Renal Function, Digoxin Therapy, and Heart Failure Outcomes: Evidence from the Digoxin Intervention Group Trial

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Abstract. Renal dysfunction is a common complication for patients with heart failure, but its association with clinical outcomes has not been fully characterized. We evaluated the association of glomerular filtration rate (GFR) with heart failure survival and the effect of digoxin on heart failure outcomes across GFR strata. A secondary analysis from the Digitalis Intervention Group trial was conducted of 6800 outpatients with systolic heart failure. Renal function was categorized as estimated GFR (expressed in ml/min per 1.73 m²). All-cause mortality (mean, 3 yr) was inversely proportional to GFR (GFR >60, 31% mortality; GFR 30 to 60, 46% mortality; GFR <30, 62% mortality; P < 0.001). Among patients with a GFR <50, lower GFR were associated with greater adjusted mortality risk (GFR <30: hazard ratio [HR], 2.06, 95% confidence interval [CI], 1.69 to 2.51; GFR 30 to 40: HR, 1.42; GFR 50 to 60: HR, 1.22, 95% CI, 1.07 to 1.39; GFR 50 to 60: HR, 1.00, referent). In contrast, participants with GFR 60 to 70 had similar risk (HR, 1.00; 95% CI, 0.88 to 1.14) compared with GFR 50 to 60, and those with GFR >70 had a slightly lower mortality hazard (0.89; 95% CI, 0.78 to 1.00). Linear spline analyses confirmed that GFR = 50 was the appropriate risk threshold; above 50, GFR had no association with mortality, whereas below 50, mortality risk increased sharply with declining GFR (spline coefficient, P < 0.0001). Digoxin efficacy did not differ by level of GFR (P = 0.19 for interaction). Renal dysfunction is strongly associated with mortality in stable outpatients with heart failure, notably in patients with estimated GFR <50 ml/min per 1.73 m². The effect of digoxin did not differ by level of renal function.

Renal dysfunction (1) is common in people with heart failure and can complicate heart failure therapy. Although renal dysfunction has been associated with increased heart failure mortality in several studies, these analyses have conflicted regarding the nature of the association. Some studies that found that renal function was associated with mortality in heart failure patients evaluated renal function as a continuous variable, thus implying a consistent, incremental mortality risk across the spectrum of creatinine or estimated glomerular filtration rate (GFR) (2,3). Other investigators either dichotomized renal function (4,5) or evaluated its association with heart failure outcomes across quartiles (6,7) and found increased mortality risk only among heart failure patients with GFR <60 ml/min. Although these studies have agreed that renal function is an important determinant of survival in the setting of heart failure, it remains unresolved whether the association of renal function with mortality is graded and continuous across a broad range of renal function or rather begins below a particular threshold of renal dysfunction.

Renal dysfunction also complicates the management of heart failure, yet the efficacy of heart failure therapies has not been well studied in the setting of chronic renal insufficiency (CRI) and is rarely addressed by current heart failure guidelines (8–11). This issue is of particular concern for the use of digoxin therapy because its clearance varies linearly with GFR, indicating that its safety and efficacy may vary on the basis of renal function (12–15). The potential for an interaction between GFR and digoxin therapy was reinforced by our recent finding that digoxin’s effectiveness seems to vary on the basis of patients’ serum digoxin concentrations (16).

To address these issues, we conducted an analysis using data collected as part of the Digitalis Intervention Group (DIG) trial, a randomized, double-blind, placebo-controlled trial that

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investigated the efficacy of digoxin among stable outpatients with New York Heart Association (NYHA) class II to III heart failure (17). As the largest clinical trial of patients with moderate to severe heart failure, the DIG trial provides an ideal cohort within which to assess the association between renal function and heart failure survival and to compare the efficacy of digoxin across levels of renal function.

**Materials and Methods**

**DIG Trial Database and Study Design**

We obtained a public-use copy of the DIG trial database from the National Heart, Lung, and Blood Institute. The DIG trial enrolled individuals who had stable heart failure and left ventricular ejection fraction (LVEF) <45% and were in sinus rhythm to assess the efficacy of digoxin therapy. Participants were randomized to digoxin or placebo at one of 302 centers in the United States or Canada between August 1991 and February 1993 and followed up through the conclusion of the DIG trial in December 1995 (17). An algorithm based on age, gender, weight, and creatinine levels determined the doses of digoxin or placebo (18). The primary results of the trial found that digoxin had no effect on mortality but did provide a reduction in the secondary combined end point of all-cause mortality plus hospitalization for worsening heart failure (17).

All DIG trial participants were eligible for inclusion in our analysis when they had serum creatinine levels measured at baseline (n = 6,800). The DIG trial excluded individuals with creatinine levels >3.0 mg/dl (18).

**Renal Function**

We categorized renal function by estimating GFR (ml/min per 1.73 m²) with the simplified Modification of Diet in Renal Disease equation [GFR = 186×(serum creatinine⁻¹.154)×(age⁻⁰.²⁰⁵)×1.212 (if black)×0.742 (if female)] (19). We used the categorizations for moderate (30 to 60) and severe (<30) CRI that were defined by the National Kidney Foundation (20). In subsequent analyses, we categorized GFR into 10-point increments with GFR 50 to 60 as the reference group to evaluate more thoroughly the association of GFR and mortality.

We first categorized serum creatinine into five groups (<1.0, 1.1 to 1.3, 1.4 to 1.6, 1.7 to 2.0, and >2.0 mg/dl) to examine differences in crude all-cause mortality risk. We subsequently categorized serum creatinine levels into four subgroups (<1.0, 1.1 to 1.5, 1.6 to 2.0, and >2.0 mg/dl) for statistical analyses of their association with the study outcomes.

**Study Outcomes**

As with the DIG trial, the primary outcome of our analysis was all-cause mortality during the study (mean follow-up, 3 yr) (18). We also evaluated the secondary outcome of all-cause mortality plus hospitalization for worsening heart failure (18). Local investigators at each clinical site, blinded to the patient’s treatment assignment, determined the cause of hospitalization.

**Statistical Analyses**

We compared baseline demographic characteristics, medical history, clinical measurements, and medication use of participants across the three categories of estimated GFR, using χ² tests for categorical variables and Wilcoxon rank sum tests for continuous variables. Unadjusted Cox proportional hazards models were used to assess the association of GFR and all-cause mortality.

To determine the independent association of GFR with all-cause mortality, we adjusted for covariates that were believed to confound the association between renal function and heart failure outcomes as identified on the basis of previous studies and clinical judgment (3,21,22). Multivariable Cox proportional hazards models were conducted for each end point and adjusted for demographic characteristics (age, gender, and race), medical history (previous diabetes, hypertension, myocardial infarction, and angina), heart failure history (ejection fraction, duration, cause, NYHA functional class, and cardiothoracic ratio), clinic measurements at baseline (body mass index, systolic BP, and heart rate), medication use (diuretics, angiotensin-converting enzyme [ACE] inhibitors, and vasodilators), and randomization to digoxin or placebo. For all proportional hazards models, we verified the proportional hazards assumption by visual inspection and by log-log plots.

We began our analyses by conducting multivariate analyses to compare the risk for adverse outcomes among participants with GFR >60, 30 to 60, and <30, the categories defined by the National Kidney Foundation. However, our comparison of unadjusted mortality risk by 10-unit increments of GFR led to the hypothesis that the association of GFR with mortality may be limited to participants with GFR <50. To test this hypothesis further, we conducted two additional analyses. First, we evaluated the association of GFR and mortality within smaller ranges of renal function—GFR <30, 30 to <40, 40 to <50, 50 to <60, 60 to <70, and ≥70—and specified GFR 50 to 60 as the reference group. Second, we used a piecewise linear spline procedure to determine whether the association of GFR and mortality differed significantly above and below a certain cut point and whether the association of GFR and mortality remained significant above the designated cut point. These linear spline analyses were repeated for GFR cut points of 30, 40, 50, 60, and 70.

The association of renal function with mortality and death or heart failure hospitalization was also evaluated using serum creatinine levels to represent renal function with the creatinine categories mentioned above. In addition, we evaluated whether a threshold could characterize the association of creatinine with heart failure mortality, using the linear spline approach described above and testing cut points at 0.1-mg/dl intervals from 1.1 to 1.7 mg/dl.

**Renal Function and Digoxin Therapy**

We evaluated the outcomes of participants who were randomly assigned to digoxin versus placebo, stratified by patients’ GFR (>60, 30 to 60, <30) at baseline. We conducted multivariate analyses to determine whether the effect of digoxin compared with placebo varied on the basis of patient renal function, adjusting for demographic, medical history, heart failure history, and medication variables listed above. We formally tested for variations in digoxin efficacy using a digoxin*renal function interaction term in Cox proportional hazards models for each end point. We repeated these analyses for subgroups on the basis of serum creatinine.

Analyses were conducted using SAS version 8.0 software (SAS Institute, Cary, NC). The analysis of the DIG trial database was approved by the Yale University School of Medicine Human Investigation Committee.

**Results**

Among the 6800 participants in the DIG trial, 3643 had estimated GFR >60, 2939 (43%) had GFR 30 to 60, and 218 (3%) had GFR <30. Those with GFR <30 were older on average, and greater proportions were white and female compared with participants with less severe renal dysfunction.
Lower levels of GFR were associated with a greater prevalence of diabetes, hypertension, angina, and ischemic heart failure and a higher average systolic BP and NYHA class. The proportion of patients who were using diuretics, nitrates, and vasodilators was greater in patients with GFR <30, whereas the use of ACE inhibitors was lower in this group (Table 1).

Mortality risk was greater for patients with lower levels of baseline GFR; however, the risk seemed to increase sharply below a GFR of 50 (Figure 1). Using our a priori categorizations of GFR, we found that annual mortality risk increased as GFR declined: 10% annual mortality risk in patients with GFR >60 (1066 deaths), 15% in patients with GFR 30 to 60 (1173 deaths), and 22% in those with GFR <30 (136 deaths). Participants with severe renal dysfunction (GFR <30) had an approximately twofold greater adjusted risk for both mortality and the combined death or hospitalization for heart failure outcome compared with patients with GFR >60, whereas participants with GFR 30 to 60 were only at modestly elevated risk (Table 2). Using GFR 50 to 60 as a reference group, the mortality hazards were 2.06 (95% confidence interval [CI], 1.69 to 2.51) for GFR <30, 1.42 (95% CI, 1.22 to 1.67) for GFR 30 to 40, and 1.22 (95% CI, 1.07 to 1.39) for GFR 40 to 50 (Figure 2). In contrast, participants with GFR 60 to 70 had similar mortality hazards (1.00; 95% CI, 0.88 to 1.14) compared with participants with GFR 50 to 60, and those with GFR >70 had only a slightly lower mortality hazard (0.89; 95% CI, 0.78 to 1.00; Figure 2).

In the analyses using piecewise linear splines, separate models tested GFR cut points of 30, 40, 50, 60, and 70. The association of GFR with mortality was statistically significant above the cut points of 30 (hazard ratio [HR], 1.06 per 10 ml/min; 95% CI, 1.03 to 1.08; \( P < 0.001 \)) or 40 (HR, 1.03; 95% CI, 1.01 to 1.06; \( P = 0.02 \)) but was NS above 50 (HR, 1.01; 95% CI, 0.98 to 1.03; \( P = 0.63 \)), 60 (HR, 0.99; 95% CI, 0.97 to 1.02; \( P = 0.52 \)), or 70 (HR, 0.98; 95% CI, 0.96 to 1.01; \( P = 0.13 \)), suggesting that the greater mortality risk associated

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**Table 1. Participant characteristics by estimated GFR in the Digitalis Intervention Group trial**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>GFR &lt;30 (N = 218)</th>
<th>GFR 30 to 60 (N = 2939)</th>
<th>GFR &gt;60 (N = 3643)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (yr)</td>
<td>72</td>
<td>68</td>
<td>60</td>
<td>0.0001</td>
</tr>
<tr>
<td>Male gender (%)</td>
<td>54</td>
<td>73</td>
<td>82</td>
<td>0.0001</td>
</tr>
<tr>
<td>White race (%)</td>
<td>94</td>
<td>91</td>
<td>80</td>
<td>0.0001</td>
</tr>
<tr>
<td>Median serum creatinine (mg/dl)</td>
<td>2.4</td>
<td>1.4</td>
<td>1.1</td>
<td>0.0001</td>
</tr>
<tr>
<td>Median GFR (ml/min per 1.73 m²)</td>
<td>27</td>
<td>50</td>
<td>73</td>
<td>0.0001</td>
</tr>
<tr>
<td>Median systolic BP (mmHg)</td>
<td>130</td>
<td>125</td>
<td>120</td>
<td>0.0001</td>
</tr>
<tr>
<td>Median heart rate (beats/min)</td>
<td>80</td>
<td>78</td>
<td>80</td>
<td>0.08</td>
</tr>
<tr>
<td>Median body mass index</td>
<td>26</td>
<td>26</td>
<td>27</td>
<td>0.0001</td>
</tr>
<tr>
<td>Median ejection fraction (%)</td>
<td>28</td>
<td>29</td>
<td>29</td>
<td>0.74</td>
</tr>
<tr>
<td>Median duration of heart failure (mo)</td>
<td>13</td>
<td>18</td>
<td>15</td>
<td>0.02</td>
</tr>
<tr>
<td>Median cardiothoracic ratio</td>
<td>0.54</td>
<td>0.53</td>
<td>0.52</td>
<td>0.0001</td>
</tr>
<tr>
<td>NYHA functional class</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>6</td>
<td>12</td>
<td>15</td>
<td>0.0001</td>
</tr>
<tr>
<td>II</td>
<td>42</td>
<td>51</td>
<td>57</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>46</td>
<td>34</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>6</td>
<td>3</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Medical history (%)</td>
<td>66</td>
<td>69</td>
<td>62</td>
<td>0.0001</td>
</tr>
<tr>
<td>previous myocardial infarction</td>
<td>66</td>
<td>69</td>
<td>62</td>
<td>0.0001</td>
</tr>
<tr>
<td>current angina</td>
<td>31</td>
<td>28</td>
<td>25</td>
<td>0.009</td>
</tr>
<tr>
<td>diabetes</td>
<td>44</td>
<td>30</td>
<td>26</td>
<td>0.0001</td>
</tr>
<tr>
<td>hypertension</td>
<td>63</td>
<td>47</td>
<td>43</td>
<td>0.0001</td>
</tr>
<tr>
<td>previous digoxin use (%)</td>
<td>45</td>
<td>43</td>
<td>45</td>
<td>0.35</td>
</tr>
<tr>
<td>Concomitant medications (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>diuretics</td>
<td>96</td>
<td>87</td>
<td>77</td>
<td>0.0001</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>88</td>
<td>94</td>
<td>96</td>
<td>0.0001</td>
</tr>
<tr>
<td>nitrates</td>
<td>52</td>
<td>47</td>
<td>39</td>
<td>0.0001</td>
</tr>
<tr>
<td>other vasodilators</td>
<td>10</td>
<td>4</td>
<td>3</td>
<td>0.0001</td>
</tr>
<tr>
<td>Dose of study medication prescribed (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.125 mg/d</td>
<td>63</td>
<td>25</td>
<td>10</td>
<td>0.0001</td>
</tr>
<tr>
<td>0.250 mg/d</td>
<td>37</td>
<td>72</td>
<td>71</td>
<td></td>
</tr>
<tr>
<td>≥0.375 mg/d</td>
<td>0</td>
<td>3</td>
<td>20</td>
<td></td>
</tr>
</tbody>
</table>

* NYHA, New York Heart Association; ACE, angiotensin-converting enzyme.
with renal dysfunction was observed predominantly among participants with GFR <50. At each of the five cut points that we tested, the piecewise linear spline analyses found that the association of GFR and mortality was significantly stronger below the GFR cut point relative to the association of GFR with outcomes at values above the cut point (P < 0.001 for each comparison).

Crude all-cause mortality was also greater for patients with higher creatinine levels (Figure 3); annual mortality risks were 9% for creatinine <1.0 (473 deaths), 11% for creatinine 1.0 to 1.5 (1281 deaths), 19% for creatinine 1.5 to 2.0 (450 deaths), and 25% for creatinine >2.0 (171 deaths). Compared with participants with creatinine levels ≤1.0 mg/dl at baseline, those with creatinine 1.6 to 2.0 and >2.0 mg/dl had significantly greater risks for mortality and heart failure hospitalization in unadjusted and adjusted analyses (Table 2). Participants with creatinine levels of 1.1 to 1.5 mg/dl had increased risk for both outcomes in unadjusted analysis only but were comparable to patients with a serum creatinine of <1.0 mg/dl in adjusted analyses. When we repeated the piecewise linear spline approach to the creatinine analyses, we found that the spline term was not statistically significant for any cut point from 1.1 and 1.7 mg/dl. Thus, these analyses did not reject the hypothesis that the association of creatinine with mortality is graded and continuous across the range of creatinine levels evaluated.

The effect of digoxin on all-cause mortality and the combined all-cause mortality plus hospitalization for worsening heart failure was comparable across GFR subgroups (Table 3). Point estimates for all-cause mortality outcome varied only from 0.93 (GFR <30) to 1.01 (GFR >60) and for the combined outcome of death or heart failure hospitalization from 0.77 (GFR <30) to 0.84 (GFR 30 to 60; P > 0.10 in both cases for interaction). Although participants with GFR <30 were treated with the lowest average dose of digoxin at the outset of the DIG trial, their serum digoxin levels were 50% greater than participants with normal renal function 1 mo after randomization (Table 4).

The effect of digoxin was similar among patients in the lower three categories of serum creatinine levels but seemed beneficial in the small subgroup with the highest creatinine levels (2.0 mg/dl), contrary to our prespecified hypothesis (Table 3). Patients with the highest creatinine levels were treated with the lowest doses of digoxin but had the highest serum digoxin concentrations (Table 4).

**Discussion**

Renal function was strongly associated with mortality and heart failure hospitalizations among stable outpatients who had heart failure and were enrolled in the DIG trial. However, the association of GFR with mortality was not linear and graded but rather increased steeply below an approximate GFR threshold of 50. Although these findings are consistent with previous studies that either dichotomized or categorized renal function (4–7), our analysis extends current knowledge by thoroughly characterizing the relationship of renal function with heart failure outcomes. Thus, our study both reinforces the importance of renal function as a prognostic factor for patients with heart failure (8–10,23–25) and characterizes the population of heart failure patients with increased renal risk for future intervention studies to target.

There are several possible explanations for why renal dysfunction has a strong association with adverse heart failure outcomes below an approximate GFR threshold of 50. Certain risk factors for heart failure mortality are increased in people with this level of renal dysfunction, which may contribute to their increased mortality risk. Hemoglobin levels seem to decrease below a GFR of 60, and the prevalence of anemia increases substantially below a GFR of 45 (26). As anemia may be a predictor of adverse outcomes in the setting of heart failure, it could mediate the association of GFR with mortality (27,28). Another possible mediator for the effect of renal dysfunction on heart failure mortality is inflammation, as large elevations of inflammatory markers, including C-reactive protein, fibrinogen, and IL-6, have been reported in people with GFR <40 (11) and are also associated with heart failure.
mortality (29,30). Renal dysfunction is also associated with activation of the renin-angiotensin-aldosterone system, which in turn has deleterious effects by promoting the progression both of heart failure and of kidney disease (31). Unfortunately, the DIG trial did not measure the levels of hemoglobin, renin, angiotensin, or inflammatory markers, so we cannot determine their contribution to the adverse outcomes of participants with renal dysfunction in this study. Heart failure patients may also become progressively resistant to diuretic therapy as renal function deteriorates, which can result in volume overload, worsening symptoms, and additional morbidity (32–34). Finally, renal dysfunction is an important predictor of adverse atherosclerotic cardiovascular outcomes, which may have contributed to its association with mortality in this study by thrombotic mechanisms that may not be related directly to heart failure (35–38).

An additional important finding from this study was that the effect of digoxin on heart failure outcomes did not vary significantly in relation to baseline renal function. Although digoxin exhibits a similar effect across GFR categories, there are still sufficient reasons to use digoxin cautiously in people with heart failure and reduced GFR. The clearance of digoxin varies linearly with renal function, so the risk of digoxin toxicity is likely to be greatest in people with renal dysfunction (12,13). This risk may have been underestimated in the DIG trial, as a result of the careful prescribing algorithm and the exclusion of patients with creatinine >3.0 mg/dl. Clinicians should make the decision of whether to use digoxin in heart failure patients with renal dysfunction in the context of the overall null results of the DIG trial and the increased serum digoxin concentrations among patients with renal dysfunction in this study despite the DIG trial’s renal dosing algorithm. If digoxin therapy is used in patients with heart failure and renal dysfunction, then a sensible approach might be to limit the daily digoxin dose to 0.125 mg or less (25).

Our findings provide compelling evidence of the need to explicitly consider renal function in the care of patients with heart failure and in clinical research studies of heart failure therapeutics. In determining the prognosis of a patient with heart failure, a GFR <50 should be integrated with other important prognostic factors, which broadly include demographic factors, characteristics of the left ventricle (ejection fraction, hypertrophy, end-systolic diameter), patient functional status (NYHA class, oxygen capacity, exercise tolerance, and quality of life), and biochemical measurements (serum sodium, inflammatory marker, and B-type natriuretic peptide levels) (3,4,7,21,22,29,30,39,40). Because they have a worse prognosis, heart failure patients with CRI should be treated aggressively with medications that have a favorable risk/benefit ratio (e.g., β-blockers and ACE inhibitors/angiotensin receptor blockers) (25), whereas the benefits and risks of invasive procedures and surgical therapies should be weighed carefully. Future intervention trials of both medical and surgical therapies in heart failure patients should ensure an adequate representation of subjects with reduced GFR, and future therapies are urgently needed to improve the outcomes of patients with these combined morbidities.
This study has several limitations to consider, including our reliance on imprecise measures of renal function. Serum creatinine levels are poor measures of renal function and may be particularly inaccurate in the setting of heart failure (41). We used the Modification of Diet in Renal Disease equation to estimate GFR, as it has been found to predict GFR well in certain populations, although it has not been validated in patients with heart failure (19). In addition, we had only baseline measurements of creatinine, which may not reflect renal function throughout the trial, although any random variations in serum creatinine levels should have biased our findings toward underestimating the association between renal dysfunction and outcomes. Although our spline analyses indicated a risk threshold of ~50, patients with estimated GFR of 50 to 70 may certainly be at increased risk compared with patients at higher GFR levels. Furthermore, patients with a creatinine level >3.0 mg/dl were excluded from the DIG trial, precluding assessment of the prognostic significance of the most severe renal dysfunction. We also did not have adequate power to conduct our analyses of the effect of digoxin across subgroups of renal function separately for men and women, which may be important given a previous study that found that the effect of digoxin on mortality differed between men and women (42).

In conclusion, we found in the setting of heart failure a strong association between renal dysfunction and mortality.
that seemed to be limited to participants with an estimated GFR <50. The efficacy of digoxin, as dosed in the DIG trial, on heart failure outcomes did not seem to differ by category of renal function. Effective and safe strategies are needed to reduce the morbidity of patients with heart failure and renal dysfunction. Future heart failure clinical trials should enroll a representative proportion of subjects with reduced GFR and should report results specific to this high-risk subgroup.

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