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# Heart failure pharmacotherapy guideline implementation and survival of patients in a community hospital: a retrospective study

## Udejanjanje smernic za zdravljenje srčnega popuščanja in preživetje bolnikov v regijski bolnišnici: retrospektivna raziskava

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## Izvleček

**Izhodišča:** Le malo raziskav je preučevalo udejanjanje smernic za zdravljenje srčnega popuščanja pri bolnikih v regionalnem okolju. Naš namen je bil preučiti farmakološko zdravljenje bolnikov s srčnim popuščanjem ob odpustu iz bolnišnice in morebitni vpliv na celotno umrljivost.

**Metode:** V retrospektivni raziskavi smo pregledali odpustno dokumentacijo hospitaliziranih bolnikov v regionalni bolnišnici, ki so bili odpuščeni ali so umrli z diagnozo srčno popuščanje v letih 2001–2003. Iz odpustnic smo povzeli osnovne značilnosti in podatke o farmakološkem zdravljenju. Podatke o preživetju smo pridobili iz centralnega registra prebivalstva.

**Rezultati:** Vključili smo 638 bolnikov (73 ± 10 let, 48 % moških, 74 % razreda NYHA III ob sprejemu). Izvid ultrazvočne preiskave srca smo imeli za 61 % bolnikov, pri 70 % bolnikov smo ugotavljali okrnjeno sistolično funkcijo (43 % vseh bolnikov). Ob odpustu so bolniki v povprečju prejeli 6 zdravil (1–14 zdravil), od tega 4 zdravila za srčno-žilne bolezni (0–10 zdravil). V opazovanem obdobju smo ugotavljali povečanje predpisovanja zaviralcev adrenergičnih receptorjev beta, predpisovanje zaviralcev konvertaze angiotenzina pa se v opazovanem obdobju ni spreminjalo. Ciljne odmerke zaviralcev adrenergičnih receptorjev beta smo svetovali v 4 %, zaviralce ACE pa v 20 %. Kombinacija zdravljenja s tremi nevrohormonskimi zdravili, ki smo jo zasledili pri 83 bolnikih (13 %), je bila v multivariantnem modelu povezana z nižjo celotno smrtnostjo (razmerje tveganj 0,69, 95-odstotni interval zaupanja 0,49–0,98). Višji odmerki zaviralcev ACE so bili povezani z boljšim izidom bolezni (razmerje tveganj 0,79, 95-odstotni interval zaupanja 0,68–0,93).

**Zaključki:** Udejanjane smernic za zdravljenje bolnikov s srčnim popuščanjem v regijski bolnišnici se je z raziskavo izkazalo za nezadostno. Farmakološko zdravljenje z nevrohormonskimi zaviralci je bilo povezano z boljšim izidom bolezni.

## Abstract

**Background:** Few studies have investigated implementation of heart failure (HF) pharmacotherapy in a non-selected community setting. We aimed to investigate pharmacotherapy at discharge from hospital and potential associations with all-cause mortality.

**Methods:** In this retrospective study, hospital discharges and deaths from a community hospital in the period 2001–2003 were screened for diagnosis of HF. Patient and pharmacotherapy information was retrieved from medical records and survival information was obtained from the Central Population Registry.

**Results:** We included 638 patients (73 ± 10 years, 48 % men, 74 % NYHA class III on admission). Echocardiography report was available for 61 %, and 70 % of those imaged (43 % of total population) had left ventricular systolic dysfunction. A median of 6 (interquartile range 1–14) drugs, 4 (interquartile range 0–10) being for cardiovascular disease, was prescribed at discharge. Over years, prescription rate of beta-blockers (BB) increased whereas it remained stable for angiotensin converting enzyme (ACE) inhibitors. A target dose of BB and ACE inhibitors was prescribed to 4 % and 20 %, respectively. Combined neurohormonal antagonist therapy was prescribed to 83 (13 %) of patients, which was associated with lower all-cause mortality risk in a multivariate model (hazard ratio 0.69, 95 % confidence interval 0.49–0.98). Higher dose of ACE inhibitors was also associated with better outcome (hazard ratio per tertile: 0.79, 95 % confidence interval 0.68–0.93).

**Conclusions:** In our non-selected community-based HF cohort, pharmacotherapy was not implemented as appropriate. When applied, pharmacological therapy with neurohormonal antagonists was associated with a better outcome.

## Introduction

Heart failure (HF) is an increasing public health problem imposing a significant burden on the patient and health care system. Despite cost-effective pharmacological therapy as summarized regularly by the European Society of Cardiology (ESC), mortality remains excessive.[1-6] Prognosis is particularly poor in patients after hospitalization for HF.[6-8] Hence, scientific community and policy makers consider hospitalizations as a major preventable event on a HF patient's journey. On the other hand, an average hospital stay of 10 days represents an invaluable chance to address open diagnostic issues and to individually tailor patient management.[9] The implementation in clinical practice, however, remains inadequate and there is little data how pharmacotherapy is associated with patient outcomes.[6-8,10]

In Slovenia, limited data is available on in-hospital HF patient management. Over time, there was a constant improvement in patient assessment and pharmacotherapy, but generally, the guidelines were not followed as appropriate.[5,11-13] This primarily holds true for some agents (e.g. beta-blockers), particularly in conjunction with certain comorbidity, when only limited proportion of patients are treated with a target dose.[14-16] Evidence regarding reduced mortality is robust only for patients with left ventricular systolic dysfunction, whereas no large-scale study reported benefit in patients with preserved left ventricular ejection fraction, who make about 50 % of general HF population. Nonetheless, the treatment of underlying cardiovascular disease and risk factors are largely the same as in patients with left ventricular systolic dysfunction.[1-4]

With little information about HF management in Slovenian hospitalized patients, we initiated this retrospective study to obtain an insight into pharmacotherapy at discharge. In addition, we evaluated the associations between pharmacotherapy and long-term outcomes.

## Methods

### Study design, patients, and data collection

In this retrospective study, all discharges between December 2000 and December 2003 from the Department of Internal Medicine at the General Hospital Murska Sobota, a community hospital serving a population of 125,000 inhabitants, were screened for patient inclusion. We identified eligible patients using the ICD-10 codes I50.0-I50.9 and included those who have been discharged alive. The National Ethics Committee revised and approved the study protocol.

Data on demographic characteristics, electrocardiogram, echocardiography, laboratory parameters and pharmacological management at discharge were retrieved from medical records. Target doses of individual pharmacological agents followed those reported by the ESC guidelines.[1] Enalapril and carvedilol target dose was used as the reference for angiotensin converting enzyme (ACE) inhibitors and beta-blockers (BB), respectively, for the comparison of daily doses in relation to a target dose. Equivalent doses of other ACE inhibitors were calculated by multiplying the daily dose by a factor between the target daily dose of the used drug and the target daily dose of enalapril or carvedilol. Estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease equation.[17] Long-term survival was assessed by cross-referencing patient data with the Central Population Registry. Our database was censored on 1.11.2008 and no patients were lost to follow-up.

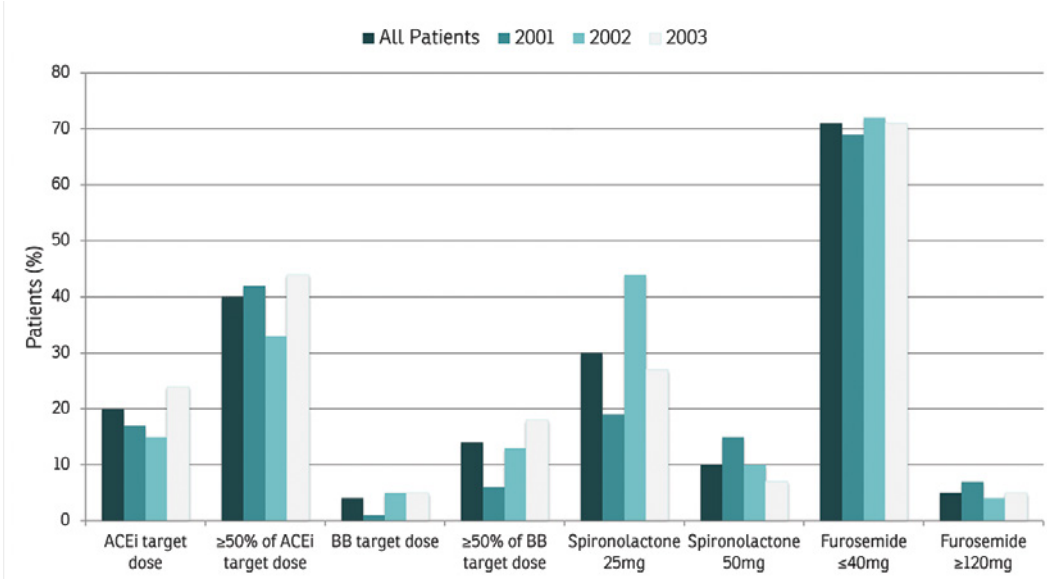



**Figure 1:** Proportion of patients treated with target dose or ≥50% of target dose. ACE – angiotensin converting enzyme; BB – beta blockers.

## Statistical analysis

Continuous variables are presented with mean ± standard deviation (SD) or as median with interquartile range (IQR). Categorical variables are presented as absolute numbers and proportions. To evaluate the differences between patients according to year of hospitalization, Student's *t*-test, the chi-squared test and the Mann–Whitney U-test were used as appropriate. Predictors of BB prescription were estimated by logistic regression model. Event-free survival was estimated from Kaplan–Meier curves and compared using the log-rank test. Cox proportional hazard models were constructed to study the relationship between pharmacotherapy and all-cause mortality. Combined neurohormonal treatment was defined as a combination of ACE inhibitor/angiotensin receptor blocker (ARB), BB, and spironolactone. Patients were divided into tertiles of enalapril equivalent daily dose: ≤5mg, 6–10 mg and > 10 mg. To determine independent predictors of all-cause mortality, adjustment for age, gender, comorbidity, and renal function was applied in a multivariate model. We report odds ratios (OR), hazard ratios (HR) and corresponding 95 % confidence intervals (CI). Data collection and all calculations were made using the software package SPSS 18.0 (SPSS Inc., 2009, Chicago, Illinois, USA). For all tests, a *P*-value of 0.05 or less (two-sided) was considered statistically significant.

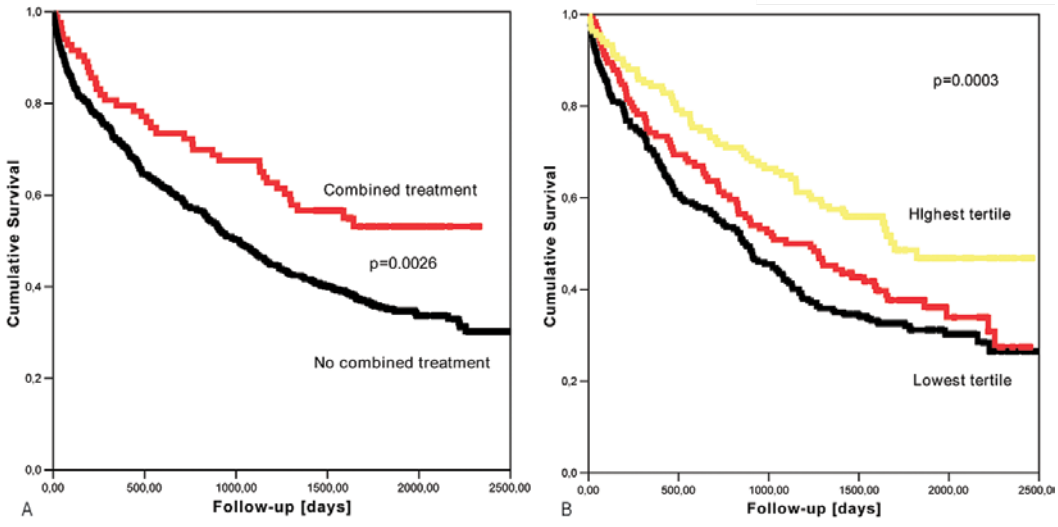
## Results

We identified 766 eligible patients and after excluding those who died during hospitalisation (N = 128), 638 patients (73 ± 10 years, 48 % men, 74 % NYHA class III on admission) were available for analysis (Table 1). Atrial fibrillation and arterial hypertension were most common comorbidities, and 52 % of patients had eGFR < 60ml/min. Echocardiography report was available for 61 % and 70 % of those imaged (43 % of total population) had left ventricular systolic dysfunction.

Patients were discharged with a median of 6 (IQR 1–14) drugs, 4 (IQR 0–10) being for cardiovascular disease. No significant differences in the number of drugs or the proportion of patients treated with key pharmacological agents were observed per different left ventricular function (p > 0.2 for all). Over years, the proportion of patients treated with ACEi/ARB remained stable whereas we recorded a decrease in the use of furosemide and digoxin and an increase in the use of BB, which nearly doubled (Table 2). Patients with chronic obstructive pulmonary disease (OR 0.35, 95 % CI 0.19–0.64) and those older than 75 years (OR 0.41, 95 % CI 0.28–0.59) were less likely to be prescribed with BB. Prescription of either target or ≥ 50 % of target dose of ACE inhibitors and BB increased over years, whereas furosemide dosing remained stable. Generally,

**Figure 2a (left):** Kaplan-Meier survival curves for treatment with combination of neurohormonal antagonists.

**Figure 2b (right):** Kaplan-Meier survival curves for treatment per angiotensin converting enzyme daily dose tertile.




<10 % of patients received > 25 mg of spironolactone (Figure 1).

During an average follow-up of 35 ± 25 months, 396 (62 %) patients died. A neurohormonal antagonists combination therapy was prescribed to 83 (13 %) of patients, which was associated with lower all-cause mortality risk (Figure 2a) (HR 0.60, 95 % CI 0.43–0.86). An increasing dose of ACE inhibitor per tertile of target dose was also associated with lower risk of all-cause mortality (Figure 3) (HR per tertile: 0.76, 95 % CI 0.66–0.87).

**Table 1:** Patient characteristics by year of hospitalization. Data are given as mean ± standard deviation or number (%).

| | All patients | Year 2001 | Year 2002 | Year 2003 | p |
|---|---|---|---|---|---|
| **Number** | 638 | 171 | 193 | 274 | |
| **Age (years)** | 73 ± 10 | 74 ± 11 | 72 ± 10 | 73 ± 10 | ns |
| **Men** | 307 (48) | 83 (49) | 93 (48) | 131 (48) | ns |
| **Ischemic heart disease** | 135 (21) | 30 (17) | 43 (22) | 62 (23) | ns |
| **Arterial hypertension** | 286 (45) | 86 (50) | 86 (45) | 114 (42) | ns |
| **Atrial fibrillation** | 335 (53) | 92 (54) | 120 (58) | 123 (45) | 0.013 |
| **Diabetes mellitus** | 208 (33) | 55 (32) | 60 (31) | 93 (34) | ns |
| **Chronic kidney disease** | 137 (21) | 37 (22) | 40 (21) | 60 (22) | ns |
| **Chronic obstructive pulmonary disease** | 106 (17) | 32 (19) | 35 (18) | 41 (15) | ns |
| **Echocardiography** | 392 (61) | 92 (54) | 125 (65) | 175 (64) | 0,03 |
| **Systolic dysfunction** | 276 (43) | 66 (39) | 88 (46) | 122 (44) | <0.01 |
| **Haemoglobin (g/l)** | 133 ± 20 | 137 ± 19 | 133 ± 19 | 131 ± 21 | 0.005 |
| **Potassium (mmol/l)** | 4.4 ± 0.5 | 4.4 ± 0.5 | 4.4 ± 0.5 | 4.4 ± 0.5 | ns |
| **Creatinine (umol/l)** | 113 ± 65 | 115 ± 75 | 105 ± 36 | 118 ± 73 | ns |
| **Estimated glomerular filtrtion rate (ml/min)** | 51 ± 20 | 51 ± 18 | 53 ± 19 | 51 ± 21 | ns |

In multivariate models for all-cause mortality, treatment with a combination of neurohormonal antagonists and with higher daily dose of ACE inhibitors was associated with lower risk for all-cause mortality (Table 3a and 3b). Both findings were independent of left ventricular systolic function.

## Discussion

To our knowledge, this is one of few reports on the prognostic implications of pharmacotherapy in a non-selected community-based HF cohort. In clinical practice, implementation of HF guidelines remains suboptimal, both in terms of neurohormonal antagonist prescription and titration. When applied, however, pharmacological therapy with neurohormonal antagonists was associated with better outcome.

Several pan-European surveys and national registries demonstrate constant improvement in pharmacotherapy patterns over last decade.[7,18,19] Our results are in line with previous reports, but show rather unsatisfactory numbers for BB prescription and titration. It needs to be stressed that in-hospital initiation appears crucial, as patients discharged home as BB naïve have less chances to be on long-term BB therapy when compared to those discharged with BB's.[20] Apparently, several reasons for such clinical practice exist, where advanced age, certain comorbidity (e.g. chronic obstructive pulmonary disease), and patient characteristics (blood pressure, heart rate) may be most relevant ones, although little evidence is supportive for such clinical practice.[21] Also, it is not trivial to titrate BB in a 14-day manner as previously advised by the guidelines.[1] The largest BB comparative study in the elderly HF patients, the CIBIS-ELD study, demonstrated that only about a quarter of patients in whom treatment with bisoprolol or carvedilol was initiated, actually were up-titrated and remained on the target dose if such strict titration scheme was applied.[22] Whether target dose is the ultimate goal in BB therapy was recently challenged. In a large meta-analysis, the heart rate was more important than BB target dose,[23] which may even be a factor preventing further titration of BB[24] or introduction of adjunct therapy with ivabradine,[4] which appears to be also safe in elderly[25] and those with concomitant COPD.[26]

Only few studies investigated whether neurohomonal antagonists are associated with clinical benefits in non-selected community HF patients. Additional analyses of the EuroHeart Failure Survey demonstrated that treatment with ACE inhibitors and BB reduced 12-week mortality by at least 20 %.[27] An Austrian subsample analysis of 341 patients showed that 81 patients were treated with triple combination of neurohormonal antagonist, which was associated with significant prognostic benefit.[10] Stoerck et al. evaluated 1054 HF patients (61 % with reduced left ventricular ejection fraction) and

**Table 2:** Pharmacological treatment. Data are given as number (%).

| | All patients | Year 2001 | Year 2002 | Year 2003 | p |
|---|---|---|---|---|---|
| Angiotensin converting enzyme inhibitors | 495 (77) | 139 (81) | 151 (78) | 205 (75) | ns |
| Beta blockers | 165 (26) | 28 (16) | 56 (29) | 81 (30) | 0.004 |
| Spironolactone | 278 (44) | 68 (40) | 108 (56) | 102 (37) | <0.001 |
| Angiotensin receptor blockers | 24 (4) | 4 (2) | 8 (4) | 12 (4) | ns |
| Furosemide | 529 (83) | 150 (88) | 161 (83) | 218 (80) | ns |
| Thiazides or thiazide like diuretics | 60 (9) | 12 (7) | 21 (11) | 27 (10) | ns |
| Digoxine | 343 (54) | 113 (66) | 101 (52) | 129 (47) | <0.001 |

reported a median 67 % and 50 % Guideline Adherence Indicator-3 (GAI-3) in patients with and without left ventricular systolic dysfunction.[8] In both cohorts, higher GAI-3 was predictive of better patient outcome. The latter was observed in our cohort and has important clinical implications. Whilst evidence about prognostic benefit of neurohormonal antagonists is available for patients with reduced left ventricular ejection fraction, it is rather intuitive that same therapy would also confer benefit for those with preserved left ventricular ejection fraction. Although the randomized studies in the field failed to provide conclusive evidence, information from clinical practice and certain sub analyses of large-scale trials are suggestive that such treatment at least should not be withheld in those patients.[4]

Our findings need to be interpreted in light of certain limitations. As per study design, we relied on data retrieved from medical records, which means that information on comorbidity and diagnostic procedures may not be complete. The inclusion criterion of ICD-10 diagnosis can be challenged; yet, this is the usual way implemented in retrospective studies and yields reliable information.[28] We are also unaware of potential contraindications that prevented introduction or uptitration of pharmacological agents. Finally, only all-cause mortality was

**Table 3:** Univariable and multivariable predictors of all-cause mortality in subjects a) treated with a combination of neurohormonal antagonists and b) per tertile of angiotensin converting enzyme inhibitor daily dose. Data are presented as hazard ratios with corresponding 95 % confidence intervals.

*a) treated with a combination of neurohormonal antagonists*

| | Univariate | Multivariate |
|---|---|---|
| **Men [vs. women]** | 0.95 [0.78–1.15] | 0.91 [0.73–1.14] |
| **Age [per 1 year increase]** | 1.03 [1.02–1.05] | 1.03 [1.02–1.04] |
| **Ischaemic heart disease** | 0.83 [0.65–1.06] | 0.77 [0.60–0.99] |
| **Arterial hypertension** | 0.69 [0.56–0.84] | 0.66 [0.54–0.82] |
| **Atrial fibrillation** | 1.13 [0.92–1.37] | 1.05 [0.85–1.29] |
| **Diabetes mellitus** | 0.89 [0.72–1.10] | 0.95 [0.76–1.18] |
| **Estimated glomerular filtration rate [per 1ml/min increase]** | 0.99 [0.98–0.99] | 0.99 [0.98–0.99] |
| **Combination of neurohormonal antagonists** | 0.76 [0.66–0.87] | 0.69 [0.49–0.98] |

*b) per tertile of angiotensin converting enzyme inhibitor daily dose*

| | Univariate | Multivariate |
|---|---|---|
| **Men [vs. women]** | 0.95 [0.78–1.15] | 1.01 [0.78–1.31] |
| **Age [per 1 year increase]** | 1.03 [1.02–1.05] | 1.03 [1.02–1.05] |
| **Ischaemic heart disease** | 0.83 [0.65–1.06] | 0.84 [0.63–1.11] |
| **Arterial hypertension** | 0.69 [0.56–0.84] | 0.85 [0.65–1.10] |
| **Atrial fibrillation** | 1.13 [0.92–1.37] | 0.97 [0.77–1.23] |
| **Diabetes mellitus** | 0.89 [0.72–1.10] | 1.05 [0.82–1.35] |
| **Estimated glomerular filtration rate [per 1ml/min increase]** | 0.99 [0.98–0.99] | 0.99 [0.98–0.99] |
| **Angiotensin converting enzyme dose [per tertile]** | 0.76 [0.66–0.87] | 0.79 [0.68–0.93] |

analysed whereas the influence of pharmacotherapy on readmissions would also be relevant due to associated costs.

## Conclusions and clinical implications

Our retrospective study gives an insight into HF pharmacotherapy at discharge, which was not satisfactory, neither in terms of agents prescribed nor in daily doses reached. Over years, there was improvement in diagnostic and therapeutic management yet the optimal goals were still not reached. Importantly, and irrespective of left ventricular function, treatment with a combination of neurohormonal antagonists and with higher doses of ACE inhibitors was associated with lower all-cause mortality. Therefore, optimization of pharmacotherapy during hospital stay should be pursued when ample opportunity exists. Whenever possible, patients should be referred to specialized HF clinics for adequate counselling and further therapy optimization with periodical follow-up.[29-31] In conjunction with that, higher standards of HF management across all levels of care, starting with the awareness, aetiological treatment, and multidisciplinary approach, should be applied according to local needs and potentials.[32,33]

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