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

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Abstract

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

Methods and Results—Of the 7788 chronic HF patients in the Digitalis Investigation Group trial, 2793 had CKD, defined as estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2. Of these, 527 had hypokalemia (serum potassium <4 mEq/L) and 2266 had normokalemia (4–4.9 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 {HR} when hypokalemia was compared with normokalemia, 1.56, 95% confidence interval {CI}, 1.25–1.95; P<0.0001). Matched HR's (95% CI's) for cardiovascular and HF mortalities, and all-cause, cardiovascular and HF hospitalizations were 1.65 (1.29–2.11; P<0.0001), 1.82 (1.28–2.57; P<0.0001), 1.16 (1.00–1.35; P=0.036), 1.27 (1.08–1.50; P=0.004) and 1.29 (1.05–1.58; P=0.014) respectively. Among 453 pairs of balanced patients with HF and CKD, all-cause mortality occurred in 47% and 38% of patients with mild hypokalemia (3.5–3.9 mEq/L) and normokalemia respectively (matched HR, 1.31, 95% CI, 1.03–1.66; P=0.027). Among 169 pairs of balanced patients with eGFR <45 ml/min/1.73 m^2, all-cause mortality occurred in 57% and 47% of patients with hypokalemia (<4 mEq/L) and normokalemia respectively (matched HR, 1.53, 95% CI, 1.07–2.19; P=0.020).

Conclusions—In patients with HF and CKD, hypokalemia is common and associated with increased mortality and hospitalization.

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Conflict of Interests

No authors have any conflicts of interest in relation to this manuscript.

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. While hyperkalemia is considered to be a more common potassium-related problem in CKD,[4] hypokalemia may be potentially under-recognized in these patients. Therefore, the purpose of this study was to examine the effect of hypokalemia on outcomes in propensity-matched cohorts of chronic HF patients with CKD.

METHODS

Source of Data

The Digoxin 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 was particularly suitable for the current analysis as it included a large sample of chronic HF patients with CKD and did not include any intervention that may have affected potassium homeostasis.

Study Patients

Of the 7788 ambulatory chronic systolic and diastolic HF patients in normal sinus rhythm enrolled in the DIG trial, 6800 had a left ventricular ejection fraction ≤45%. Over 90% of DIG participants were receiving angiotensin-converting enzyme (ACE) inhibitors and nearly 80% were receiving non-potassium-sparing diuretics. At the time of the DIG trial, beta-blockers were not approved for use in HF. Patients with a serum creatinine >2.5mg/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 were available for these analyses.[6]

Chronic Kidney Disease

Of the 6278 patients, 2793 (44%) had CKD, defined as an estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2 body surface area.[4, 7] To determine if the effect of hypokalemia in HF patients with CKD can be replicated in those with more advanced CKD, we assembled a separate cohort of 961 HF patients with more advanced CKD (Stage ≥3B, defined as eGFR <45 ml/min/1.73 m^2).[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 HF patients, potassium levels of <4 and ≥5 mEq/L have been shown to be associated with poor outcomes when compared with 4–5 mEq/L.[1, 6] Therefore, we defined hypokalemia as potassium <4 mEq/L and normokalemia as 4–4.9 mEq/L. Of the 2793 patients with HF and CKD (eGFR <60 ml/min/1.73 m^2), 527 (19%) had hypokalemia.

Because hypokalemia was mild (3.5–3.9 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 HF patients with more advanced CKD (eGFR <45 ml/min/1.73 m^2), we assembled a cohort of 961 HF patients with CKD Stage ≥3B (eGFR <45 ml/min/1.73 m^2). Of these, 178 (19%) had hypokalemia and only 26 (3%) patients had more severe hypokalemia (potassium <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 two groups would be balanced on all measured baseline characteristics. [11–16] We began by estimating propensity scores for hypokalemia for each patient using a non-parsimonious multivariable logistic regression model.[2, 16–22] A patient's propensity 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 two 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.[13, 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, 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% suggests inconsequential residual bias.[16–22] Using a 1 to 1 greedy matching protocol, described elsewhere in detail, we matched 522 (99% of 527) patients with hypokalemia with 522 patients with normokalemia, who had similar propensity scores.[16–22]

We repeated the above process to assemble three additional cohorts of patients as follows: (1) Using 2724 HF and CKD (GFR <60 ml/min/1.73 m^2) patients with normokalemia (n=2266) and mild hypokalemia (potassium 3.5–3.9 mEq/L; n=458), we assembled a matched cohort of 453 pairs of patients; (2) Using 2335 HF and CKD (GFR <60 ml/min/1.73 m^2) patients 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/1.73 m^2) with normokalemia (n=783) and 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 Chi square and Wilcoxon rank-sum tests for the pre-match data, and McNemar's test and paired sample t-test for post-match 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.[27] 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 using Cox proportional hazards models, entering interaction terms for the subgroup (e.g. sex by hypokalemia for the sex subgroup). All statistical tests were evaluated using two-tailed 95% confidence levels

and a p-value <0.05 considered significant. Data analyses were performed using SPSS for Windows version 15.[26]

RESULTS

Patient Characteristics

The mean (±SD) age of the 1044 matched patients was 68 (±10) years, 404 (39%) were women and 105 (10%) were non-whites. 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 pre-match imbalances were balanced after matching (Table 1 and Figure 1). Post-match absolute standardized differences for all observed covariates were below 10% suggesting substantial improvement in covariate balance between the groups (Figure 1).[3, 16, 25] Pre- and post-match absolute standardized differences for propensity scores were 48.3% 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% confidence interval {CI}, 1.25–1.95; 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, 1.27, 95% CI, 1.08–1.50; 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, 1.31, 95% CI, 1.03–1.66; 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, 2.07, 95% CI, 1.12–3.83; 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, 0.94–1.95; P=0.102).

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, 1.53, 95% CI, 1.07–2.19; 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 reduction in cardiovascular mortality (sign-score test P <0.0001), all-cause hospitalization (sign-score test P =0.004) and cardiovascular hospitalization (sign-score test P=0.003), and 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 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, 1.11–1.64; P=0.003), but not in those without (HR, 1.13, 95% CI, 0.84–1.51; P=0.420; p for interaction, 0.321; *data not shown*). HR's (95% CIs) for HF hospitalization for matched patients with and without IHD were 1.46, 95% CI, 1.14–1.87; P=0.003) and 1.00 (95% CI, 0.70–1.42; P=0.978; p for interaction, 0.073; *data not shown*).

DISCUSSION

The findings of the current study suggest that in ambulatory patients with chronic HF and CKD receiving ACE inhibitors and non-potassium-sparing diuretics, hypokalemia (<4 mEq/L) was common and was associated with increased mortality and hospitalizations. Further, we demonstrate that hypokalemia was mild (3.5–3.9 mEq/L) in most patients, and that even mild hypokalemia was associated with poor outcomes. Additionally, hypokalemia also increased risk of death in those with more advanced CKD (eGFR <45 ml/min/1.73 m^2). To the best of our knowledge this is the first report of an association between hypokalemia and poor outcomes in propensity-matched cohorts of HF patients with CKD. The findings are important as both CKD and hypokalemia are highly prevalent in HF. While 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 HF patients 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 potentially explain the poor outcomes associated with hypokalemia. For example, we had no data on diuretic doses, which may be a potential confounder, as sicker HF patients were more likely to receive larger doses of diuretics and develop more severe hypokalemia. Diuretic use is associated with poor outcomes, which 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. Further, 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, NYHA 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, suggesting 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 HF patients 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 the current analysis, we observed that hypokalemia was associated with both increased death and hospitalization, suggesting that the effect of hypokalemia in HF patients with CKD may be both sudden and non-sudden in nature. The progressive deleterious effects of hypokalemia in HF patients 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] little is known about the effect of hypokalemia in patients with chronic IHD. Although the prevalence of hypokalemia was lower in patients with IHD (Table 1, pre-match), 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 HF patients in general.[1, 2] Among the 3739 patients *without* CKD and with valid serum potassium (*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 ACE inhibitors and that even a mild reduction in serum potassium level (3.5–3.9 mEq/L) was associated with poor outcomes. These findings are important because patients with HF and CKD often require larger doses of diuretics 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 prior reports and expert opinions, it may be suggested that serum potassium should be routinely monitored in HF patients with CKD and carefully maintained between 4 and 5 mEq/L.[1, 2, 6, 9, 40]

There are a few limitations of our study. The MDRD formula may underestimate GFR in patients with GFR >60 ml/min/1.73 m^2.[41] However, all patients in our analysis had eGFR <60 ml/min/1.73 m^2. Further, we were able to replicate our key findings in more advanced CKD patients. As previously mentioned, diuretic dose was not available. B-type natriuretic peptide (BNP) 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 beta-blocker use was not collected in the DIG 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 beta-2 receptors.[42–44] Therefore, the prevalence of hypokalemia may be somewhat lower in patients receiving carvedilol and metoprolol extended-release, the two most commonly used beta-blockers in HF.[45] 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 HF patients 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. Further, hypokalemia in these patients is mostly mild (3.5–3.9 mEq/L) but even the mild hypokalemia is associated with poor outcomes. Serum potassium should be routinely monitored in HF patients with CKD, and should be carefully maintained between 4 and 5 mEq/L.

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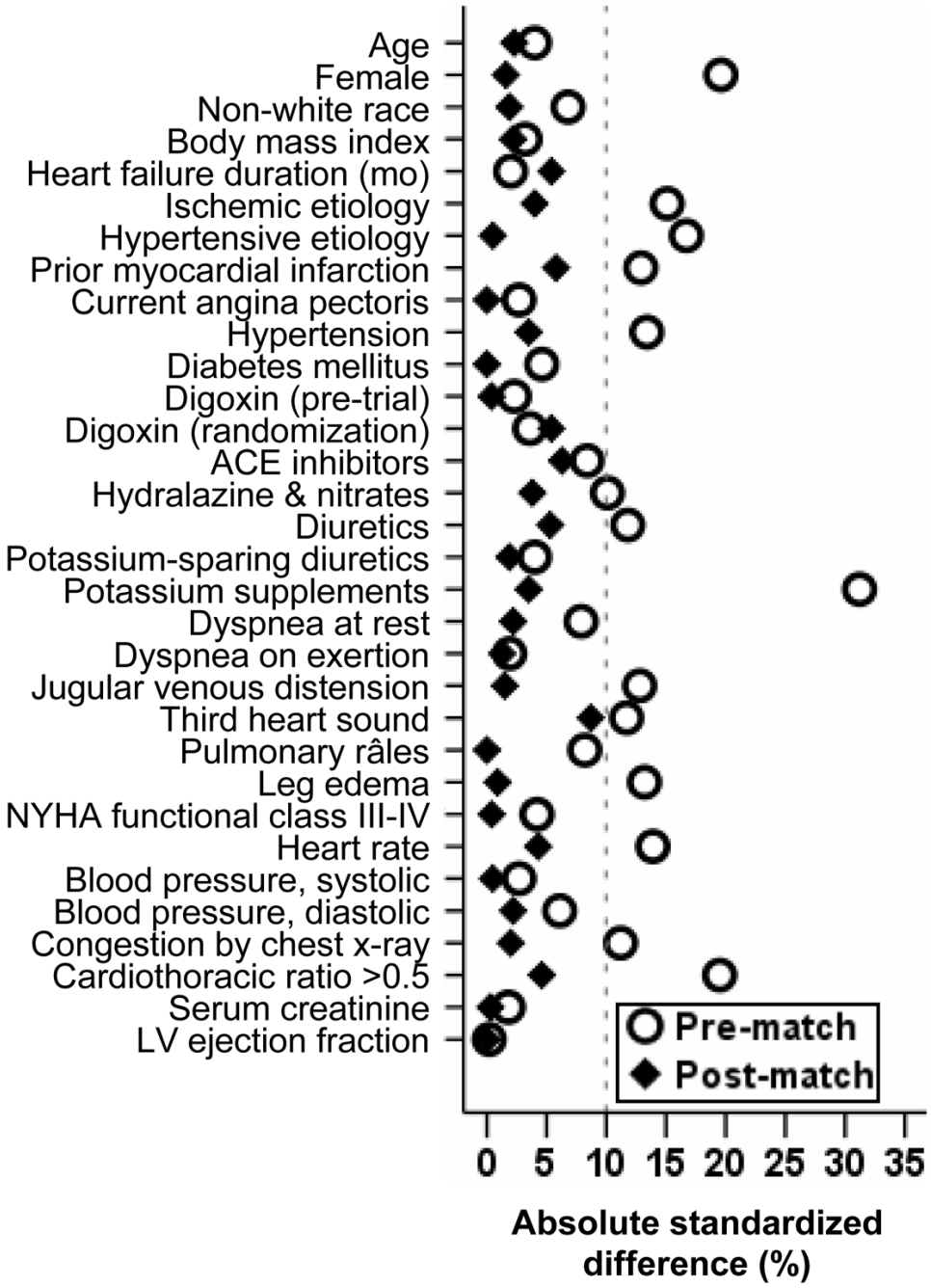
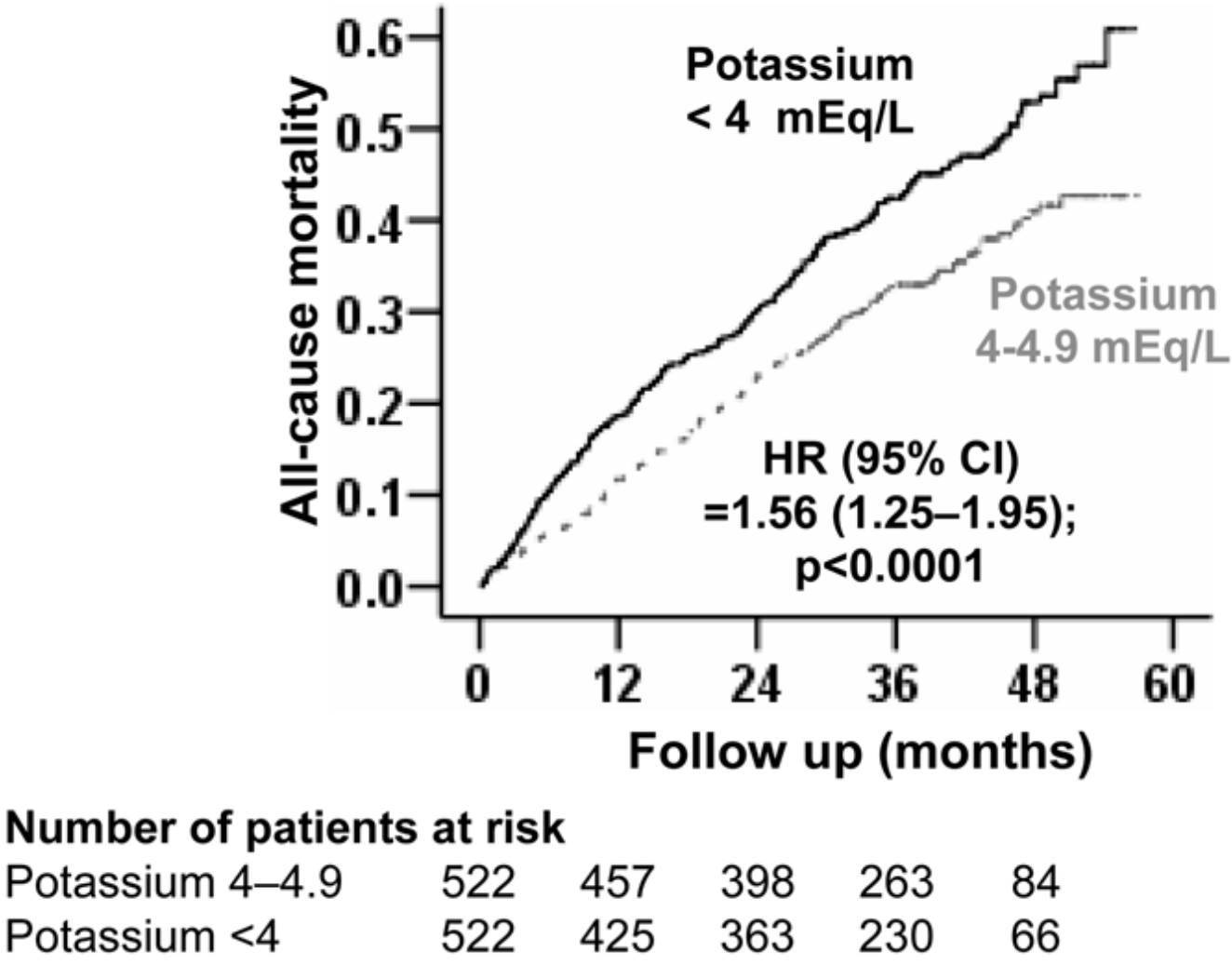


Figure 1.

Love plot displaying pre- and post-match absolute standardized differences for baseline covariates between patients with normokalemia (4–4.9 mEq/L) and hypokalemia (<4 mEq/L)



Number of patients at risk

Potassium 4–4.9	522	457	398	263	84
Potassium <4	522	425	363	230	66

Figure 2.
Kaplan-Meier plots for all-cause mortality by serum potassium levels

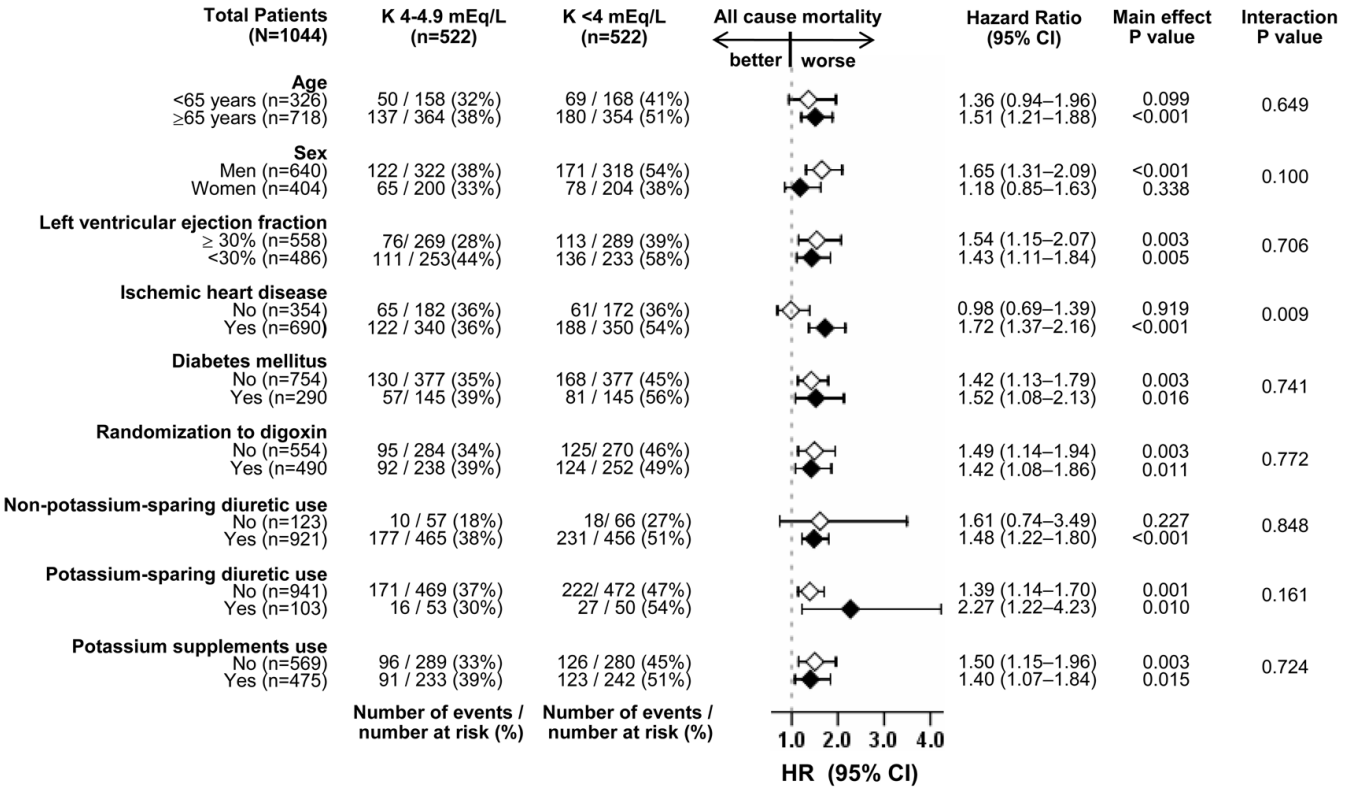


Figure 3.

Association of hypokalemia (serum potassium <4 mEq/L) with all-cause mortality in subgroups of patients with chronic heart failure with chronic kidney disease

Circ Heart Fail. Author manuscript; available in PMC 2011 March 1.

Table 1

Baseline characteristics of chronic heart failure patients with chronic kidney disease, by potassium levels, before and after propensity score matching

Variable	Before matching			After matching		
	Potassium 4–4.9 mEq/L (n = 2266)	Potassium <4 mEq/L (n = 527)	P value	Potassium 4–4.9 mEq/L (n = 522)	Potassium <4 mEq/L (n = 522)	P value
Age, years	68 ± 9	68 ± 10	0.405	68 ± 10	68 ± 10	0.718
Female	680 (30%)	207 (39%)	<0.001	200 (38%)	204 (39%)	0.830
Non-white	180 (8%)	52 (10%)	0.150	54 (10%)	51 (10%)	0.830
Body mass index, kg/m^2	27 ± 5	27 ± 5	0.507	27 ± 5	27 ± 5	0.729
Duration of heart failure, months	30 ± 37	29 ± 37	0.684	28 ± 36	29 ± 37	0.379
Ischaemic heart disease	1674 (74%)	353 (67%)	0.001	340 (65%)	350 (67%)	0.513
Prior myocardial infarction	1508 (67%)	318 (60%)	0.007	300 (58%)	315 (60%)	0.361
Hypertension	1113 (49%)	294 (56%)	0.006	298 (57%)	289 (55%)	0.596
Diabetes mellitus	675 (30%)	146 (28%)	0.344	145 (28%)	145 (28%)	1.000
Medications						
Pre-trial digoxin use	942 (42%)	225 (43%)	0.638	221 (50%)	222 (50%)	1.000
Trial use of digoxin	1133 (50%)	254 (48%)	0.456	238 (46%)	252 (48%)	0.409
Angiotensin-converting enzyme inhibitors	2096 (93%)	475 (90%)	0.071	484 (93%)	475 (91%)	0.362
Diuretics	1888 (83%)	461 (88%)	0.019	465 (89%)	456 (87%)	0.439
Potassium-sparing diuretics	189 (8%)	50 (10%)	0.397	53 (10%)	50 (10%)	0.838
Potassium supplement	721 (32%)	247 (47%)	<0.001	233 (45%)	242 (46%)	0.504
Symptoms and signs of heart failure						
Dyspnea on exertion	1751 (77%)	403 (77%)	0.693	395 (78%)	398 (76%)	0.882
Jugular venous distension	299 (13%)	94 (18%)	0.006	87 (17%)	90 (17%)	0.858
Third heart sound	549 (24%)	155 (29%)	0.014	173 (33%)	152 (29%)	0.182
Pulmonary râles	384 (17%)	106 (20%)	0.085	103 (20%)	103 (20%)	1.000
Lower extremity edema	507 (22%)	148 (28%)	0.005	146 (28%)	144 (28%)	0.942
New York Heart Association class III–IV	822 (36%)	202 (38%)	0.378	196 (38%)	197 (38%)	0.949
Heart rate, beats per minute	78 ± 13	80 ± 13	0.004	79 ± 13	80 ± 13	0.471
Systolic blood pressure, mm Hg	129 ± 21	129 ± 23	0.569	129 ± 23	129 ± 23	0.933

Variable	Before matching			After matching		
	Potassium 4–4.9 mEq/L (n = 2266)	**Potassium <4 mEq/L (n = 527)**	**P value**	**Potassium 4–4.9 mEq/L (n = 522)**	**Potassium <4 mEq/L (n = 522)**	**P value**
Diastolic blood pressure, mm Hg	74 ± 11	75 ± 12	0.206	75 ± 11	75 ± 12	0.715
Chest radiograph findings						
Pulmonary congestion	327 (14%)	98 (19%)	0.016	99 (19%)	95 (18%)	0.793
Cardiothoracic ratio >0.5	1400 (62%)	374 (71%)	<0.001	358 (69%)	369 (71%)	0.472
Serum creatinine, mg/dL	1.53 ± 0.34	1.53 ± 0.40	0.703	1.52 ± 0.35	1.52 ± 0.39	0.963
Estimated GFR, ml/min/1.73 m^2	47 ± 9	47 ± 10	0.527	47 ± 9	47 ± 10	0.701
Ejection fraction, %	32 ± 13	32 ± 14	0.969	33 ± 14	32 ± 14	0.995

Values are presented as n (%) or mean ± standard deviation. GFR=glomerular filtration rate

Table 2

Serum potassium <4 mEq/L and outcomes in patients with chronic HF and CKD

	Events (%); rate per 10,000 person-years				
Outcomes	**Serum potassium 4–4.9 mEq/L (N=522)**	**Serum potassium <4 mEq/L (N=522)**	**Absolute rate difference* (per 10,000 person-years)**	**HR (95% CI)**	**P value**
Mortality					
All-cause	187 (36%); 1276	249 (48%); 1864	+ 587	1.56 (1.25–1.95)	<0.001
Cardiovascular	145 (28%); 990	204 (39%); 1527	+ 537	1.65 (1.29–2.11)	<0.001
Progressive HF	71 (14%); 485	111 (21%); 831	+ 346	1.82 (1.28–2.57)	<0.001
Hospitalization					
All-cause	358 (69%); 4403	376 (72%); 5288	+ 885	1.16 (1.00–1.35)	0.036
Cardiovascular	275 (53%); 2753	309 (59%); 3657	+ 904	1.27 (1.08–1.50)	0.004
Worsening HF	177 (34%); 1451	203 (39%); 1931	+ 481	1.29 (1.05–1.58)	0.014

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

Table 3

Serum potassium 3.5–3.9 mEq/L and outcomes in patients with chronic HF and CKD

	Events (%); rate per 10,000 person-years				
Outcomes	**Serum potassium 4–4.9 mEq/L (N=453)**	**Serum potassium 3.5–3.9 mEq/L (N=453)**	**Absolute rate difference* (per 10,000 person-years)**	**HR (95% CI)**	**P value**
Mortality					
All-cause	173 (38%); 1401	212 (47%); 1819	+ 418	1.31 (1.03–1.66)	0.027
Cardiovascular	135 (30%); 1094	176 (39%); 1511	+ 417	1.34 (1.03–1.74)	0.030
Progressive HF	60 (13%); 486	92 (20%); 790	+ 304	1.58 (1.06–2.34)	0.025
Hospitalization					
All-cause	306 (68%); 4454	320 (71%); 5031	+ 577	1.17 (0.96–1.44)	0.121
Cardiovascular	227 (50%); 2633	264 (58%); 3515	+ 882	1.31 (1.05–1.64)	0.016
Worsening HF	145 (32%); 1408	171 (38%); 1851	+ 443	1.29 (0.99–1.67)	0.057

*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

	Events (%); rate per 10,000 person-years				
Outcomes	**Serum potassium 4–4.9 mEq/L (N=65)**	**Serum potassium <3.5 mEq/L (N=65)**	**Absolute rate difference* (per 10,000 person-years)**	**HR (95% CI)**	**P value**
Mortality					
All-cause	25 (38%); 1276	36 (55%); 2236	+ 961	2.07 (1.12–3.83)	0.021
Cardiovascular	19 (29%); 969	27 (42%); 1677	+ 708	2.09 (1.02–4.29)	0.044
Progressive HF	9 (14%); 459	20 (31%); 1242	+ 783	2.83 (1.12–7.19)	0.028
Hospitalization					
All-cause	52 (80%); 5714	55 (85%); 8209	+ 2495	1.18 (0.71–1.95)	0.523
Cardiovascular	44 (68%); 3894	44 (68%); 5116	+ 1222	1.29 (0.76–2.20)	0.347
Worsening HF	30 (46%); 1974	33 (51%); 2821	+ 847	1.24 (0.65–2.34)	0.517

*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.

Table 5

Serum potassium <4 mEq/L and outcomes in patients with chronic HF and stage ≥3B CKD (eGFR <45 ml/min/1.73 m^2)

	Events (%); rate per 10,000 person-years				
Outcomes	**Serum potassium 4–4.9 mEq/L (N=169)**	**Serum potassium <4 mEq/L (N=169)**	**Absolute rate difference* (per 10,000 person-years)**	**HR (95% CI)**	**P value**
Mortality					
All-cause	80 (47%); 1822	97 (57%); 2487	+ 665	1.53 (1.07–2.19)	0.020
Cardiovascular	63 (37%); 1435	79 (47%); 2026	+ 591	1.49 (1.00–2.21)	0.049
Progressive HF	25 (15%); 569	53 (31%); 1359	+ 790	2.47 (1.41–4.34)	0.002
Hospitalization					
All-cause	119 (70%); 5085	135 (80%); 7258	+ 2173	1.54 (1.11–2.14)	0.010
Cardiovascular	93 (55%); 3218	109 (64%); 4781	+ 1563	1.33 (0.94–1.90)	0.110
Worsening HF	68 (40%); 1960	71 (42%); 2383	+ 423	1.26 (0.83–1.93)	0.282

*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.