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Mild hyperkalemia and outcomes in chronic heart failure: A propensity matched study

Mustafa I. Ahmed, MD[1], **O. James Ekundayo, MD, DrPH**[1], **Marjan Mujib, MBBS**[1], **Ruth C. Campbell, MD**[1], **Paul W. Sanders, MD**[1,2], **Bertram Pitt, MD**[3], **Gilbert J. Perry, MD**[1,2], **George Bakris, MD**[4], **Inmaculada Aban, PhD**[1], **Thomas E. Love, PhD**[5], **Wilbert S. Aronow, MD**[6], and **Ali Ahmed, MD, MPH**[1,2]

[1] University of Alabama at Birmingham, Birmingham, Alabama, USA

[2] VA Medical Center, Birmingham, Alabama, USA

[3] University of Michigan, Ann Arbor, Michigan, USA

[4] University of Chicago, Chicago, Illinois, USA

[5] Case Western Reserve University, Cleveland Ohio, USA

[6] New York Medical College, Valhalla, New York, USA

Abstract

Background—Compared with serum potassium levels 4–5.5 mEq/L, those <4 mEq/L have been shown to increase mortality in chronic heart failure (HF). Expert opinions suggest that serum potassium levels >5.5 mEq/L may be harmful in HF. However, little is known about the safety of serum potassium 5–5.5 mEq/L.

Methods—Of the 7788 chronic HF patients in the Digitalis Investigation Group trial, 5656 had serum potassium 4–5.5 mEq/L. Of these, 567 had mild hyperkalemia (5–5.5 mEq/L) and 5089 had normokalemia (4–4.9 mEq/L). Propensity scores for mild hyperkalemia were used to assemble a balanced cohort of 548 patients with mild hyperkalemia and 1629 patients with normokalemia. Cox regression models were used to estimate hazard ratios (HR) and 95% confidence intervals (CI) for association between mild hyperkalemia and mortality during a median follow-up of 38 months.

Results—All-cause mortality occurred in 36% and 38% of matched patients with normokalemia and mild hyperkalemia respectively (HR, 1.07; 95% CI, 0.90–1.26; P= 0.458). Unadjusted, multivariable-adjusted, and propensity-adjusted HRs for mortality associated with mild hyperkalemia were 1.33 (95% CI, 1.15–1.52; P<0.0001), 1.16 (95% CI, 1.01–1.34; P=0.040) and 1.13 (95% CI, 0.98–1.31; P=0.091) respectively. Mild hyperkalemia had no association with cardiovascular or HF mortality or all-cause or cardiovascular hospitalization.

Conclusion—Serum potassium 4–4.9 mEq/L is optimal and 5–5.5 mEq/L appears relatively safe in HF. Despite lack of an intrinsic association, the bivariate association of mild-hyperkalemia with mortality suggests that it may be useful as a biomarker of poor prognosis in HF.

*Corresponding author: Ali Ahmed, MD, MPH, University of Alabama at Birmingham, 1530 3rd Ave South, CH-19, Ste-219, Birmingham AL 35294-2041; Telephone: 1-205-934-9632; Fax: 1-205-975-7099; Email: aahmed@uab.edu.

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Keywords

Mild hyperkalemia; heart failure; mortality; hospitalization

1. Introduction

According to the American College of Cardiology and American Heart Association 2005 guidelines for chronic heart failure (HF), many experts believe that in patients with chronic HF serum potassium levels between 4 and 5 mEq/L may be optimal [1]. However, other experts have suggested that serum potassium levels up to 5.5 may be beneficial and safe in chronic HF [2]. We have previously demonstrated that compared with serum potassium levels between 4 and 5.5 mEq/L, serum potassium levels <4 mEq/L are associated with increased risk of death in chronic HF [3]. However, there is little data concerning the safe upper limit for serum potassium in chronic HF. The objective of the current propensity-matched study was to compare outcomes of chronic HF patients with serum potassium 4–4.9 mEq/L with those with serum potassium 5–5.5 mEq/L.

2. Materials and methods

2.1. Source of data

We used public-use copies of the Digitalis Investigation Group (DIG) trial datasets obtained from the National Heart, Lung, and Blood Institute (NHLBI) for the current analysis. The rationale, design and results of the DIG trial have been previously published in detail [4,5]. In brief, 7788 chronic HF patients (6800 with left ventricular ejection fraction ≤45%) were recruited from 302 centers (186 in the United States and 116 in Canada) during 1991–1993 and were randomized to digoxin or placebo.

2.2. Mild hyperkalemia

Of the 7788 DIG participants, 6857 had data on baseline serum potassium levels. We excluded 1189 patients with serum potassium <4 mEq/L and 12 patients with serum potassium >5.5 mEq/L. Of the 5656 patients included in the current analysis, 567 had mild hyperkalemia (5–5.5 mEq/L) and 5089 had normokalemia (4–4.9 mEq/L). Data on socio-demographic, clinical, sub-clinical and laboratory variables were collected at baseline.

2.3. Study outcomes

The primary outcome for the current study was all-cause mortality. Secondary outcomes were mortality due to cardiovascular causes and progressive HF, and hospitalization due to all causes, cardiovascular causes and worsening HF. Outcomes data were complete for 99% of the patients.

2.4. Assembly of a balanced study cohort

Propensity score for an exposure is the conditional probability of receiving that exposure given a set of measured baseline characteristics and can be used to assemble a matched cohort in which those exposed and unexposed would be balanced on all measured baseline characteristics [6–9]. Propensity scores for mild hyperkalemia were estimated for each of the 5656 patients using a non-parsimonious multivariable logistic regression model based on all measured baseline covariates displayed in Figure 1 [10–14]. Using a 1 to 3 greedy matching protocol described elsewhere [10–14], we were able to match all but 19 of the 567 patients with mild hyperkalemia with 1629 patients with normokalemia. Absolute standardized differences for baseline covariates were examined to assess pre-match imbalances and post-

match balances with results presented as a Love plot [10–14]. An absolute standardized difference of 0% indicates no bias, with values under 10% considered to be inconsequential.

2.5. Statistical analysis

Matched Cox regression models were used to determine associations between mild hyperkalemia and outcomes during 38 months of median follow up. To assess the effect of loss of participants during matching, we repeated our analysis in all 5656 pre-match patients using three different statistical models: (1) unadjusted, (2) multivariable-adjusted, using all covariates used in the propensity score model, and (3) propensity score-adjusted. Considering significant imbalance in baseline prevalence of diabetes mellitus (DM) and chronic kidney disease (CKD) between patients with mild hyperkalemia and normal serum potassium, we separately analyzed the association of mild hyperkalemia and all-cause mortality adjusting for DM alone, CKD alone and both DM and CKD. CKD was defined as glomerular filtration rate <60 ml/min/1.73 m^2 estimated using the Modified Diet in Renal Disease formula [15]. Subgroup analyses were conducted to determine the homogeneity of association between mild hyperkalemia and all-cause mortality. All statistical tests were two-tailed with a p-value <0.05 considered significant. All data analyses were performed using SPSS for Windows version 15 (SPSS Inc., Chicago, IL).

3. Results

3.1. Patient characteristics

Matched patients had a mean (±SD) age of 65 (±10) years, 21% were female and 13% were non-white. Before matching, the prevalence of DM and CKD were significantly higher among those with serum potassium 5–5.5 mEq/L compared to those with serum potassium 4–4.9 mEq/L. The prevalence of DM and CKD, along with other baseline characteristics was well balanced after matching (Table 1 and Figure 1). Post-match absolute standardized differences for all measured covariates were <5% suggesting substantial covariate balance across groups after matching (Figure 1).

3.2. Mild hyperkalemia and outcomes

Among matched participants, 798 (37%) participants died from all causes during 6180 person-years of follow up. All-cause mortality occurred in 38% (rate 1387/10000 person-years) and 36% (rate, 1260/10000 person-years) of participants with mild hyperkalemia and normokalemia respectively (matched hazard ratio {HR}, 1.07; 95% confidence interval {CI}, 0.90–1.26; P = 0.458; Table 2 and Figure 2). When we used serum potassium as a continuous variable, each unit increase in serum potassium was associated with a non-significant 7% increase in risk of total mortality (HR, 1.07; 95% CI, 0.90–1.28; P = 0.423). Associations between mild hyperkalemia and all-cause mortality in various subgroups of patients are displayed in Figure 3.

In the full pre-match cohort of 5656 patients, all-cause mortality occurred in 40% and 31% of patients with mild hyperkalemia and normokalemia respectively (unadjusted HR, 1.33; 95% CI, 1.15–1.52; P<0.0001). When we used serum potassium as a continuous variable, each unit increase in serum potassium was associated with a significant 29% increase in risk of total mortality (unadjusted HR, 1.29; 95% CI, 1.13–1.47; P <0.0001). Multivariable-adjusted and propensity-adjusted HRs were respectively 1.16 (95% CI, 1.01–1.34; P=0.040) and 1.13 (95% CI, 0.98–1.31; P=0.091). Post-match associations of mild hyperkalemia with other outcomes are displayed in Table 2. Associations of mild hyperkalemia and all-cause mortality among 5656 pre-match patients after adjustment for DM alone, CKD alone and both DM and CKD are displayed in Table 3.

4. Discussion

There are several important findings of the current study. First, chronic HF patients with normokalemia and mild hyperkalemia had rather similar baseline characteristics except for a significantly higher prevalence of DM and CKD in those with mild hyperkalemia. Second, mild hyperkalemia had a significant bivariate association with all-cause mortality, suggesting that it can be used as an early biomarker to identify chronic HF patients at increased risk of death. Third, mild hyperkalemia had no intrinsic association with all-cause mortality suggesting that serum potassium levels between 5 and 5.5 mEq/L may be relatively safe in these patients. Taken together with our previous finding of an increased mortality associated with serum potassium <4 mEq/L [3,13], these findings suggest that the optimal level of serum potassium in chronic HF may be between 4 and 5.5 mEq/L, with levels between 4 and 5 mEq/L being the most optimal, which is also in keeping with expert opinion [2].

The substantial imbalance in the distribution of DM and CKD between patients with mild hyperkalemia and normokalemia explains in part the significant bivariate association between mild hyperkalemia and all-cause mortality. Both DM and CKD are known to be associated with increased mortality in chronic HF [16,17]. Yet, these patients may be deprived of therapy with life-saving drugs such as an angiotensin-converting enzyme inhibitor, as they are also more prone to develop hyperkalemia. Interestingly, the association between mild hyperkalemia and all-cause mortality remained significant despite adjustment for DM, CKD, or both (Table 3). This suggests possible confounding by other covariates and/or residual confounding by DM and CKD, despite adjustment in a regression model. The persistence of a significant association between mild hyperkalemia and all-cause mortality after multivariable risk adjustment indicates that the use of the traditional regression-based multivariable risk adjustment models would have led us to conclude that mild hyperkalemia had an independent association with all-cause mortality in chronic HF. However, the association lost significance after adjustment for propensity scores in the pre-match cohort and in the propensity-matched cohort highlighting the conservative nature of propensity score methods.

Despite their popular use for risk adjustment, multivariable regression models are often limited by improper assumptions and imbalances on measured baseline covariates between exposed and unexposed groups. The issue of covariate imbalance is particularly important as in the presence of such imbalance regression adjustments are based on extrapolations beyond data and may not be trustworthy [18]. Propensity scores, on the other hand, may be used to assemble cohorts in which exposed and unexposed patients are well-balanced on all measured baseline covariates. Perhaps more importantly, risk adjustment using propensity methods is done during study design and investigators remain blinded to study outcomes, thus mimicking a key feature of randomized clinical trials [9]. This is even more important for studies of non-drug exposures as patients cannot be randomized to non-drug exposures such as mild hyperkalemia.

The lack of an intrinsic association between mild hyperkalemia and all-cause mortality may also be due to lack of an effect of a mild elevation of serum potassium levels on cardiac rhythm. As opposed to hypokalemia, mild hyperkalemia may be considered less harmful in chronic HF and levels up to 5.5 mEq/L have been recommended to be safe in these patients [2]. The effect of serum potassium levels between 5.5 and 6.5 mEq/L without electrocardiographic evidence of hyperkalemic cardiac arrhythmias is currently unknown [2]. However, because mild hyperkalemia is a harbinger of more severe hyperkalemia, patients with serum potassium between 5.5 and 6.5 mEq/L may quickly develop more severe hyperkalemia, especially in the presence of DM and CKD [19–21]. Therefore, serum

potassium in patients with chronic HF should be kept between 4 and 5.5 mEq/L and preferably between 4 and 5 mEq/L. HF patients with serum potassium levels between 5 and 5.5 mEq/L should be closely monitored, especially in those with DM and CKD. This caution is also supported by the late separation of Kaplan-Meier plots after the first two years of follow-up in our matched patients. The development of more severe hyperkalemia in patients with mild hyperkalemia may potentially explain the late increase in mortality in those patients, which may be significant during a longer follow-up and/or in a larger sample size. The progression to more severe hyperkalemia may also in part be mediated via the progression of DM and CKD during follow-up. Although the baseline prevalence of DM and CKD was similar in our matched patients with mild hyperkalemia and normokalemia, it is possible that DM and CKD in those with mild hyperkalemia were more severe and/or advanced, and may have progressed at a faster rate during follow-up.

Over 90% of the DIG participants were receiving angiotensin-converting enzyme inhibitors, a life-saving neurohormonal antagonist known to raise serum potassium. There is no need to discontinue the use of these and other neurohormonal antagonists such as angiotensin receptor blockers and aldosterone inhibitors in chronic HF patients with serum potassium between 5 and 5.5 mEq/L. However, patients with serum potassium levels between 5 and 5.5 mEq/L may require long-term serial monitoring of serum potassium for early identification of progression to more severe hyperkalemia, in which case, it may be prudent to reduce the dose of the offending drug. Eplerenone, a selective aldosterone receptor inhibitor, in 25 to 50 mg/day dosages, has been shown to reduce mortality in post-acute myocardial infarction patients with systolic HF treated with standard therapy without causing severe hyperkalemia (serum potassium ≥6.0 mEq/L) when serum potassium was periodically monitored [21]. In that study, DM and CKD were also strong predictors of severe hyperkalemia, but the presence of these conditions did not neutralize the mortality benefit of eplerenone.

A few limitations of this study must be acknowledged. Our study was based on trial-eligible, young, predominantly male HF patients in normal sinus rhythm from the pre-beta-blocker era of HF therapy. Therefore, these findings may need to be replicated in more contemporary cohorts of HF patients. We had no data on serum potassium during follow-up and underestimation of true associations due to regression dilution is possible [22].

In conclusion, serum potassium levels between 4 and 5 mEq/L are optimal in patients with chronic HF. Although serum potassium levels 5–5.5 mEq/L appear to be relatively safe, considering the risk of development of more severe hyperkalemia, serum potassium levels should be closely monitored in these patients. Despite the lack of an intrinsic effect of mild-hyperkalemia on mortality, its bivariate association with mortality suggests that it may be a useful biomarker of poor prognosis in HF.

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The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [23].

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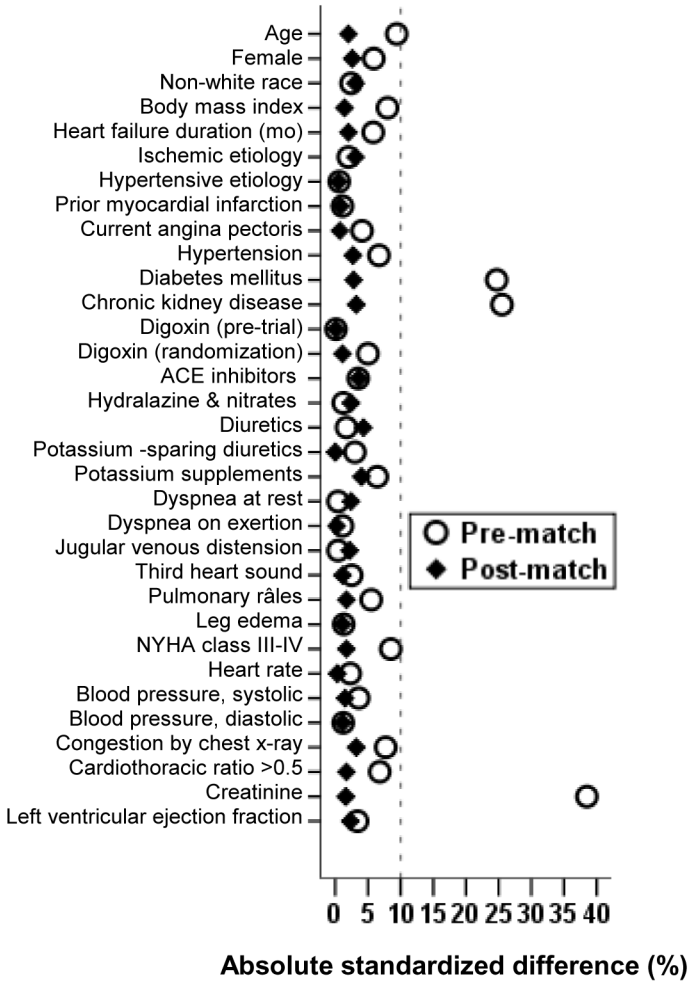
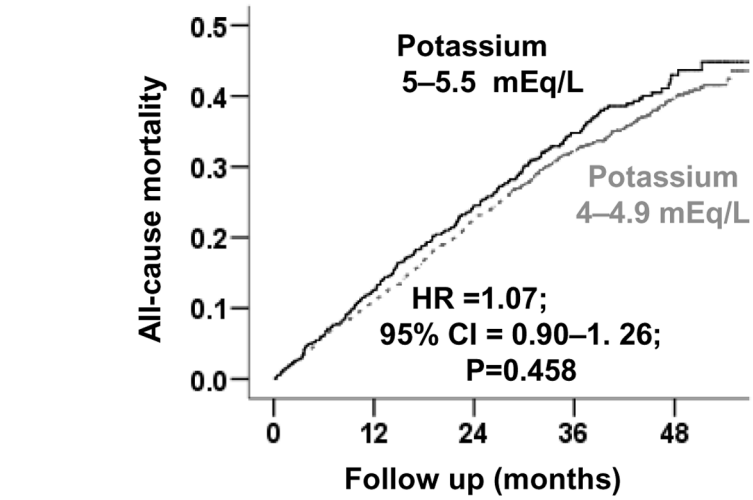


Figure 1.

Love plot displaying absolute standardized differences for baseline covariates for patients with normal potassium levels (4–4.9 mEq/L) and mild hyperkalemia (5–5.5 mEq/L), before and after propensity score matching (ACE=angiotensin converting enzyme, NYHA = New York Heart Association)



Number of patients at risk

Potassium 4–4.9	1629	1444	1248	866	300
Potassium 5–5.5	548	479	410	263	85

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

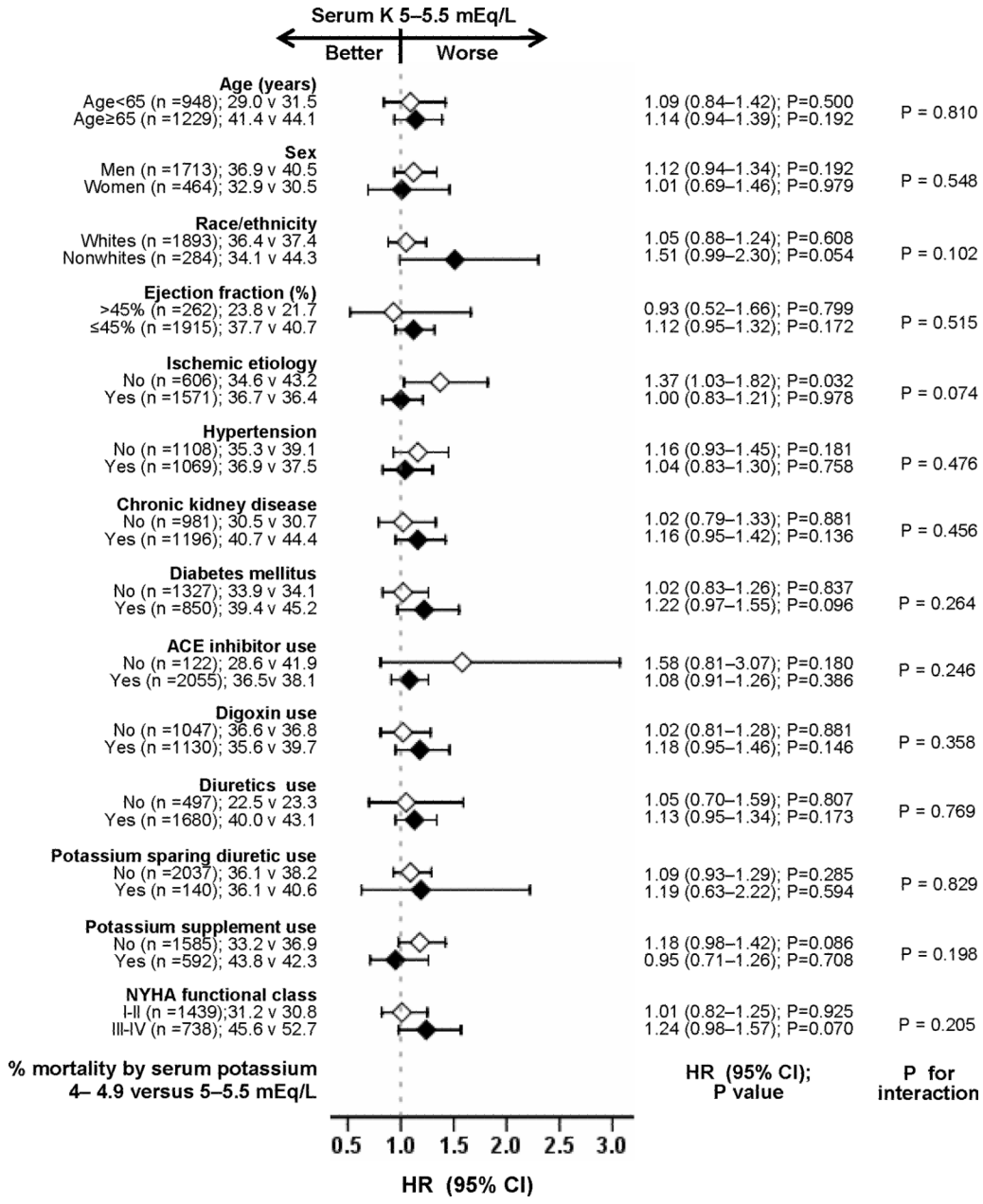


Figure 3.

Hazard ratio (HR) and 95% confidence interval (CI) for all-cause mortality associated with mild hyperkalemia in subgroups of patients with chronic heart failure (ACE=angiotensin-converting enzyme, K=potassium, NYHA=New York Heart Association)

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Table 1

Baseline patient characteristics, by serum potassium, before and after propensity score matching

	Before matching			After matching		
N (%) or mean (±SD)	**Serum potassium 4–4.9 mEq/L (n= 5089)**	**Serum potassium 5–5.5 mEq/L (n = 567)**	**P value**	**Serum potassium 4–4.9 mEq/L (n = 1629)**	**Serum potassium 5–5.5 mEq/L (n = 548)**	**P value**
Age (years)	64 (±11)	65 (±10)	0.046	65 (±10)	65 (±10)	0.668
Female	1197 (24%)	121 (21%)	0.244	346 (21%)	118 (22%)	0.885
Non-white	674 (13%)	71 (13%)	0.630	214 (13%)	70 (13%)	0.827
Body mass index, kg/m^2	27 (±5)	27 (±5)	0.063	27 (±5)	27 (±5)	0.848
Duration of heart failure (mo)	29 (±36)	31 (±39)	0.160	29 (±38)	30 (±38)	0.973
Primary cause of heart failure						
Ischemic	3574 (70%)	407 (72%)	0.832	1178 (72%)	393 (72%)	0.947
Hypertensive	474 (9%)	53 (9%)		156 (10%)	50 (9%)	
Idiopathic	723 (14%)	73 (13%)		198 (12%)	71 (13%)	
Others	318 (6%)	34 (6%)		97 (6%)	34 (6%)	
Prior myocardial infarction	3251 (64%)	369 (65%)	0.573	1048 (64%)	358 (65%)	0.674
Current angina pectoris	1375 (27%)	164 (29%)	0.334	439 (30%)	160 (29%)	0.308
Hypertension	2326 (46%)	278 (49%)	0.132	805 (49%)	264 (48%)	0.615
Diabetes mellitus	1415 (28%)	224 (40%)	<0.0001	642 (39%)	208 (38%)	0.546
Chronic kidney disease	2266 (45%)	323 (57%)	<0.0001	892 (55%)	304 (56%)	0.770
Medications						
Pre-trial digoxin use	2113 (42%)	233 (41%)	0.845	686 (42%)	226 (41%)	0.721
Trial use of digoxin	2528 (50%)	294 (52%)	0.326	848 (52%)	282 (52%)	0.809
Angiotensin-converting enzyme inhibitors	4747 (93%)	536 (95%)	0.254	1538 (94%)	517 (94%)	0.950
Diuretics	3912 (77%)	431 (76%)	0.646	1265 (78%)	415 (76%)	0.353
Potassium-sparing diuretics	354 (7%)	34 (6%)	0.391	108 (7%)	32 (6%)	0.514
Potassium supplement	1491 (29%)	147 (26%)	0.093	450 (28%)	142 (26%)	0.436
Symptoms and signs of HF						
Dyspnea at rest	1099 (22%)	124 (22%)	0.881	354 (22%)	117 (21%)	0.851
Dyspnea on exertion	3835 (75%)	429 (76%)	0.874	1228 (75%)	411 (75%)	0.857
Limitation of activity	3873 (76%)	432 (76%)	0.964	1243 (76%)	415 (76%)	0.785
Jugular venous distension	622 (12%)	68 (12%)	0.874	195 (12%)	64 (12%)	0.855

N (%) or mean (±SD)	Before matching			After matching		
	Serum potassium 4–4.9 mEq/L (n= 5089)	Serum potassium 5–5.5 mEq/L (n = 567)	P value	Serum potassium 4–4.9 mEq/L (n = 1629)	Serum potassium 5–5.5 mEq/L (n = 548)	P value
Third heart sound	1187 (23%)	125 (22%)	0.494	341 (21%)	120 (22%)	0.633
Pulmonary râles	793 (16%)	99 (18%)	0.245	273 (17%)	93 (17%)	0.909
Lower extremity edema	1047 (21%)	114 (20%)	0.794	322 (20%)	108 (20%)	0.976
New York Heart Association class						
Class I	732 (14%)	77 (14%)	0.220	225 (14%)	76 (14%)	0.982
Class II	2785 (55%)	291 (51%)		854 (52%)	284 (52%)	
Class III	1481 (29%)	189 (33%)		524 (32%)	178 (33%)	
Class IV	91 (2%)	10 (2%)		26 (2%)	10 (2%)	
Heart rate (/minute),	78 (±13)	78 (±12)	0.450	78 (±13)	78 (±12)	0.890
Systolic blood pressure (mm Hg)	127 (±20)	128 (±21)	0.558	128 (±21)	128 (±21)	0.896
Diastolic blood pressure (mm Hg)	75 (±11)	75 (±11)	0.950	75 (±11)	75 (±11)	0.634
Chest radiograph findings						
Pulmonary congestion	692 (14%)	61 (11%)	0.059	181 (11%)	58 (11%)	0.733
Cardiothoracic ratio >0.5	3045 (60%)	321 (57%)	0.138	953 (59%)	310 (57%)	0.428
Serum creatinine (mg/dL)	1.27 (±0.35)	1.43 (±0.48)	<0.0001	1.39 (±0.41)	1.39 (±0.43)	0.966
Estimated glomerular filtration rate, ml/min per 1.73 m2	64 (±20)	58 (±27)	<0.0001	59 (±20)	59 (±27)	0.441
Ejection fraction (%)	32 (±12)	31 (±13)	0.301	31 (±12)	31 (±13)	0.890

Table 2

Outcomes by baseline serum potassium in the matched cohort

Outcomes	Rate per 10000 person-years (events/total follow up in years)		Absolute rate difference (per 10000 person-years)*	Hazard ratio when potassium 5–5.5 mEq/L is compared with potassium 4–4.9 mEq/L (95% confidence interval)**	P value
	Serum potassium 4–4.9 mEq/L (n=1629)	Serum potassium 5–5.5 mEq/L (n=548)			
All-cause mortality	1260 (588/4666)	1387 (210/1514)	+ 127	1.07 (0.90–1.26)	0.458
Cardiovascular mortality	986 (460/4666)	1090 (165/1514)	+ 104	1.08 (0.89–1.30)	0.455
Heart failure mortality	420 (196/4666)	555 (84/1514)	+ 135	1.28 (0.97–1.69)	0.079
All-cause hospitalization	4493 (1148/2555)	4561 (379/831)	+ 68	0.98 (0.85–1.12)	0.727
Cardiovascular hospitalization	2888 (900/3116)	3231 (315/975)	+ 342	1.05 (0.91–1.22)	0.515
Heart failure hospitalization	1344 (519/3862)	1488 (189/1270)	+ 144	1.10 (0.92–1.33)	0.287

* Absolute differences in event rates 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 5 – 5.5 mEq/L group (before values were rounded).

** Post-match hazard ratios (95% confidence intervals) are adjusted for matching.

Table 3

Mild-hyperkalemia* and all-cause mortality in the pre-match cohort

Outcomes	Hazard ratio when potassium 5–5.5 mEq/L is compared with potassium 4–4.9 mEq/L (95% confidence interval)	P value
Unadjusted	1.33 (1.15–1.52)	<0.0001
Adjusted for diabetes mellitus	1.27 (1.10–1.46)	0.001
Adjusted for chronic kidney disease	1.27 (1.10–1.46)	0.001
Adjusted for both diabetes mellitus and chronic kidney disease	1.22 (1.06–1.41)	0.006
Multivariable adjusted (forward model)	1.16 (1.01–1.34)	0.040
Multivariable adjusted (backward model)	1.16 (1.01–1.34)	0.043
Multivariable adjusted (forced entry model)	1.16 (1.01–1.34)	0.040
Propensity score adjusted	1.13 (0.98–1.31)	0.091

* Mild-hyperkalemia is defined as serum potassium level 5–5.5 mEq/L