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Association of diuretic treatment at hospital discharge in patients with heart failure with all-cause short- and long-term mortality: A propensity score-matched analysis from SwedeHF

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ABSTRACT

Aims: Diuretics are recommended for treating congestive symptoms in heart failure (HF). The short- and long-term prognostic effects of diuretic treatment at hospital discharge have not been studied in randomized clinical trials or in a Western world population. We aimed to determine the association of diuretic treatment at discharge with the risk of short-and long-term all-cause mortality in real-life patients in Sweden with HF irrespective of EF.
Methods and results: From a Swedish nationwide HF register 26,218 patients discharged from hospital were included in the present study. A total of 87% of patients were treated with and 13% were not treated with diuretics at hospital discharge. In a 1:1 propensity score-matched cohort of 6564 patients, the association of diuretic treatment at hospital discharge with the risk of 90-day all-cause mortality was neutral (HR 0.89, 95% CI 0.74–1.07, $p = 0.21$) whereas the risk of long-term all-cause mortality (median follow-up: 2.85 years) was increased (HR 1.15, 95% CI 1.06–1.24, $p < 0.001$).
Conclusion: Diuretic treatment at hospital discharge was not associated with short-term mortality whereas it was associated with increased long-term mortality. Although we accounted for a wide range of clinical features, measured or unmeasured factors could still explain this increase in risk. However, our results suggest that diuretic treatment at hospital discharge may be regarded as a marker of increased long-term mortality.

1. Introduction

Heart failure (HF) is a major health problem worldwide, with an estimated prevalence of approximately 2% in Western countries [1–3]. Evidence-based treatments with prognostic benefits have continuously been introduced in chronic HF during the last decades [4], coinciding with a decreased long-term mortality in chronic HF [5]. However; five-year mortality in HF is still almost 50% [6]. The relative risk for future all-cause mortality is higher in patients at hospital discharge when compared to ambulatory settings [7] and post-discharge 90-day mortality in HF is nearly 10% [8]. Diuretics are recommended as the first-line treatment of symptomatic congestion in international guidelines, but the prognostic short- and long-term effects have not been studied in randomized clinical trials [9,10]. In registry data, the diuretic treatment rate prior to hospitalization has been 65% compared to 83% at hospital discharge and 84% in ambulatory settings [11]. However, the association of diuretic treatment at hospital discharge with short-term mortality has never been studied and the association of diuretic treatment at hospital discharge with long-term mortality has never been studied in a Western world population. Diuretic treatment at hospital discharge has previously been associated with increased long-term mortality in a Japanese cohort of 2549 patients [12] but major epidemiological, therapeutic and prognostic differences between patients with HF in Japan and in the Western world are well-known [13].

Therefore, we aimed to investigate the association of diuretic treatment at discharge with short- and long-term mortality in a nationwide Western world cohort of real-life patients with HF.

2. Material and methods

2.1. Study subjects and registries

The Swedish Heart Failure Registry (SwedeHF) is a nationwide register introduced throughout Sweden in 2003, and records approximately 80 variables [14]. The inclusion criterion is clinician-diagnosed HF, irrespective of ejection fraction (EF). Patients are included either at hospital discharge or as outpatients, either hospital-based or in primary care. Baseline variables are recorded online into a database managed by the Uppsala Clinical Research Center, Uppsala, Sweden. In SwedeHF discharge reports, the latest

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available data or examination result during the hospitalization is recorded for each variable. A recorded treatment in the hospital discharge report in SwedeHF was considered as active treatment at discharge in the present study. The protocol, registration form, and annual report are available at http://www.ucr.uu.se/rikssvikt. Individual patient consent is not required or obtained, but patients are informed of entry into the register and are allowed to opt out.

Patients who were registered in SwedeHF between January 1, 2004 and December 31, 2011 were eligible for inclusion in the present study. During this period, 69,068 registrations (baseline and re-registrations) occurred at 61 hospitals and 64 primary care centres. Of these, 45,174 were unique, first-time registrations (Fig. 1). Exclusion criteria are shown in Fig. 1. The final study population consisted of 26,218 patients that were discharged alive from hospital (57% males, 43% females). In this study, mortality data were obtained monthly from the Swedish Population Registry, with final data collection on January 15, 2013.

Establishment registration of the register and analysis of the data were approved by a multisite ethics committee. The investigation conforms to the principles outlined in the Declaration of Helsinki. The present study was approved by the Regional Ethical Review Boards of Gothenburg University (540-11, T063-13) and Linköping University (2012/202-31).

2.2. Multiple imputation, propensity scoring and matching

To avoid bias attributable to missing baseline variables, multiple imputation ($n = 10$) was performed for variables with missing data, using fully conditional specification [15]. The propensity score (PS) confers a propensity from 0 to 1 to receive a specific treatment in a specific cohort given a set of known baseline variables. The aim of the PS is to adjust for potential selection bias, confounding, and differences between treatment groups in observational studies [16]. The PS for diuretic treatment was estimated from 46 baseline variables (all baseline variables presented in Table 1, summarized in e-Appendix) using logistic regression. The PS for an individual patient was the mean PS for all 10 imputations using the across approach method [17]. A PS-matched cohort was defined with matching 1:1 for diuretic treatment or not and without replacement, with each untreated patient matched with the closest treated patient. A difference in PS of <0.01 was accepted. This resulted in a matched cohort of 6564 patients ($n = 3282$ in each of the diuretic and non-diuretic groups).

2.3. Statistical analysis

Continuous variables are presented as mean (standard deviation) or median (interquartile range) if non-normally distributed. Estimated glomerular filtration rate was calculated from available data on age and serum creatinine [18]. Categorical variables are presented as counts and percentages. Comparisons between groups were made using the chi-square test for categorical variables, the independent samples *t*-test for normally distributed continuous variables, and the Mann–Whitney *U* test for continuous variables with a skewed distribution. Standardized differences were calculated. Subsequent analyses were made with a propensity score based on imputed data. Survival data are shown using Kaplan–Meier curves and compared with the log rank test. We estimated the association of diuretic treatment at discharge with 90-day (short-term) all-cause mortality and long-term all-cause mortality in all included patients. Unadjusted hazard ratios (HRs) for the association between diuretic treatment and all-cause mortality were estimated using Cox regression analyses. In a second model, the PS for diuretic treatment was entered in a Cox Regression as an additional covariate to adjust for confounders. In a third model, analyses were performed in a PS-matched cohort. We confirmed the assumption of proportional hazards by a visual examination of the log (minus log) curves. HRs for the association between diuretic treatment and long-term all-cause mortality in subgroups were estimated. Possible interactions were considered by entering interaction terms between diuretic treatment and the subgroup variables. Quantification of the effects of hypothetical unmeasured confounders necessary to change our results was performed [19].

All analyses were conducted using SPSS version 22.0 (IBM Corp., Armonk, NY, USA) and Python Essentials for Statistics version 22 (The Python Software Foundation, Wilmington, DE, USA). A two-sided *P* value <0.05 was considered statistically significant.

3. Results

3.1. Baseline demographic and clinical characteristics in the original cohort

Baseline characteristics in patients with or without diuretics are shown in Table 1. Overall, there were 26,218 patients discharged from hospital (14,840 males, 11,378 females; mean age: 77.1 (11.6) years), 22,881 (87%) were treated with diuretics at discharge and 3337 (13%) were not. Patients without diuretics were generally younger, more frequently male, had a shorter duration of HF, were less frequently former HF inpatients, more likely to be in NYHA classes I–II, had less frequently pulmonary congestion on chest X-ray, lower levels of NT-proBNP, and a higher estimated glomerular filtration rate, than those treated with diuretics. A low EF (<40%) was marginally more common in patients without diuretics than in those with diuretics (56% vs 53%).

3.2. The association of diuretic treatment with mortality in the original cohort

The long-term all-cause mortality rate (Table 1), the HR for 0–90-day all-cause mortality (HR 1.62, 95% confidence interval [CI]

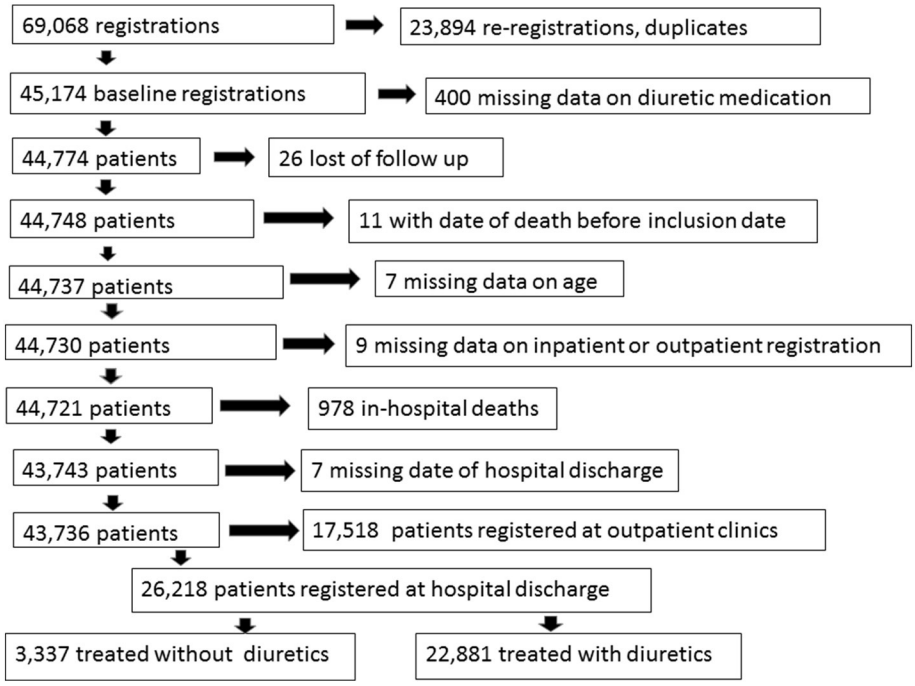

Fig. 1. Flow chart of patient inclusion.