Published in final edited form as:

Int J Cardiol. 2010 May 28; 141(2): 167–174. doi:10.1016/j.ijcard.2008.11.195.

Oral Potassium Supplement Use and Outcomes in Chronic Heart Failure: A Propensity-Matched Study

O. James Ekundayo, MD, DrPH^a, Chris Adamopoulos, MD^b, Mustafa I. Ahmed, MD^a, Bertram Pitt, MD^c, James B. Young, MD^d, Jerome L. Fleg, MD^e, Thomas E. Love, PhD^f, Xuemei Sui, MD, MPH^g, Gilbert J. Perry, MD^{a,h}, David S. Siscovick, MD, MPHⁱ, George Bakris, MD^j, and Ali Ahmed, MD, MPH^{a,h,*}

^aUniversity of Alabama at Birmingham, Birmingham, AL, USA

^bPapageorgiou General Hospital, Thessaloniki, Greece

^cUniversity of Michigan, Ann Arbor, Michigan, USA

^dCleveland Clinic Foundation, Cleveland Ohio, USA

^eNational Heart, Lung, and Blood Institute, Bethesda, Maryland, USA

^fCase Western Reserve University, Cleveland, Ohio, USA

^gUniversity of South Carolina, Columbia, South Carolina, USA

^hVA Medical Center, Birmingham, AL, USA

ⁱUniversity of Washington, Seattle, Washington, USA

^jUniversity of Chicago, Chicago, Illinois, USA

Abstract

Background—Hypokalemia is common in heart failure (HF) and is associated with increased mortality. Potassium supplements are commonly used to treat hypokalemia and maintain normokalemia. However, their long-term effects on outcomes in chronic HF are unknown. We used a public-use copy of the Digitalis Investigation Group (DIG) trial dataset to determine the associations of potassium supplement use with outcomes using a propensity-matched design.

Methods—Of the 7788 DIG participants with chronic HF, 2199 were using oral potassium supplements at baseline. We estimated propensity scores for potassium supplement use for each patient and used them to match 2131 pairs of patients receiving and not receiving potassium supplements. Matched Cox regression models were used to estimate associations of potassium supplement use with mortality and hospitalization during 40 months of median follow-up.

Results—All-cause mortality occurred in 818 (rate, 1327/10000 person-years) and 802 (rate, 1313/10000 person-years) patients respectively receiving and not receiving potassium supplements (hazard ratio {HR} when potassium supplement use was compared with nonuse, 1.05; 95% confidence interval {CI}, 0.94–1.18; P=0.390). All-cause hospitalizations occurred in 1516 (rate,

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

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Conflict of Interest Disclosure: None

4777/10,000 person-years) and 1445 (rate, 4120/10,000 person-years) patients respectively receiving and not receiving potassium supplements (HR, 1.15; 95% CI, 1.05–1.26; $P=0.004$). HR (95% CI) for hospitalizations due to cardiovascular causes and worsening HF were respectively 1.19 (95% CI, 1.08–1.32; $P=0.001$) and 1.27 (1.12–1.43; $P<0.0001$).

Conclusion—The use of potassium supplements in chronic HF was not associated with mortality. However, their use was associated with increased hospitalization due to cardiovascular causes and progressive HF.

Keywords

Heart failure; potassium supplement; mortality; hospitalization; propensity score

1. Introduction

Hypokalemia is common in heart failure (HF) and is associated with poor outcomes [1]. Oral potassium supplements are often used to treat hypokalemia and maintain normokalemia in HF patients with low serum potassium levels. However, the long-term effects of potassium supplement use on outcomes in chronic HF are unknown. The objective of this study was to examine the associations of potassium supplement use with mortality and hospitalization in a propensity-matched cohort of ambulatory chronic HF patients.

2. Materials and methods

2.1. Study patients

The Digitalis Investigation Group (DIG) trial was a multi-center randomized clinical trial, the design and results of which have been reported previously [2,3]. Briefly, 7788 ambulatory chronic HF patients (6800 had left ventricular ejection fraction $\leq 45\%$) in normal sinus rhythm receiving angiotensin-converting enzyme inhibitors and diuretics were randomized to receive digitalis and placebo. Overall, 2199 (28%) patients were receiving oral potassium supplements at baseline and 5589 (72%) patients were not receiving potassium supplements. Data on the use of potassium supplements were available from all 7788 participants.

2.2. Study design: propensity score matching

We focus our current analysis to a subset of 4262 patients, who were assembled through propensity score matching [4–7]. Because patients in the DIG trial were not randomized to receive potassium supplements, the probabilities of actually receiving potassium supplements varied according to the baseline characteristics of those patients. The propensity matching approach allows the assembly of a cohort who would be well-balanced in all measured baseline covariates. Importantly, this can be done without access to the outcomes data, thus maintaining a degree of blindness, which is a key feature of randomized clinical trials [4–7].

The propensity score for potassium supplement use for a patient is the conditional probability of receiving these drugs given that patient's baseline characteristics [4–7]. We estimated propensity scores for the use of potassium supplements for each of the 7788 patients with a non-parsimonious multivariable logistic regression model using baseline characteristics presented in Figure 1, and checking for plausible interactions [1,8–10]. We then matched patients who were receiving potassium supplements with those who were not receiving potassium supplements but had similar propensity to receive them [1,8–10]. Using a greedy matching protocol, we were able to match 97% (2131 of 2199) of patients receiving potassium supplements, yielding a matched cohort of 4262 patients. We then estimated absolute standardized differences to assess pre-match imbalances and post-match balance in baseline

covariates and presented those findings as a Love plot [1,8–12]. An absolute standardized difference of 0% would suggest no residual bias, and those below 10% suggest negligible bias.

2.3. Study outcomes

The primary outcomes for the current analysis were all-cause mortality and all-cause hospitalization, and secondary outcomes included mortality and hospitalizations due to cardiovascular causes and HF. DIG participants were followed for a median of 38 months and vital status data were complete for 99% of the patients [13].

2.4. Statistical analysis

For descriptive analyses, we used Pearson Chi square and Wilcoxon rank-sum tests for the pre-match, and McNemar's test and paired sample t-test for the post-match comparisons, as appropriate. For the pre-match comparison, of the 5589 patients not receiving potassium supplements, a random sample of 2131 patients were selected and were compared with 2131 matched patients receiving potassium supplements. This was done to have similar pre- and post-match sample sizes ($n=4262$), and to avoid overestimation of significant p values from a larger sample size ($n=7788$). We then used Kaplan-Meier plots and matched Cox regression analysis to estimate associations of potassium supplement use with total and cause-specific deaths and hospitalizations in the matched cohort [1,8]. Formal sensitivity analyses were conducted to determine the effect of a potential hidden confounder on our study findings [14]. Subgroup analyses were conducted to determine the homogeneity of the association between potassium supplement use and mortality. All statistical tests were evaluated using two-tailed 95% confidence levels, using SPSS-15 for Windows [15].

3. Results

3.1. Patient characteristics

Patients ($n=4262$) had a mean ($\pm$ SD) age of 64 (± 11) years, 28% were women and 16% were nonwhites. There were significant pre-match imbalances in key baseline covariates including gender, race, comorbidity, disease severity and baseline serum potassium, all of which were balanced after matching (Table 1). Absolute standardized differences for all measured covariates were below 5% indicating negligible post-match bias (Figure 1).

3.2. Potassium supplement use and mortality

During a median follow up of 40 months, 1620 (38%) patients died from all causes, 1290 (30%) due to cardiovascular causes and 607 (14%) due to progressive HF. All-cause mortality occurred in 818 (rate, 1327/10000 person-years) and 802 (rate, 1313/10000 person-years) patients receiving and not receiving potassium supplements respectively (hazard ratio {HR} when potassium supplement use was compared with its nonuse, 1.05; 95% confidence interval {CI}, 0.94–1.18; $P=0.390$; Figure 2a and Table 2). This association was homogeneous across a wide spectrum of HF patients (Figure 3). Associations between potassium supplement use and cause-specific mortalities are displayed in Table 2. In the pre-match cohort of 4262 patients, 1503 (35%) died from all causes. All-cause mortality occurred in 818 (38%) and 685 (32%) patients receiving and not receiving potassium supplements respectively (HR, 1.30; 95% CI, 1.17–1.43; $P<0.0001$).

3.3. Potassium supplement use and hospitalization

Overall, hospitalizations due to all causes, cardiovascular causes, and worsening HF occurred respectively in 2961 (69%), 2362 (55%) and 1483 (35%) patients. All-cause hospitalizations occurred in 1516 (rate, 4777/10000 person-years) and 1445 (rate, 4120/10000 person-years) patients receiving and not receiving potassium supplements respectively (HR for potassium

supplement use, 1.15; 95% CI, 1.05–1.26; $P=0.004$; Figure 2b and Table 3). Results of our sensitivity analysis suggest that in the absence of hidden bias, a sign-score test for matched data with censoring provides strong evidence (two-tailed $p=0.003$) that the use of potassium supplement was associated with an increased risk of all-cause hospitalization. A hidden covariate that would increase the odds of potassium supplement use by only 4.9% may potentially explain away this association [14]. Associations between potassium supplement use and cause-specific hospitalizations are displayed in Table 3.

4. Discussion

Findings from the current analysis demonstrate that oral potassium supplement use was not associated with all-cause mortality in chronic HF, but was associated with increased all-cause hospitalization, which was mostly driven by cardiovascular and HF hospitalizations. Considering that the use of potassium supplements is a marker of hypokalemia, the lack of an independent association between potassium supplement use and all-cause mortality suggest that potassium supplements may have eliminated the increased mortality associated with hypokalemia [1]. However, the association between potassium supplement use and increased cardiovascular hospitalization, which was primarily driven by an increase in HF hospitalization, is somewhat puzzling. Even though the underlying mechanism for this latter association remains unclear, data from animal studies suggest a possible association between plasma potassium and salt appetite [16,17]. To the best of our knowledge this is first report of an association between potassium supplement use and outcomes in a propensity-matched cohort of chronic HF patients in which those receiving and not receiving potassium supplements were well-balanced in all measured baseline covariates.

Hypokalemia is associated with increased mortality without increase in hospitalization suggesting that most hypokalemia-associated deaths may be sudden and caused by fatal arrhythmias [1]. We find a reversal of these associations in those using oral potassium supplements: no association with mortality and an association with increased hospitalization. Potassium supplement use is only indicated to treat and prevent hypokalemia and thus may be considered a marker of hypokalemia. Yet, our findings suggest that hypokalemia-associated mortality was eliminated in those receiving potassium supplements [1]. This is likely mediated via the correction of hypokalemia. It is unknown whether potassium supplements have intrinsic survival benefit in HF. In patients with hypertension, potassium-sparing diuretics, but not potassium supplements, have been shown to reduce the risk of cardiac arrest [18–20]. Findings from the current analysis suggest that in patients with chronic HF potassium supplements may eliminate hypokalemia-associated deaths. However, potassium supplements do not correct other electrolyte imbalances such as hypomagnesemia, and may not also efficiently replenish tissue potassium [21]. Aldosterone antagonists, such as spironolactone, on the other hand, may replenish body potassium, and also prevent disease progression and mortality in HF [22–25].

Our findings suggest that potassium supplements neutralize the excess deaths associated with hypokalemia, and support their use to correct hypokalemia. However, our findings also suggest that potassium supplements may not provide any additional mortality reduction. Therefore, once hypokalemia has been corrected, aldosterone antagonists may be preferable over chronic potassium supplements for the maintenance of normokalemia [23,24,26]. When aldosterone antagonists are used, potassium supplements are often not needed and may even be deleterious [27]. This is also suggested by our subgroup analyses in which the subgroup of patients receiving potassium-sparing diuretics were the only subgroup in which the use of potassium supplements was associated with a trend toward increased mortality (Figure 3). For patients who fail to maintain normokalemia despite the use of aldosterone antagonists in appropriate doses, potassium supplements may be used judiciously to maintain serum potassium between 4 and 5 mEq/L [1,28]. HF patients, who are elderly, have diabetes or renal insufficiency, or

are receiving inhibitors of the renin-angiotensin system or beta-blockers, or non-steroidal anti-inflammatory drugs, are at increased risk of hyperkalemia [29,30]. Aldosterone antagonists and potassium supplements should be used with caution along with close monitoring of serum potassium levels in these patients.

A rather unexpected finding of our study was increased hospitalizations associated with the use of potassium supplements. While we do not have a clear mechanistic insight into this association, data from animal studies suggest that potassium supplements may increase salt appetite [16,17]. This notion is also supported by the fact that hyperkalemia-associated hospitalizations were mostly due to cardiovascular causes and worsening HF. We had no data on diuretic dosages and it is possible that use of potassium supplements was a marker of disease severity and use of higher doses of diuretics. Symptomatic HF patients receiving higher doses of diuretics are more likely to develop hypokalemia and receive potassium supplements. However, our matched patients were well balanced in all measured baseline characteristics that also included markers of symptoms and disease severity. Finally, the association between potassium supplement use and hospitalization was relatively sensitive to a potential unmeasured covariate. However, sensitivity analysis cannot determine if such a hidden confounder exists. For a covariate to become a confounder it should be a strong predictor of hospitalization and not be strongly correlated with any of the measured covariates in our study.

Our study has several limitations. Patients in our study were predominantly white, male, relatively young, and in normal sinus rhythm, from the pre-beta-blocker era of HF therapy, which may limit generalizability. Thus, the results of this study should be interpreted with caution, and need to be replicated in contemporary propensity-matched HF populations, and preferably in prospective randomized clinical trials.

In conclusion, the use of potassium supplements was not associated with mortality but was associated with increased hospitalization in chronic HF patients. Once hypokalemia has been corrected with potassium supplements, aldosterone antagonists may be preferable for the maintenance of normokalemia in those with recurrent hypokalemia requiring chronic oral potassium supplement use.

Acknowledgments

The Digitalis Investigation Group (DIG) study was conducted and supported by the NHLBI in collaboration with the DIG Investigators. This Manuscript was prepared using a limited access dataset obtained by the NHLBI and does not necessarily reflect the opinions or views of the DIG Study or the NHLBI.

Funding/Support: Dr. Ahmed is supported by the National Institutes of Health through grants from the National Heart, Lung, and Blood Institute (5-R01-HL085561-02 and P50-HL077100), and a generous gift from Ms. Jean B. Morris of Birmingham, Alabama.

References

1. Ahmed A, Zannad F, Love TE, et al. A propensity-matched study of the association of low serum potassium levels and mortality in chronic heart failure. *Eur Heart J* 2007;28:1334–1343. [PubMed: 17537738]
2. The Digitalis Investigation Group. Rationale, design, implementation, and baseline characteristics of patients in the DIG trial: a large, simple, long-term trial to evaluate the effect of digitalis on mortality in heart failure. *Control Clin Trials* 1996;17:77–97. [PubMed: 8721804]
3. The Digitalis Investigation Group. The effect of digoxin on mortality and morbidity in patients with heart failure. *N Engl J Med* 1997;336:525–533. [PubMed: 9036306]
4. Rosenbaum PR, Rubin DB. The central role of propensity score in observational studies for causal effects. *Biometrika* 1983;70:41–55.

5. Rosenbaum PR, Rubin DB. Reducing bias in observational studies using subclassification on the propensity score. *J Am Stat Asso* 1984;79:516–524.
6. Rubin DB. Using propensity score to help design observational studies: Application to the tobacco litigation. *Health Services and Outcomes Research Methodology* 2001;2:169–188.
7. Rubin DB. On principles for modeling propensity scores in medical research. *Pharmacoepidemiol Drug Saf* 2004;13:855–857. [PubMed: 15386710]
8. Ahmed A, Husain A, Love TE, et al. Heart failure, chronic diuretic use, and increase in mortality and hospitalization: an observational study using propensity score methods. *Eur Heart J* 2006;27:1431–1439. [PubMed: 16709595]
9. Ahmed A, Perry GJ, Fleg JL, Love TE, Goff DC Jr, Kitzman DW. Outcomes in ambulatory chronic systolic and diastolic heart failure: a propensity score analysis. *Am Heart J* 2006;152:956–966. [PubMed: 17070167]
10. Ahmed A, Aban IB, Vaccarino V, et al. A propensity-matched study of the effect of diabetes on the natural history of heart failure: variations by sex and age. *Heart* 2007;93:1584–1590. [PubMed: 17488764]
11. D'Agostino RB Jr. Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. *Stat Med* 1998;17:2265–2281. [PubMed: 9802183]
12. Normand ST, Landrum MB, Guadagnoli E, et al. Validating recommendations for coronary angiography following acute myocardial infarction in the elderly: a matched analysis using propensity scores. *J Clin Epidemiol* 2001;54:387–398. [PubMed: 11297888]
13. Collins JF, Howell CL, Horney RA. Determination of vital status at the end of the DIG trial. *Control Clin Trials* 2003;24:726–730. [PubMed: 14662278]
14. Rosenbaum, PR. Sensitivity to Hidden Bias. In: Rosenbaum, PR., editor. *Observational Studies*. 2 ed.. New York: Springer-Verlag; 2002. p. 110-124.
15. SPSS for Windows, Rel. 15. program. Chicago, IL: SPSS Inc; 2008.
16. Michell AR. Relationships between individual differences in salt appetite of sheep and their plasma electrolyte status. *Physiol Behav* 1976;17:215–219. [PubMed: 996157]
17. Michell AR. Plasma potassium and sodium appetite; the effect of potassium infusion in sheep. *Br Vet J* 1978;134:217–224. [PubMed: 667588]
18. Siscovick DS, Raghunathan TE, Psaty BM, et al. Diuretic therapy for hypertension and the risk of primary cardiac arrest. *N Engl J Med* 1994;330:1852–1857. [PubMed: 8196728]
19. Laragh JH, Sealey JE. K(+) depletion and the progression of hypertensive disease or heart failure. The pathogenic role of diuretic-induced aldosterone secretion. *Hypertension* 2001;37:806–810. [PubMed: 11230377]
20. Siegel D, Hulley SB, Black DM, et al. Diuretics, serum and intracellular electrolyte levels, and ventricular arrhythmias in hypertensive men. *JAMA* 1992;267:1083–1089. [PubMed: 1735925]
21. Delgado, MC.; Delgado-Almeida, A. Abnormal potassium. In: Mohler, IER., editor. *Advanced Therapy in Hypertension and Vascular Disease*. Elsevier: Decker, B.C. Inc; 2006. p. 261-299.
22. Packer M. Potential role of potassium as a determinant of morbidity and mortality in patients with systemic hypertension and congestive heart failure. *Am J Cardiol* 1990;65:45E–51E.
23. Pitt B, Remme W, Zannad F, et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 2003;348:1309–1321. [PubMed: 12668699]
24. Pitt B, Zannad F, Remme WJ, et al. Randomized Aldactone Evaluation Study Investigators. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. *N Engl J Med* 1999;341:709–717. [PubMed: 10471456]
25. Weber KT, Villarreal D. Aldosterone and antialdosterone therapy in congestive heart failure. *Am J Cardiol* 1993;71:3A–11A.
26. Gennari FJ. Hypokalemia. *N Engl J Med* 1998;339:451–458. [PubMed: 9700180]
27. Hunt SA, Abraham WT, Chin MH, et al. ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult. A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure). Developed in Collaboration

With the American College of Chest Physicians and the International Society for Heart and Lung Transplantation. Endorsed by the Heart Rhythm Society. *Circulation* 2005;112:e154–e235. [PubMed: 16160202]

28. Macdonald JE, Struthers AD. What is the optimal serum potassium level in cardiovascular patients? *J Am Coll Cardiol* 2004;43:155–161. [PubMed: 14736430]
29. Petch MC, McKay R, Bethune DW. The effect of beta, adrenergic blockade on serum potassium and glucose levels during open heart surgery. *Eur Heart J* 1981;2:123–126. [PubMed: 6115752]
30. Ahuja TS, Freeman D Jr, Mahnken JD, Agraharkar M, Siddiqui M, Memon A. Predictors of the development of hyperkalemia in patients using angiotensin-converting enzyme inhibitors. *Am J Nephrol* 2000;20:268–272. [PubMed: 10970978]

Fig. 1.

Love plots for absolute standardized differences in covariates between patients receiving and not receiving potassium supplements, before and after propensity score matching. (ACE=angiotensin-converting enzyme; NYHA=New York Heart Association)

Figure 2a

Figure 2b

Fig. 2. Kaplan-Meier plots for all-cause mortality and all-cause hospitalization by the use of oral potassium supplements.

Fig. 3. Hazard ratios (HR) and 95% confidence intervals (CI) for all-cause mortality associated with potassium supplement use in subgroups of patients with chronic heart failure. (ACE=angiotensin-converting enzyme)

Table 1

Baseline patient characteristics

Variables	Before matching*			After matching		
	No potassium supplement use (N = 2131)	Potassium supplement use (N = 2131)	P values	No potassium supplement use (n = 2131)	Potassium supplement use (n = 2131)	P values
Age(yrs)	63.6 (±11)	64.2 (±11)	0.086	64.2 (±11)	64.2 (±11)	0.858
Female	496 (23%)	582 (27%)	0.002	598 (28%)	582 (27%)	0.605
Non-white	269 (13%)	350 (16%)	<0.0001	348 (16%)	350 (16%)	0.967
Body mass index (kg/m ²)	27.3 (±5.3)	27.6 (±5.7)	0.088	27.5 (±5.6)	27.6 (±5.7)	0.567
Duration of HF (mo)	30 (±39)	30 (±36)	0.976	30 (±36)	30 (±36)	0.975
Primary cause heart failure						
Ischemic	1503 (71%)	1372 (64%)	<0.0001	1357 (64%)	1372 (64%)	0.646
Hypertensive	203 (10%)	261 (12%)	0.004	259 (12%)	261 (12%)	0.963
Idiopathic	281 (13%)	338 (16%)	0.013	346 (16%)	338 (16%)	0.771
Others	144 (7%)	160 (8%)	0.341	169 (8%)	160 (8%)	0.649
Prior myocardial infarction	1361 (64%)	1254 (59%)	0.001	1216 (57%)	1254 (59%)	0.237
Current angina	598 (28%)	541 (25%)	0.048	536 (25%)	541 (25%)	0.886
Hypertension	964 (45%)	1102 (52%)	<0.0001	1108 (52%)	1102 (52%)	0.876
Diabetes	594 (28%)	647 (30%)	0.074	651 (31%)	647 (30%)	0.921
Chronic kidney disease	904 (42%)	1053 (49%)	<0.0001	995 (47%)	1053 (49%)	0.082
Medications						
Digoxin (pretrial use)	839 (39%)	1068 (50%)	<0.0001	1078 (51%)	1068 (50%)	0.769
Digoxin (trial use)	1063 (50%)	1054 (50%)	0.783	1050 (49%)	1054 (50%)	0.927
ACE inhibitors	1999 (94%)	2004 (94%)	0.749	1991 (93%)	2004 (94%)	0.436
Hydralazine & nitrates	15 (1%)	33 (2%)	0.009	38 (2%)	33 (2%)	0.583
Diuretics	1512 (71%)	2025 (95%)	<0.0001	2020 (95%)	2025 (95%)	0.332
PS diuretics	182 (9%)	130 (6%)	0.002	149 (7%)	130 (6%)	0.252
Symptoms and signs of heart failure						
Dyspnea at rest	440 (21%)	541 (25%)	<0.0001	543 (26%)	541 (25%)	0.972

Variables	Before matching*			After matching		
	No potassium supplement use (N = 2131)	Potassium supplement use (N = 2131)	P values	No potassium supplement use (n = 2131)	Potassium supplement use (n = 2131)	P values
Dyspnea on exertion	1572 (74%)	1687 (79%)	<0.0001	1688 (79%)	1687 (79%)	1.000
Jugular venous distension	253 (12%)	328 (15%)	0.001	345 (16%)	328 (15%)	0.499
Third heart sound	456 (21%)	563 (26%)	<0.0001	578 (27%)	563 (26%)	0.631
Pulmonary rales	312 (15%)	382 (18%)	0.004	398 (19%)	382 (18%)	0.551
Lower extremity edema	374 (18%)	565 (27%)	<0.0001	558 (26%)	565 (27%)	0.815
NYHA class III-IV	608 (29%)	780 (37%)	<0.0001	779 (37%)	780 (37%)	1.000
Heart rate (beats per minute)	78 (±13)	80 (±13)	<0.0001	80 (±12)	80 (±13)	0.836
Systolic BP (mmHg)	128 (±21)	127 (±21)	0.034	127 (±21)	127 (±21)	0.416
Diastolic BP (mmHg)	76 (±11)	75 (±11)	0.033	75 (±12)	75 (±11)	0.694
Chest radiograph findings						
Pulmonary congestion	281 (13%)	354 (17%)	0.002	357 (17%)	354 (17%)	0.934
Cardiothoracic ratio >0.5	1191 (56%)	1411 (66%)	<0.0001	1410 (66%)	1411 (66%)	1.000
Serum potassium (mg/dL)	4.4 (±0.5)	4.3 (±0.5)	<0.0001	4.3 (±0.5)	4.3 (±0.5)	0.554
Serum creatinine (mg/dL)	1.3 (±0.4)	1.3 (±0.4)	0.002	1.3 (±0.4)	1.3 (±0.4)	0.696
Ejection fraction (%)	33 (±12)	31 (±13)	<0.0001	30 (±12)	31 (±13)	0.370

ACE=angiotensin converting enzyme; BP=blood pressure; HF=heart failure.

* Of the 5589 patients not receiving potassium supplements, a random sample of 2131 patients were selected and paired with 2131 matched patients receiving potassium supplements. This was done to have similar pre- and post-match sample sizes, and to avoid overestimation of significant p values from a larger sample size.

Mortality by potassium supplement use

Table 2

Outcomes	Rate / 10000 person-years follow up (total number of events / follow-up in years)		Rate difference (per 10,000 person-years)*	Hazard ratio (95% CI) [†]	P value
	No potassium supplement use (N = 2131)	Potassium supplement use (N = 2131)			
All-cause	1313 (802 / 6109)	1327 (818 / 5928)	+ 67	1.05 (0.94–1.18)	0.390
Cardiovascular	1044 (638 / 6109)	1100 (652 / 5928)	+ 56	1.07 (0.95–1.22)	0.275
Worsening heart failure [‡]	476 (291 / 6109)	533 (316 / 5928)	+ 57	1.18 (0.98–1.42)	0.081
Other cardiac [§]	521 (318 / 6109)	516 (306 / 5928)	– 5	0.98 (0.82–1.17)	0.784
Other vascular [¶]	47 (29 / 6109)	51 (30 / 5928)	+4	1.15 (0.63–2.09)	0.648
Non-cardiac, non-vascular	196 (120 / 6109)	214 (127 / 5928)	+ 18	1.08 (0.81–1.43)	0.611
Unknown	72 (44 / 6109)	66 (39 / 5928)	– 6	0.69 (0.42–1.16)	0.161

* Absolute rate differences were calculated by subtracting the rates of death in the potassium-supplement group from the rates of death in the no potassium-supplement group (before values were rounded).

[†] Hazard ratios and confidence intervals (CI) were estimated from matched Cox proportional-hazards models.

[‡] This category includes patients who died from worsening heart failure, even if the final event was an arrhythmia.

[§] This category includes deaths presumed to result from arrhythmia without evidence of worsening heart failure and deaths due to atherosclerotic coronary disease, bradyarrhythmias, low-output states, and cardiac surgery.

[¶] This category includes deaths due to stroke, embolism, peripheral vascular disease, vascular surgery, and carotid endarterectomy.

Table 3

Hospitalization by potassium supplement use

Cause for hospitalization*	Rate / 10000 person-years follow up (total number of events / follow-up in years)		Rate difference (/ 10,000 person-years) [†]	Matched hazard ratio (95% CI) [‡]	P value
	No potassium Supplement use (N = 2131)	Potassium supplement use (N = 2131)			
All-cause	4120 (1445 / 3507)	4777 (1516 / 3173)	+ 657	1.15 (1.05–1.26)	0.004
Cardiovascular	2690 (1127 / 4189)	3284 (1235 / 3761)	+ 594	1.19 (1.08–1.32)	0.001
Worsening heart failure	1318 (676 / 5129)	1717 (807 / 4701)	+ 399	1.27 (1.12–1.43)	<0.0001
Ventricular arrhythmia, cardiac arrest	147 (88 / 5990)	132 (77 / 5812)	– 15	1.07 (0.75–1.53)	0.715
SV arrhythmias [§]	170 (101 / 5931)	195 (112 / 5745)	+ 25	1.06 (0.78–1.44)	0.697
AV block, bradyarrhythmia	15 (9 / 6098)	19 (11 / 5906)	+ 4	1.14 (0.41–3.15)	0.796
Suspected digoxin toxicity	58 (35 / 6052)	53 (31 / 5887)	– 5	0.92 (0.53–1.61)	0.923
Myocardial infarction	215 (128 / 5947)	191 (111 / 5807)	– 24	0.93 (0.69–1.24)	0.603
Unstable angina	417 (236 / 5661)	483 (262 / 5429)	+ 66	1.16 (0.95–1.41)	0.157
Stroke	155 (93 / 5985)	215 (124 / 5755)	+ 60	1.26 (0.93–1.71)	0.140
Coronary revascularization [¶]	65 (39 / 6034)	70 (41 / 5846)	+ 5	1.07 (0.64–1.79)	0.793
Cardiac transplantation	18 (11 / 6093)	31 (18 / 5896)	+ 13	2.60 (0.93–7.29)	0.069
Other cardiovascular ^{**}	468 (265 / 5665)	521 (283 / 5427)	+ 53	1.09 (0.90–1.32)	0.400
Respiratory infection	290 (170 / 5860)	320 (181 / 5665)	+ 30	1.18 (0.92–1.51)	0.189
Other non-cardiovascular	1509 (743 / 4924)	1547 (730 / 4720)	+ 38	1.05 (0.93–1.19)	0.414

Cause for hospitalization [*]	Rate / 10000 person-years follow up (total number of events / follow-up in years)		Rate difference (/ 10,000 person-years) [†]	Matched hazard ratio (95% CI) [‡]	P value
	No potassium Supplement use (N = 2131)	Potassium supplement use (N = 2131)			
Unspecified	20 (12 / 6095)	27 (16 / 5910)	+ 7	1.83 (0.68–4.96)	0.232
Number of hospitalizations	9714 (986 / 1015)	11893 (1093 / 919)	+ 2179		

^{*} Data shown include the first hospitalization of each patient due to each cause.

[†] Absolute differences were calculated by subtracting the percentage of patients hospitalized in the potassium supplement group from the percentage of patients hospitalized in the no potassium supplement group (before values were rounded).

[‡] Hazard ratios and confidence intervals (CI) were estimated from a Cox proportional-hazards models that used the first hospitalization of each patient for each reason.

[§] Supraventricular (SV) arrhythmias include Atrioventricular (AV) block and bradyarrhythmias

[¶] This category includes coronary-artery bypass grafting and percutaneous transluminal coronary angioplasty

^{**} This category includes embolism, venous thrombosis, peripheral vascular disease, hypertension, other vascular surgery, cardiac catheterization, other types of catheterization, pacemaker implantation, installation of automatic implantable cardiac defibrillator, electrophysiologic testing, transplant-related evaluation, nonspecific chest pain, atherosclerotic heart disease, hypotension, orthostatic hypotension, and valve operation