinuation of enalapril, and initiation of other cardiovascular medication during the study period. Given the uniform and standardized management, follow-up, and ascertainment of outcomes, this bias is lessened. Residual confounding is also less likely to explain the large increases in mortality associated with poor baseline kidney dysfunction or the rapid decline in kidney function. Also, because we did not have consistent measurements of urinalysis in all patients with eGFR >60 ml/min per 1.73 m², we are unable to predict the true prevalence of impaired kidney function at higher levels, according to the K/DOQI definitions. In addition, change in NYHA functional class, as a marker of worsening heart failure, is limited as it describes only functional rather than structural changes and may be too insensitive to detect smaller or early changes in heart function. However, worsening NYHA functional class is a clinically relevant measure of change in heart function.

Clinical Implications

Kidney dysfunction is common among patients with heart failure. The K/DOQI classification system seems helpful for categorizing kidney impairment. This study corroborates the use of eGFR as a powerful predictor of mortality in an independent, high-risk population. It seems that patients who have systolic dysfunction and have eGFR <60 ml/min per 1.73 m² are a particularly high-risk group but that ACE inhibition is associated with a significant reduction in mortality, even in those with relatively advanced kidney disease.

Because we demonstrate that rapid decline in eGFR both is common and is associated with higher rates of death, independent of baseline kidney function, heart failure class, or progression of heart failure, clinicians will need to recognize that serial measurement of eGFR are important in determining prognosis. Efforts should be made to identify factors that are responsible for the rapid decline in eGFR, and this study raises the important question as to whether strategies that are aimed at preserving eGFR might lead to improved mortality in those with heart failure.

Conclusion

Kidney dysfunction that is classified according to the K/DOQI classification system using eGFR is associated with increased mortality among patients with asymptomatic and symptomatic left ventricular systolic dysfunction. A significant proportion of patients with systolic dysfunction will develop rapid decline in kidney function, regardless of baseline kidney function. This rapid decline in kidney function is associated with a marked increase in mortality, independent of worsening heart failure and baseline kidney function. Rate of change in kidney function may provide a new powerful tool for risk stratifying patients with heart failure beyond baseline kidney function. These findings need to be confirmed in large, prospective studies as understanding of the impact of renal impairment may lead to novel therapeutic strategies in reducing mortality in patients with heart failure.

Acknowledgments

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We acknowledge Dr. Min Gao, biostatistician, for assisting with the analysis.

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different definitions of worsening renal function in congestive heart failure. *J Card Fail* 8: 136–141, 2002
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Access to UpToDate on-line is available for additional clinical information at http://www.jasn.org/

This article by Khan et al., showing a relationship between kidney function and mortality in heart failure patients is related to the In-Depth Review by Berl and Henrich about kidney–heart interaction in this month’s CJASN (pages 8–18).