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Original Article

Therapy modifications during hospitalization in patients with chronic heart failure

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ABSTRACT

Background: Guidelines on suggested pharmacological treatments for heart failure (HF) are not optimally implemented in clinical practice and whether pharmacotherapy adjustment actually happens in daily practice is largely unknown. We aimed to investigate pharmacotherapy modifications during hospitalization.
Methods: This was a prospective observational survey where all admissions were screened for HF; 210 patients were included. The guideline adherence index (GAI) and modified GAI (mGAI, if ≥50% of target dose) were used to grade the pharmacotherapy.
Results: Among 198 patients discharged alive (mean age 77 years, 51% male), 49% had preserved left ventricular ejection fraction (PLVEF) and 30% had left ventricular systolic dysfunction (LVSD); the echocardiography report was unavailable for 21%. Angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, beta-blockers and mineralocorticoid receptor antagonists were prescribed to 78%, 58% and 20% of patients on admission and 72%, 65% and 23% at discharge, respectively. Overall, 14% of patients met GAI-3, but at discharge only 7% met mGAI-3. One of the key drugs was stopped or down-titrated in 27%. During follow-up, 21% of patients died (25% with LVSD). Patients with LVSD discharged with at least one HF drug had a lower risk of death than patients with none (HR = 0.142, 95% CI = 0.029–0.683, $p = 0.015$). Patients with PLVEF had better prognosis than LVSD patients when no HF drugs were prescribed at discharge (HR = 0.075, 95% CI = 0.009–0.627, $p = 0.017$).
Conclusions: The pharmacotherapy of HF patients did not improve significantly during hospitalization, remaining suboptimal. Treatment with key drugs was terminated or reduced in a significant proportion of patients, mostly without specific written justification.

1. Introduction

Long-term healthcare registries show that the implementation of the guidelines [1,2] on treatment of heart failure (HF) in clinical practice has improved over the years and that life-saving therapies are widely used in such patients [3–9]. Even when patients are hospitalized because of condition deterioration, there is ample opportunity for optimization of individual pharmacotherapy, and prescription of guideline-recommended drugs usually increases during hospitalization [6,7,9–11]. Different forms of guideline adherence index/indicator (GAI) have been used to assess implementation of the recommendations in practice, and studies have demonstrated that the GAI predicts outcome [5,7,12,13]. However, non-prescription, drug termination and dose adjustment are also reasonable in some patients and could be guided by the patient's situation and side effects [1,2,9,12,14–16]. These reasons are widely underreported and often not documented in medical records, especially reasons of a contextual nature [12,16]. They therefore remain unknown in individual patients, which could lead to overestimation of guideline non-implementation, and also to potential hazards for the patient if such therapies are restarted.

The aim of this study was to evaluate modifications of HF pharmacotherapy during hospitalization in order to analyze current clinical practice. Survival analysis was used to investigate the effects of drug therapy on patient outcome.

2. Methods

2.1. Survey design, patient population and inclusion criteria

The survey was part of a larger study in hospitalized patients in Slovenia. The protocol of the survey was reviewed and approved by

Abbreviations: ACEI, Angiotensin-converting enzyme inhibitor; ARB, Angiotensin receptor blocker; BB, Beta-blocker; CI, Confidence interval; eGFR, Bstimated glomerular filtration rate; GAI, Guideline-adherence index; HF, Heart failure; HR, Hazard ratio; LVEF, Left ventricular ejection fraction; LVSD, Left ventricular systolic dysfunction; PLVEF, Preserved left ventricular ejection fraction; MDRD, Modification of Diet in Renal Disease; MRA, Mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-peptide of brain natriuretic peptide; NYHA, New York Heart Association.

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the National Ethics Committee and is available at clinicaltrials.gov (NCT01855165).

We prospectively screened all admissions during a 14-week enrollment period at the University Clinic Golnik in 2013. Patients were included if they met at least one of four inclusion criteria [17]:

- known HF diagnosis prior to admission,
- echocardiography report confirming left ventricular dysfunction,
- symptoms and signs of HF with elevated serum natriuretic peptide (NT-proBNP), and
- treatment with a loop diuretic within 24 h after admission for reasons other than renal failure.

We excluded patients with any terminal chronic disease (e.g. cancer, chronic obstructive pulmonary disease, chronic kidney disease, etc.) and those who died during hospitalization. None of the authors was included in patient management. The included patients were divided into three HF subgroups according to the echocardiography report:

- left ventricular systolic dysfunction (LVSD), when left ventricular ejection fraction (LVEF) was <55%
- preserved left ventricular ejection fraction (PLVEF), when LVEF was ≥55% or a qualitative description of "preserved ejection fraction" or "mild left ventricular dysfunction" was given, and
- no echocardiography report

We retrieved the demographic characteristics, medical histories, laboratory test results, echocardiography reports, and pharmacological treatments at admission and discharge. We also recorded the reasons for admission, the proportion of patients with anemia (serum hemoglobin level < 120 g/L in women, <130 g/L in men), and the proportions of patients with the following findings on admission: $K^+ > 5.0$ mmol/L, estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2, and systolic blood pressure < 90 mm Hg. Renal function in all the patients was estimated using the simplified Modification of Diet in Renal Disease (MDRD) equation [18].

We evaluated the prescription, mean dose, and proportion of patients prescribed the target dose at admission and discharge for the following drugs: angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin receptor blockers (ARBs), beta-blockers (BBs) and mineralocorticoid receptor antagonists (MRAs) [1]. The target dose was set as the maximum daily dose recommended in the guidelines [1], with the exception of losartan where the target was set at 100 mg (instead of 150 mg) as used in the European Society of Cardiology-HF Pilot Survey [10]. Where the daily dose was stated as a range, the target dose was set at the lower limit, except in the case of lisinopril where the upper limit was used. Target doses were then considered equivalently effective within each pharmacological class, as already implemented [19]. Adherence to the guidelines was evaluated using the GAI [5]. In our survey, GAI-1, GAI-2, and GAI-3 represent the prescription of one, two, or all three neurohormonal antagonists. The indexes were also used in a modified form (mGAI) to simultaneously describe the prescription and reaching ≥50% of the target dose. In addition, we assessed therapy modification by following two main changes: the prescription or discontinuation of a drug, and up-titration to >50% of the target dose or down-titration to <50%. When a drug was discontinued and/or down-titrated, we searched the discharge letter for the physician's explanation of the modification. We also noted the prescription of loop diuretics and digoxin. For GAI-5, the prescription of loop diuretics and digoxin was added to GAI-3.

For survival analysis, we obtained all-cause mortality data from the Central Population Registry of Slovenia. Patient follow-up started at discharge and ended after a period of 6 months was exceeded for the last discharged patient. Primary categorization according to drug therapy resulted in subgroups that were too small; therefore, we used a simplified GAI comprising only two categories: patients discharged with at least one HF drug (GAI-123) and those discharged with none (GAI-0).

2.2. Statistical analysis

All statistical calculations were performed using IBM SPSS Statistics for Windows, Version 22.0. A p-value < 0.05 was considered statistically significant. McNemar's chi-square test and Wilcoxon signed-rank test were used for categorical data; t-test was used for continuous data. All tests were two-sided. Continuous variables are reported as mean (standard deviation; SD) or median (1st quartile–3rd quartile; IQR). The multivariate Cox proportional hazards model was used for survival analysis. A regression model was built to investigate the effects of the GAI on survival adjusted for potential effect of patient HF subgroup, age, sex and natriuretic peptide value (log_{10}-transformed NT-proBNP) on survival. Interaction terms among between GAI and patient HF subgroup were also tested. The results are presented as hazard ratios (HRs) with respective 95% confidence intervals (95% CIs).

3. Results

3.1. Patient characteristics

Of 210 eligible patients (15% of all admissions during the screening period), 198 were discharged alive after a mean (SD) of 11 (SD: 7) days and their data were analyzed. Overall, 49% of the patients had PLVEF and 30% had LVSD; the echocardiography report was not available for 21% (Fig. 1). Three inclusion criteria were met in 45% of patients, 34% reached two, 15% one, and in 6% of all the four criteria were met. The presence of symptoms and signs with elevated NT-proBNP was the most commonly met criterion (86% of patients). The mean (SD) age of the patients was 77 (SD: 8) years and 51% of the patients were male. The female patients were significantly older than the males: 78 (SD: 8) vs. 75 (SD: 8) years, $p = 0.007$, t-test. Patients with PLVEF were significantly older than those with LVSD: 78 (SD: 8) vs. 74 (SD: 9) years, $p = 0.027$, t-test. The patient characteristics are shown in Table 1.

Overall, 84% of the patients were in NYHA functional classes III and IV, making HF decompensation the most common primary reason for admission (58%). Other common reasons were infections (11%), chronic

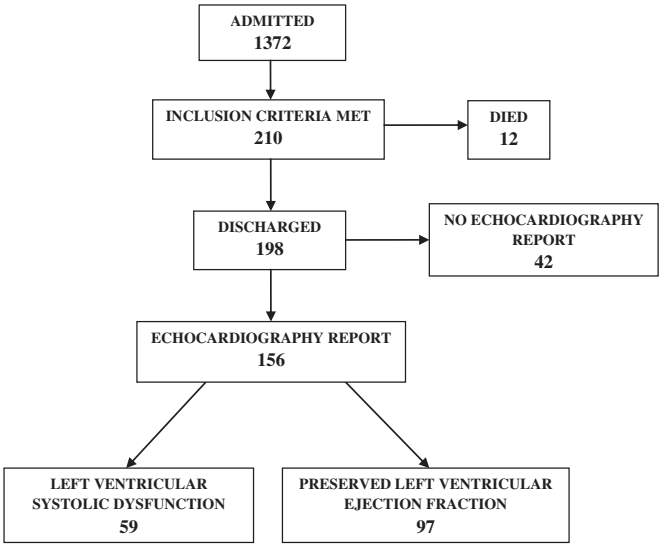

Fig. 1. Patient flow chart.