Hypokalemia and Outcomes in Patients With Chronic Heart Failure and Chronic Kidney Disease: Findings From Propensity-Matched Studies

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Background—Little is known about the effects of hypokalemia on outcomes in patients with chronic heart failure (HF) and chronic kidney disease.

Methods and Results—Of the 7788 patients with chronic HF in the Digitalis Investigation Group trial, 2793 had chronic kidney disease, defined as estimated glomerular filtration rate <60 mL/min per 1.73 m². Of these, 527 had hypokalemia (serum potassium <4 mEq/L; mild) and 2266 had normokalemia (4 to 4.9 mEq/L). Propensity scores for hypokalemia were used to assemble a balanced cohort of 522 pairs of patients with hypokalemia and normokalemia. All-cause mortality occurred in 48% and 36% of patients with hypokalemia and normokalemia, respectively, during 57 months of follow-up (matched hazard ratio when hypokalemia was compared with normokalemia, 1.56; 95% CI, 1.25 to 1.95; P<0.0001). Matched hazard ratios (95% CIs) for cardiovascular and HF mortalities and all-cause, cardiovascular, and HF hospitalizations were 1.65 (1.29 to 2.11; P<0.0001), 1.82 (1.28 to 2.57; P<0.0001), 1.16 (1.00 to 1.35; P=0.036), 1.27 (1.08 to 1.50; P=0.004), and 1.29 (1.05 to 1.58; P=0.014), respectively. Among 453 pairs of balanced patients with HF and chronic kidney disease, all-cause mortality occurred in 47% and 38% of patients with mild hypokalemia (3.5 to 3.9 mEq/L) and normokalemia, respectively (matched hazard ratio, 1.31; 95% CI, 1.03 to 1.66; P=0.027). Among 169 pairs of balanced patients with estimated glomerular filtration rate <45 mL/min per 1.73 m², all-cause mortality occurred in 57% and 47% of patients with hypokalemia (<4 mEq/L; mild) and normokalemia, respectively (matched hazard ratio, 1.53; 95% CI, 1.07 to 2.19; P=0.020).

Conclusions—In patients with HF and chronic kidney disease, hypokalemia (serum potassium <4 mEq/L) is common and associated with increased mortality and hospitalization. (Circ Heart Fail. 2010;3:253-260.)

Key Words: heart failure ▪ chronic kidney disease ▪ hospitalization ▪ hypokalemia ▪ mortality ▪ propensity score

Hypokalemia is common in heart failure (HF) and is associated with poor outcomes.1,2 Chronic kidney disease (CKD) is also common in HF and is also associated with poor outcomes.3 However, little is known about the prevalence and effect of hypokalemia in chronic HF patients with CKD. Although hyperkalemia is considered to be a more common potassium-related problem in CKD,4 hypokalemia may potentially be underrecognized in these patients. Therefore, the purpose of this study was to examine the effect of hypokalemia on outcomes in propensity-matched cohorts of patients with chronic HF with CKD.

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Source of Data
The Digitalis Investigation Group (DIG) trial was a randomized, clinical trial of digoxin in HF, conducted in 302 centers in the United States and Canada between 1991 and 1993.5 We obtained a public-use copy of the DIG data from the National Heart, Lung, and Blood Institute. The DIG data were particularly suitable for this analysis because they included a large sample of patients with chronic HF with CKD and did not include any intervention that may have affected potassium homeostasis.

Received August 4, 2009; accepted December 16, 2009.
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Circ Heart Fail is available at http://circheartfailure.ahajournals.org DOI: 10.1161/CIRCHEARTFAILURE.109.899526

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Study Patients
Of the 7788 ambulatory patients with chronic systolic and diastolic HF in normal sinus rhythm enrolled in the DIG trial, 6800 had a left ventricular ejection fraction <45%. More than 90% of DIG participants were receiving angiotensin-converting enzyme inhibitors and ~80% were receiving nonpotassium-sparing diuretics. Patients with a serum creatinine >2.5 mg/dL were excluded. Of the 7788 patients, 6857 (88%) had data on baseline serum potassium. After excluding 579 patients with potassium ≥5 mEq/L, a cohort of 6278 patients was available for these analyses.6

Chronic Kidney Disease
Of the 6278 patients, 2793 (44%) had CKD, defined as an estimated glomerular filtration rate (GFR) <60 mL/min per 1.73 m² body surface area using the Modification of Diet in Renal Disease (MDRD) formula.4,7 To determine whether the effect of hypokalemia in patients with HF with CKD can be replicated in those with more advanced CKD, we assembled a separate cohort of 961 patients with HF with more advanced CKD (stage ≥3B, defined as an estimated GFR <45 mL/min per 1.73 m²).8

Hypokalemia
Although hypokalemia has traditionally been defined as serum potassium <3.5 mEq/L, in patients with HF, potassium levels <4 mEq/L are considered low, and levels between 4 and 5 mEq/L are considered optimal.1,6,9 In patients with HF, potassium levels of <4 and ≥5 mEq/L have been shown to be associated with poor outcomes when compared with 4 to 5 mEq/L.1,6 Therefore, we defined hypokalemia as serum potassium <4 mEq/L and normokalemia as 4 to 4.9 mEq/L. Of the 2793 patients with HF and CKD (GFR <60 mL/min per 1.73 m²), 527 (19%) had hypokalemia. Because hypokalemia was mild (3.5 to 3.9 mEq/L) in 87% of the 527 patients with hypokalemia, we separately examined the effect of mild hypokalemia and more severe hypokalemia (both versus normokalemia). Finally, to determine the effect of hypokalemia in patients with HF with more advanced CKD (GFR <45 mL/min per 1.73 m²), we assembled a cohort of 961 patients with HF with CKD stage ≥3B (estimated GFR <45 mL/min per 1.73 m²). Of these, 178 (19%) had hypokalemia and only 26 (3%) patients had more severe hypokalemia (potassium levels <3.5 mEq/L).

Study Outcomes
The primary outcome of our study was all-cause mortality. Secondary outcomes were cardiovascular and HF mortality, and all-cause, cardiovascular, and HF hospitalizations. Vital status data were complete for 99% of patients during 57 months of follow-up.10

Assembly of Balanced Study Cohorts
Because of the imbalances in baseline patient characteristics between patients with normokalemia and hypokalemia (Table 1 and Figure 1), we used propensity score matching to assemble a cohort in which these 2 groups would be balanced on all measured baseline characteristics.11–16 We began by estimating propensity scores for hypokalemia for each patient by using a nonparsimonious multivariable logistic-regression model.2,16–22 A patient’s propensity score for hypokalemia is his/her probability of having hypokalemia given his/her measured baseline characteristics. In the model, hypokalemia was the dependent variable and 32 measured baseline patient characteristics (Figure 1) and 2 significant clinically important interaction terms (“creatinine by diuretic use” and “creatinine by angiotensin-converting enzyme inhibitor use”) were included as covariates.

The efficacy of the propensity score model was assessed by estimating absolute standardized differences for each covariate between the groups.11,16–23 Standardized differences directly quantify biases in the means (or proportions) of covariates across the groups and are expressed as percentages of the pooled standard deviations,11,13,12,24,25 which are presented as a Love plot.16–22 An absolute standardized difference of 0% on a covariate indicates no residual bias for that covariate, and values <10% suggest inconsequential residual bias.16–22 By using a 1-to-1 greedy matching protocol, described elsewhere in detail, we matched 522 (99% of 527) patients with hypokalemia to 522 patients with normokalemia, who had similar propensity scores.16–22

We repeated the aforementioned process to assemble 3 additional cohorts of patients as follows: (1) using 2724 patients with HF and CKD (GFR <60 mL/min per 1.73 m²) with normokalemia (n=2266) and mild hypokalemia (potassium 3.5 to 3.9 mEq/L; n=458), we assembled a matched cohort of 453 pairs of patients; (2) using 2335 patients with HF and CKD (GFR <60 mL/min per 1.73 m²) with normokalemia (n=2266) and more severe hypokalemia (potassium <3.5 mEq/L; n=69), we assembled a matched cohort of 65 pairs of patients; and (3) using 961 patients with HF and CKD stage ≥3B (GFR <45 mL/min per 1.73 m²), with normokalemia (n=783), and with hypokalemia (potassium <4 mEq/L; n=178), we assembled a matched cohort of 169 pairs of patients.

Statistical Analysis
For descriptive analyses, we used Pearson χ² and Wilcoxon rank-sum tests for the prematch data and the McNemar test and paired-sample t test for postmatch comparisons, as appropriate. Kaplan-Meier plots and matched Cox regression analysis were used to estimate associations of hypokalemia with various outcomes. Matched Cox regression models are essentially stratified Cox regression models, in which the matching variable is the unit for stratification. We confirmed the assumption of proportional hazards by a visual examination of the log (minus log) curves. We conducted a formal sensitivity analysis to quantify the degree of a hidden bias that would need to be present to invalidate conclusions based on significant associations between hypokalemia and outcomes among matched patients.24 To determine the homogeneity of the associations of hypokalemia with all-cause mortality among patients with HF and CKD, we examined the association in various subgroups of matched patients. We then formally tested for first-order interactions by using Cox proportional-hazards models, entering interaction terms for the subgroup (eg, sex by hypokalemia for the sex subgroup). All statistical tests were evaluated with 2-tailed 95% confidence levels, and a P value <0.05 was considered significant. Data analyses were performed with SPSS version 15 for Windows.27

Results

Patient Characteristics
The mean (±SD) age of the 1044 matched patients was 68 (±10) years, 404 (39%) were women, and 105 (10%) were nonwhites. Before matching, patients with mild hypokalemia were more likely to be women, have a history of hypertension and cardiomegaly, and receive diuretics and potassium supplements. These and other prematch imbalances were balanced after matching (Table 1 and Figure 1). Postmatch absolute standardized differences for all observed covariates were <10%, suggesting substantial improvement in covariate balance between the groups (Figure 1).3,16,25 Prematch and postmatch absolute standardized differences for propensity scores were 48.30% and 0.04%, respectively.

Hypokalemia and Mortality in Patients With HF and CKD
All-cause mortality occurred in 48% and 36% of patients with hypokalemia and normokalemia, respectively (matched hazard ratio [HR] when hypokalemia was compared with normokalemia, 1.56; 95% CI, 1.25 to 1.95; P<0.0001; Table 2 and Figure 2). Associations of hypokalemia with cardiovascular and HF mortalities among matched patients are displayed in Table 2.
Hypokalemia and Hospitalization in Patients With HF and CKD

Cardiovascular hospitalization occurred in 59% and 53% of patients with hypokalemia and normokalemia, respectively (matched HR for hypokalemia, 1.27; 95% CI, 1.08 to 1.50; \(P=0.004\); Table 2). Associations of hypokalemia with all-cause and HF hospitalizations among matched patients are displayed in Table 2.

Mild Hypokalemia and Outcomes in Patients With HF and CKD

All-cause mortality occurred in 47% and 38% of patients with mild hypokalemia and normokalemia, respectively (matched HR for mild hypokalemia, 1.31; 95% CI, 1.03 to 1.66; \(P=0.027\); Table 3). Associations of mild hypokalemia with other outcomes are displayed in Table 3.

More Severe Hypokalemia and Outcomes in Patients With HF and CKD

All-cause mortality occurred in 55% and 38% of patients with more severe hypokalemia and normokalemia, respectively (matched HR for more severe hypokalemia, 2.07; 95% CI, 1.12 to 3.83; \(P=0.021\); Table 4). Associations of more severe hypokalemia with other outcomes in patients with HF and CKD are displayed in Table 4. Among the 527 patients with hypokalemia, all-cause mortality occurred in 55% and 47%...
of those with more severe and mild hypokalemia, respectively (propensity-score-adjusted HR for more severe hypokalemia, 1.36; 95% CI, 0.94 to 1.95; \(P = 0.102\); data not shown).

Hypokalemia and Outcomes in Patients With HF and More Advanced CKD

All-cause mortality occurred in 57% and 47% of patients with hypokalemia and normokalemia, respectively (matched HR for hypokalemia, 1.53; 95% CI, 1.07 to 2.19; \(P = 0.020\); Table 5). Associations of hypokalemia with other outcomes in these patients are displayed in Table 5.

Findings From Sensitivity Analyses

For all-cause mortality, in the absence of a hidden bias, a sign-score test for matched data with censoring provided strong evidence (\(P < 0.0001\)) that patients with normokalemia clearly outlived those with hypokalemia. A hidden covariate that is a near-perfect predictor of total mortality would need to increase the odds of hypokalemia by 25.2% to explain away this association. Hypokalemia was also associated with a reduction in cardiovascular mortality (sign-score test \(P = 0.004\)), all-cause hospitalization (sign-score test \(P = 0.003\)), and cardiovascular hospitalization (sign-score test \(P = 0.003\)). A hidden covariate would need to increase the odds of hypokalemia by 28.9%, 8.9%, and 11.1%, respectively, to explain away these associations.

Findings From Subgroups Analyses

The effect of hypokalemia on all-cause mortality was significant only in patients with ischemic heart disease (IHD), but not in those without (\(P\) for interaction, 0.009; Figure 3). The effect of hypokalemia on cardiovascular hospitalization was significant only among matched patients with IHD (HR, 1.35; 95% CI, 1.11 to 1.64; \(P = 0.003\)), but not in those without (HR, 1.13; 95% CI, 0.84 to 1.51; \(P = 0.420\); for interaction, 0.321; data not shown). HRs (95% CIs) for HF hospitalization for matched patients with and without IHD were 1.46 (95% CI, 1.14 to 1.87; \(P = 0.003\)) and 1.00 (95% CI, 0.70 to 1.42; \(P = 0.978\); for interaction, 0.073; data not shown).

Discussion

The findings of this study suggest that in ambulatory patients with chronic HF and CKD receiving angiotensin-converting

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**Table 2. Serum Potassium < 4 mEq/L and Outcomes in Patients With Chronic HF and CKD**

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Serum Potassium 4 to 4.9 mEq/L (n=522)</th>
<th>Serum Potassium &lt; 4 mEq/L (n=522)</th>
<th>Absolute Rate Difference* (per 10 000 Person-Years)</th>
<th>HR (95% CI)</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality All-cause</td>
<td>187 (36); 1276</td>
<td>249 (48); 1864</td>
<td>+587</td>
<td>1.56 (1.25 to 1.95)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>145 (28); 990</td>
<td>204 (39); 1527</td>
<td>+537</td>
<td>1.65 (1.29 to 2.11)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Progressive HF</td>
<td>71 (14); 485</td>
<td>111 (21); 831</td>
<td>+346</td>
<td>1.82 (1.28 to 2.57)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>358 (69); 4403</td>
<td>376 (72); 5288</td>
<td>+885</td>
<td>1.16 (1.00 to 1.35)</td>
<td>0.036</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>275 (53); 2753</td>
<td>309 (59); 3657</td>
<td>+904</td>
<td>1.27 (1.08 to 1.50)</td>
<td>0.004</td>
</tr>
<tr>
<td>Worsening HF</td>
<td>177 (34); 1451</td>
<td>203 (39); 1931</td>
<td>+481</td>
<td>1.29 (1.05 to 1.58)</td>
<td>0.014</td>
</tr>
</tbody>
</table>

*Absolute differences in rates of events per 10 000 person-years of follow-up were calculated by subtracting the event rates in the serum potassium 4 to 4.9 mEq/L group from the event rates in the serum potassium < 4 mEq/L group.
Table 3. Serum Potassium 3.5 to 3.9 mEq/L and Outcomes in Patients With Chronic HF and CKD

<table>
<thead>
<tr>
<th>Events (%)</th>
<th>Rate per 10,000 Person-Years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Serum Potassium 4 to 4.9 mEq/L (n=453)</td>
</tr>
<tr>
<td>Mortality</td>
<td></td>
</tr>
<tr>
<td>All-cause</td>
<td>173 (38); 1401</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>135 (30); 1094</td>
</tr>
<tr>
<td>Progressive HF</td>
<td>60 (13); 486</td>
</tr>
<tr>
<td>Hospitalization</td>
<td></td>
</tr>
<tr>
<td>All-cause</td>
<td>306 (68); 4454</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>227 (50); 2633</td>
</tr>
<tr>
<td>Worsening HF</td>
<td>145 (32); 1408</td>
</tr>
</tbody>
</table>

*Absolute differences in rates of events per 10,000 person-years of follow-up were calculated by subtracting the event rates in the serum potassium 4 to 4.9 mEq/L group from the event rates in the serum potassium 3.5 to 3.9 mEq/L group.

Table 4. Serum Potassium <3.5 mEq/L and Outcomes in Patients With Chronic HF and CKD

<table>
<thead>
<tr>
<th>Events (%)</th>
<th>Rate per 10,000 Person-Years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Serum Potassium 4 to 4.9 mEq/L (n=65)</td>
</tr>
<tr>
<td>Mortality</td>
<td></td>
</tr>
<tr>
<td>All-cause</td>
<td>25 (38); 1276</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>19 (29); 969</td>
</tr>
<tr>
<td>Progressive HF</td>
<td>9 (14); 459</td>
</tr>
<tr>
<td>Hospitalization</td>
<td></td>
</tr>
<tr>
<td>All-cause</td>
<td>52 (80); 5714</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>44 (68); 3894</td>
</tr>
<tr>
<td>Worsening HF</td>
<td>30 (46); 1974</td>
</tr>
</tbody>
</table>

*Absolute differences in rates of events per 10,000 person-years of follow-up were calculated by subtracting the event rates in the serum potassium 4 to 4.9 mEq/L group from the event rates in the serum potassium <3.5 mEq/L group.

enzyme inhibitors and nonpotassium-sparing diuretics, hypokalemia (<4 mEq/L) was common and associated with increased mortality and hospitalizations. Furthermore, we demonstrate that hypokalemia was mild (3.5 to 3.9 mEq/L) in most patients, and that even mild hypokalemia was associated with poor outcomes. In addition, hypokalemia also increased the risk of death in those with more advanced CKD (GFR <45 mL/min per 1.73 m²). To the best of our knowledge, this is the first report of an association between hypokalemia and poor outcomes in propensity-matched cohorts of patients with HF and CKD. The findings are important, as both CKD and hypokalemia are highly prevalent in HF. Although the presence of CKD increases the risk of hyperkalemia and associated complications, these findings demonstrate that underestimating the presence and the risk of hypokalemia in patients with HF with CKD is also a concern.

There are several potential explanations for the associations between hypokalemia and poor outcomes in patients with chronic HF and CKD: confounding by imbalances in measured baseline characteristics, confounding by unmeasured baseline characteristics, and/or an intrinsic effect of low serum potassium. Bivariate associations between hypokalemia and poor outcomes may potentially be explained by residual bias. However, all measured baseline characteristics were well balanced among our propensity-matched patients with normokalemia and hypokalemia. Therefore, hypokalemia-associated poor outcomes observed in our study may not be explained by imbalances in any of the measured baseline characteristics.

Confounding by an unmeasured baseline characteristic may also explain the poor outcomes associated with hypokalemia. For example, we had no data on diuretic doses that may be a potential confounder, because sicker patients with HF were more likely to receive larger doses of diuretics and develop more severe hypokalemia. Diuretic use is associated with poor outcomes that has been shown to be dose-dependent.16,28,29 Although the prevalence of diuretic use was similar, it is possible that those with hypokalemia were using higher doses of diuretics. However, this is unlikely to explain away the observed associations, as the findings from our sensitivity analysis suggest that these associations were robust and rather insensitive to the potential confounding effect of an unmeasured covariate. Furthermore, the potential effect of an unmeasured confounder can also be indirectly assessed by examining balance on variables that might be strongly correlated with that unmeasured confounder.23 For example, New York Heart Association class and symptoms and signs of fluid volume overload would be strongly correlated with the diuretic doses. However, in our study, these markers of higher diuretic doses were balanced after matching, suggest-
ing that any confounding effect by diuretic dose would likely be minimal. Finally, the observation that the associations between hypokalemia and poor outcomes were observed at various degrees of hypokalemia and at various stages of CKD also highlights the robustness of those associations.

The notion that the associations between hypokalemia and poor outcomes may be intrinsic in nature is biologically plausible. Hypokalemia is known to enhance membrane excitability, increase cardiac automaticity, delay ventricular repolarization, and predispose patients to reentrant arrhythmias.30–33 Hypokalemia-associated deaths have often been attributed to cardiac arrhythmias and sudden cardiac death. We have previously demonstrated that in patients with HF with and without CKD, hypokalemia was associated with increased risk of death without an increase in hospitalization, suggesting sudden death may have precluded hospitalization in those patients.1,2 However, in this analysis, we observed that hypokalemia was associated with both increased death and hospitalization, suggesting that the effect of hypokalemia in patients with HF with CKD may be both sudden and nonsudden in nature. The progressive deleterious effects of hypokalemia in patients with HF with CKD may also be mediated by aldosterone, which has been shown to cause myocardial fibrosis, diastolic dysfunction, and disease progression in HF.33–36 Although the effect of hypokalemia in the setting of acute myocardial infarction is well known,37–39

### Table 5. Serum Potassium <4 mEq/L and Outcomes in Patients With Chronic HF and CKD Stage ≥3B (Estimated GFR <45 mL/min per 1.73 m²)

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Serum Potassium 4–4.9 mEq/L (n=169)</th>
<th>Serum Potassium &lt;4 mEq/L (n=169)</th>
<th>Absolute Rate Difference* (per 10 000 Person-Years)</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mortality</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause</td>
<td>80 (47); 1822</td>
<td>97 (57); 2487</td>
<td>+665</td>
<td>1.53 (1.07 to 2.19)</td>
<td>0.020</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>63 (37); 1435</td>
<td>79 (47); 2026</td>
<td>+591</td>
<td>1.49 (1.00 to 2.21)</td>
<td>0.049</td>
</tr>
<tr>
<td>Progressive HF</td>
<td>25 (15); 569</td>
<td>53 (31); 1359</td>
<td>+790</td>
<td>2.47 (1.41 to 4.34)</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>Hospitalization</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause</td>
<td>119 (70); 5085</td>
<td>135 (80); 7258</td>
<td>+2173</td>
<td>1.54 (1.11 to 2.14)</td>
<td>0.010</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>93 (55); 3218</td>
<td>109 (64); 4781</td>
<td>+1563</td>
<td>1.33 (0.94 to 1.90)</td>
<td>0.110</td>
</tr>
<tr>
<td>Worsening HF</td>
<td>68 (40); 1960</td>
<td>71 (42); 2383</td>
<td>+423</td>
<td>1.26 (0.83 to 1.93)</td>
<td>0.282</td>
</tr>
</tbody>
</table>

*Absolute differences in rates of events per 10 000 person-years of follow-up were calculated by subtracting the event rates in the serum potassium 4 to 4.9 mEq/L group from the event rates in the serum potassium <4 mEq/L group.

Figure 3. Association of hypokalemia (serum potassium <4 mEq/L) with all-cause mortality in subgroups of patients with chronic HF with CKD.
little is known about the effect of hypokalemia in patients with chronic IHD. Even though the prevalence of hypokalemia was lower in patients with IHD (Table 1, prematch), the effects of hypokalemia were worse in those with IHD (Figure 3), suggesting that infarcted/ischemic myocardium may provide a more suitable substrate for the adverse effects of hypokalemia.

An interesting observation of our study is that the prevalence of hypokalemia in patients with HF and CKD was high (19%) and similar to that in patients with HF in general. Among the 3739 patients without CKD and with valid serum potassium levels (excluded from the current analysis), only 18% had potassium <4 mEq/L (data not shown). This is important, as hyperkalemia is often considered a more common problem of potassium homeostasis in patients with CKD. However, findings from our study suggest that hypokalemia is common in patients with HF and CKD receiving angiotensin-converting enzyme inhibitors and that even a mild reduction in serum potassium level (3.5 to 3.9 mEq/L) was associated with poor outcomes. These findings are important because patients with HF and CKD often require larger doses of diuretics, thus increasing their risk of hypokalemia. Yet, hypokalemia in these patients is less likely to be treated for fear of causing hyperkalemia. Therefore, taken together with our previous reports and expert opinions, it may be suggested that serum potassium should be routinely monitored in patients with HF with CKD and carefully maintained between 4 and 5 mEq/L.1,2,6,9,40

There are a few limitations of our study. We used the MDRD formula to estimate GFR that may underestimate GFR in patients with GFR >60 mL/min per 1.73 m². However, all patients in our analysis had an estimated GFR <60 mL/min per 1.73 m². Furthermore, we were able to replicate our key findings in more patients with advanced CKD. As previously mentioned, diuretic dose was not available. B-type natriuretic peptide levels were also not available and could have provided further data on HF severity. Findings of our study are based on predominantly white men in normal sinus rhythm. Data on β-blocker use were not collected in the Digi trial, as these drugs were not approved for use in HF at that time. The transfer of potassium from plasma into cells is facilitated by stimulation of β2 receptors. Therefore, the prevalence of hypokalemia may be somewhat lower in patients receiving carvedilol and metoprolol extended-release, the 2 most commonly used β-blockers in HF. However, the effect of hypokalemia on outcomes is unlikely to be substantially different from that observed in our study. Future studies may examine the effect of hypokalemia in contemporary patients with HF with CKD.

In conclusion, in ambulatory patients with chronic HF and CKD, hypokalemia (<4 mEq/L) is common and associated with increased mortality and hospitalization. Furthermore, hypokalemia in these patients is mostly mild (3.5 to 3.9 mEq/L), indicating that even mild hypokalemia is associated with poor outcomes. Serum potassium should be routinely monitored in patients with HF with CKD and should be carefully maintained between 4 and 5 mEq/L.

Acknowledgments
The DIG study was conducted and supported by the National Heart, Lung, and Blood Institute in collaboration with the DIG Investigators. This manuscript was prepared with use of a limited-access dataset obtained by the National Heart, Lung, and Blood Institute and does not necessarily reflect the opinions or views of the DIG Study or the National Heart, Lung, and Blood Institute.

Sources of Funding
Dr Ahmed was supported by the National Institutes of Health through grants (R01-HL085561 and R01-HL097047) from the National Heart, Lung, and Blood Institute and a gift from Jean B. Morris of Birmingham, Alabama; Dr Sanders was supported by the National Institutes of Health grants R01 DK046199 and P30 DK079337.

Disclosures
None.

References

**CLINICAL PERSPECTIVE**

In patients with chronic kidney disease (CKD), a high serum potassium level, or hyperkalemia, is considered to be a more common potassium imbalance of concern than low serum potassium, or hypokalemia. In patients with chronic heart failure (HF), on the other hand, hypokalemia is more common (than hyperkalemia) and has been shown to be associated with increased mortality in these patients. CKD is common in chronic HF, yet little is known about the prevalence and impact of hypokalemia in patients with chronic HF with CKD. The findings of this study demonstrate that approximately one fifth of all patients with HF with CKD had hypokalemia, as defined by a serum potassium level <4 mEq/L, and the vast majority of these patients had mild hypokalemia (serum potassium between 3.5 and 4 mEq/L). The presence of hypokalemia, even mild hypokalemia, was associated with a significant increased risk of mortality and hospitalization in patients with HF and CKD during 57 months of follow-up. Low-serum potassium was similarly associated with a significant higher risk of poor outcomes in patients with HF with more advanced CKD (estimated glomerular filtration rate, <45 mL/min per 1.73 m²). These findings are important, as the presence and danger of hypokalemia in patients with HF with CKD may potentially be underestimated. In patients with HF and CKD, hypokalemia was common and mostly mild and was associated with poor outcomes. Serum potassium should be routinely monitored and maintained between 4 and 5 mEq/L to avoid even mild hypokalemia in patients with HF and CKD.
Hypokalemia and Outcomes in Patients With Chronic Heart Failure and Chronic Kidney Disease: Findings From Propensity-Matched Studies

_Circ Heart Fail._ 2010;3:253-260; originally published online January 26, 2010;
doi: 10.1161/CIRCHEARTFAILURE.109.899526

_Circulation: Heart Failure_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-3289. Online ISSN: 1941-3297

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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