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A propensity-matched study of low serum potassium and mortality in older adults with chronic heart failure☆

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Abstract

Objective: Most HF patients are older adults, yet the associations of low serum potassium and outcomes in these patients are unknown. We studied the effect of low serum potassium in a propensity-matched population of elderly HF patients.
Methods: Of the 7788 patients in the Digitalis Investigation Group trial, 4036 were ≥65 years. Of these, 3598 had data on baseline serum potassium and 324 with potassium ≥5 mEq/L were excluded. Remaining patients were categorized into low (<4 mEq/L; $n=590$) and normal (4–4.9 mEq/L; $n=2684$) potassium groups. Propensity scores for low-potassium, calculated for each patient, were used to match 561 low-potassium and 1670 normal-potassium patients. Association of low potassium and outcomes were assessed using matched Cox regression analyses.
Results: Patients had a mean (±SD) age of 72 (±6) years, 29% were women and 12% were non-whites. Of the 561 low-potassium patients, 500 had low-normal (3.5–3.9 mEq/L) potassium. All-cause mortality occurred in 37% (rate, 1338/10,000 person-years) normal-potassium and 43% (rate, 1594/10,000 person-years) low-potassium patients (hazard ratio {HR} for low-potassium, 1.22; 95% confidence interval {CI}, 1.04–1.44; $p=0.014$). Low-normal (3.5–3.9 mEq/L) potassium levels had a similar association with mortality (HR, 1.19, 95% CI, 1.00–1.41, $p=0.049$). Low (HR, 1.10; 95% CI, 0.96–1.25; $p=0.175$) or low-normal (HR=1.09, 95% CI=0.95–1.25, $p=0.229$) serum potassium levels were not associated with all-cause hospitalization.
Conclusions: In a propensity-matched population of elderly ambulatory chronic HF patients, well-balanced in all measured baseline covariates, low and low-normal serum potassium were associated with increased mortality but had no association with hospitalization.
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Keywords: Heart failure; Elderly; Potassium; Mortality; Hospitalization; Propensity score

1. Introduction

Hypokalemia is common in heart failure (HF) and is associated with increased mortality [1–3]. A recent study of propensity-matched population of ambulatory chronic HF suggested that serum potassium <4 mEq/L may be associated with increased mortality without any effect on hospitalization. Most HF patients are older adults and yet the effect of low serum potassium in older adults with HF has

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not been well-studied. A subgroup analysis of the above study found no difference in the effect of low serum potassium on mortality between patients <65 years and those ≥65 years [2]. However, patients in that subgroup analysis were not propensity-matched, and that subgroup analysis did not provide data on other outcomes.

Older adults are often excluded from clinical trials and studies and evidence for these patients is often extrapolated from subgroup analyses. However, because propensity-matched studies can be conduced in a cost-efficient manner, these studies can be used to derive evidence for elderly patients [2,4,5]. Thus, the objective of this study was to determine the long-term effects of low serum potassium on mortality and hospitalization in a cohort of propensity score matched chronic systolic and diastolic HF patients 65 years of age or older.

2. Methods

2.1. Study design

We conducted a non-randomized propensity-matched study of the Digoxin Investigation Group (DIG) trial, which was a randomized clinical trial of digoxin in HF conducted in 302 centers (186 in the United States and 116 in Canada) over 32 months during 1991–1993 [6]. Detailed descriptions of the rationale, design, implementation, and results of the DIG trial have been reported elsewhere [6].

2.2. Study patients

All of the 7788 DIG participants were ambulatory chronic systolic and diastolic HF patients in normal sinus rhythm. Of these, 6800 had left ventricular ejection fraction ≤45%. Most DIG participants were receiving angiotensin-converting enzyme (ACE) inhibitors and diuretics. Beta-blockers were not approved for HF during the DIG trial and data on beta-blocker use were not collected. Of the 7788 patients, 4036 (52%) patients were aged ≥65 years of age, and of them 3598 (89%) had valid data on baseline serum potassium levels. We excluded patients with a serum potassium level of ≥5 mEq/L from our analysis based on a preliminary analysis that suggested an increased risk of death associated with serum potassium at these levels. Thus we restricted our analysis to a subset of 590 low-potassium patients (<4 mEq/L) and 2684 normal-potassium (4–4.9 mEq/L) patients, of whom a matched cohort of 2231 patients were used for main analyses.

2.3. Low serum potassium

Serum potassium values below 4 mEq/L have been suggested as low in HF [7], and these patients may be at increased risk of death [2]. Therefore, we defined low serum potassium as <4 mEq/L. Of the 3274 patients in our analysis, 590 (18%) had serum potassium <4 mEq/L, of whom 561 (95%) were included in the matched analysis. Of the 561 patients with serum potassium <4 mEq/L, 61 patients had serum potassium <3.5 mEq/L, and of these only 12 patients had serum potassium <3 mEq/L.

2.4. Study outcomes

The primary outcomes were all-cause mortality and all-cause hospitalization. We also studied mortality and hospitalizations due to cardiovascular causes and HF. All study outcomes were ascertained by blinded study investigators. DIG participants were followed for a median of 38 months and vital status data were complete for 99% of the patients.

2.5. Statistical analysis

There were significant imbalances in baseline patient characteristics between patients with low (<4 mEq/L) and normal (4–4.9 mEq/L) serum potassium levels (Table 1, pre-match data). We used propensity scores to balance baseline covariates between patients with low (<4 mEq/L) and normal (4–4.9 mEq/L) serum potassium. The propensity score for hypokalemia of a patient may be defined as the conditional probability of that patient's developing hypokalemia given his/her baseline covariates. We estimated propensity scores for low serum potassium for each of the 3274 patients using a non-parsimonious multivariable logistic regression model [3,8,9]. In the model, low serum potassium was used as the dependent variable, and 32 measured baseline patient characteristics (Fig. 1, except for chronic kidney disease, which was a derived variable) were included as covariates. Clinically plausible interaction terms were tested but were not included in the final model due to lack of significant interactions [10]. We then used the propensity scores to match 561 (95% of 590) patients with low serum potassium with 1670 (62% of 2684) patients with normal serum potassium levels.

Pre-match imbalances in baseline covariates between groups and post-match balance achieved were assessed by estimating pre- and post-match absolute standardized differences of covariates between the two groups [2,11–13]. 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. An absolute standardized difference of 0% on a covariate indicates no residual bias for that covariate, and an absolute standardized difference below 10% suggests inconsequential residual bias [12]. We then compared baseline characteristics of matched patients using McNemar and paired sample *t* tests.

We used Kaplan–Meier plots and matched Cox regression analysis to estimate associations of low potassium with various outcomes. We confirmed the assumption of proportional hazards by a visual examination of the log (minus log) curves. We then repeated our analyses using serum potassium as a continuous variable. To determine whether the loss of sample size in the matching process affected our