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# DOSE UP-TITRATION OF NEUROHORMONE BLOCKERS FOR CHRONIC HEART FAILURE TREATMENT IN REAL CLINICAL PRACTICE: DATA FROM SINGLE UNIVERSITY CENTRE

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**Key words:** chronic heart failure, neurohormonal antagonists, dose up-titration.

**Summary**

Objective. To describe treatment peculiarities of ambulatory chronic heart failure patients' in one of Lithuania's university centres, participating in European Society of Cardiology EURObservation Research Programme (EORP) Heart Failure Long-Term Registry.

Methods. 240 ambulatory patients with chronic heart failure were entered in European Society of Cardiology EURObservation Research Programme (EORP) Heart Failure Long-Term Registry from our university centre between May 2011 and March 2013. Follow-up data were collected after 12 months. Registered data about heart failure treatment were included to this study. Statistical analysis was performed with SPSS 22 program.

Results. In our centre 67,1% of patients received angiotensin converting enzyme inhibitors at target doses, one third (34,3%) had not reached target doses due to symptomatic hypotension. Beta blockers were up-titrated to target doses for 82,5% of patients and the main reasons for failure to reach their target dose were: symptomatic bradycardia (12,7%), symptomatic hypotension (10,7%). Mineralocorticoid receptor antagonists were up-titrated to a target doses just for half of the patients – 52,1% and the most frequent reason for not reaching target doses was hyperkalemia (15,4%).

Conclusions. Angiotensin converting enzyme inhibitors, beta-blockers and mineralocorticoid receptors antagonists, except angiotensin receptor blockers, were prescribed in a guideline-recommended doses. The main reasons why the target doses of neurohormone blockers have not been achieved were symptomatic hypotension for angiotensin converting enzyme inhibitors, symptomatic bradycardia for beta-blockers and hyperkalemia for mineralocorticoid receptors antagonists.

## Introduction

Chronic heart failure (CHF) is a major public health problem. Diagnosis of CHF carries substantial risk of morbidity and mortality, despite advances in management [1]. The aims of CHF treatment are to reduce the risk of mortality, control symptoms and improve quality of life [2]. Optimal implementation of evidence-based therapies such as neurohormonal blockade with adequate doses of these drugs can improve patients' outcomes [2-3]. The rate of use of renin–angiotensin–aldosterone system blockers (ACE-inhibitors, angiotensin receptor blockers, aldosterone blockers) and beta-adrenergic blockers is satisfactory. However, the number of patients treated with appropriate doses is suboptimal [4].

**The aim of the present** analysis is to describe the characteristics of ambulatory CHF patients treatment in one of Lithuania's university centres. The analysis covers up-titration peculiarities of standard neurohormone blockers.

## Material and methods

Patients' data from our centre were entered in the European Society of Cardiology EURObservation Research Programme Heart Failure Long-Term Registry (ESC HFL-TR) on a one-day-per-week basis from May 2011 to March 2013. Follow-up data were registered one year later based on a visit to the clinical centre after 12 months or follow-up by phone. Registered data includes information about patient's physical examination, previous history, co-morbidities, treatment, laboratory data, and changes in HF treatment after 12 months. Statistical analysis was performed


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with SPSS 22 program. Ethics Committee's approval No. BC-LSMU (R)-166 of 02/03/2011.

**Results**

**Patients' characteristics.** CHF cohort was consisted of 240 patients. The age was in an average of 66 yrs (74-56 yrs) and the majority of patients were male. Medium systolic blood pressure (SBP) was 137 mmHg (151 – 120 mmHg) and almost 13% of patients who entered the registry had SBP of ≤110 mmHg. The mean heart rate (HR) of the patients was 72 beats per minute (84-65 bpm). The medium left ventricular ejection fraction (LVEF) was 30% (45-20%); only 24% of all patients had LVEF >45%. Atrial fibrillation was registered for 6% of patients. Just for a small proportion of CHF patients was known diabetes mellitus (12,5%). Patients' characteristics data are presented on Table 1.

**Up-titration of neurohormone blockers.** In our centre 67,1% of patients received ACE inhibitors at target doses (Figure 1). However, 41,7% of patients were still in up-titration phases, one third (34,3%) had not reached target doses due to symptomatic hypotension, 4,6% – due to worsening renal function and just a few patients had not reached target doses due to cough (1,9%) or hyperkalemia (0,9%).

Beta blockers (BBs) were up-titrated to target doses for 82,5% of patients. The main reasons for failure to reach the target dose of BBs were as follows: symptomatic bradycardia (12,7%) and symptomatic hypotension (10,7%). Other reasons were as follows: bronchospasm – 5,4% of patients, worsening HF – 6,3% of patients and for the rest 11,2% of patients the reasons were "other or unknown".

Mineralocorticoid receptor antagonists (MRAs) were up-titrated to a target doses just for half of the patients – 52,1%. The most frequent reason for not reaching target doses was hyperkalemia (15,4%) and just a few patients were not up-titrated because of worsening renal function (2,2%) or gynecomastia (2,2%). It is noticeable that for almost 19,1% of cases the reasons of absence of up-titration were not provided ("other or unknown").

Analyzing dose titration peculiarities of angiotensin II receptor blockers (ARBs), only 16,7% of patients in our centre received ARBs at target doses.

**Table 1.** Baseline characteristics

| Patients' characteristics | Number of CHF patients |
|---|---|
| Age (years), median (IQR) | 66 (74-56) |
| 75+ years, % | 23,33 |
| Females, % | 34,17 |
| BMI (kg/m), median (IQR) | 27,5 (31,5-24,3) |
| SBP (mmHg), median (IQR) | 137 (151-120) |
| SBP ≤ 110 mmHg, % | 12,92 |
| HR (bpm), median (IQR) | 72 (84-65) |
| EF (%), median (IQR) | 30 (45-20) |
| EF >45 % | 24,17 |
| Prior hospitalization, % | 10 |
| Ischaemic aetiology, % | 10,71 |
| Atrial fibrillation, % | 6,25 |
| Diabetes mellitus, % | 12,5 |
| Hypertension, % | 75,83 |
| Chronic obstructive pulmonary disease, % | 10 |
| Prior stroke/ transient ischemic attack, % | 12,08 |
| Hepatic dysfunction, % | 4,58 |

**Discussion**

Guidelines of the management of CHF recommend a long-term treatment with three main neurohormonal blockers: ACE inhibitors, BBs, and MRAs [5,6]. Optimal therapy for CHF involves target-dose titration of medications [6]. According to European Society of Cardiology guidelines, neurohormonal blockers should be started with a very low initial dose and then up-titrated to the maximal tolerated dose [7]. Analyzing the number of patients receiving optimal background drug therapy, 67,1% of patients in our centre received ACE inhibitors at target dose, while data from other ESC HF Long-Term Registry centres show that the target dose have been reached just for 29,3% of patients [8]. Just 16,7% of our patients and 24,1% – from other European centres [8] were treated with angiotensin receptors

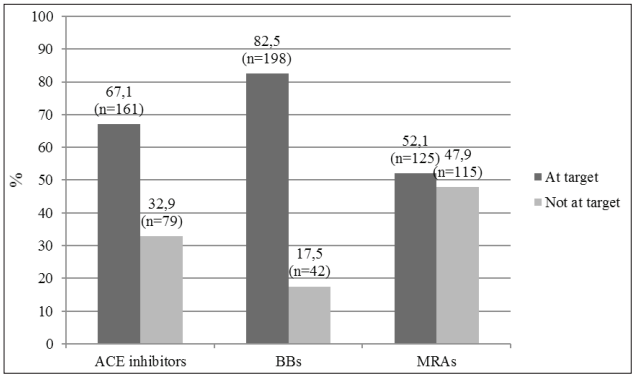


**Figure 1.** Number of patients at target doses of recommended neurohormone blockers. ACE inhibitors, angiotensin converting enzyme inhibitors; BBs, beta-blockers; MRAs, mineralocorticoid receptor antagonists.

blockers (ARBs) at a target dose. BBs were up-titrated to target doses for 17,5% of patients according to overall European data [8]; contrarily majority of patients from our centre – 82,5% – with CHF reached target doses of BBs suggested by the recent CHF guidelines. The target doses of MRAs have been reached for almost half of the patients in our centre and in less proportion (30,5%) in other European cardiology centres [8].

**Conclusions**

1. ACE-inhibitors, beta-blockers and mineralocorticoid receptors antagonists, except angiotensin receptors blockers, were prescribed in a guideline-recommended target doses.

2. The main reasons why the target doses of neurohormone blockers have not been achieved were as follows: symptomatic hypotension for ACE-inhibitors, symptomatic bradycardia for beta-blockers and hyperkalemia for mineralocorticoid receptors antagonists.

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## NEUROHORMONŲ BLOKATORIŲ DOZĖS DIDINIMO YPATUMAI GYDANT ŠIRDIES NEPAKANKAMUMĄ: UNIVERSITETINIO CENTRO DUOMENŲ ANALIZĖ

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Raktažodžiai: lėtinis širdies nepakankamumas, neurohormonų blokatoriai, vaisto dozės didinimas

Santrauka

Darbo tikslas. Įvertinti ambulatorinių pacientų, sergančių lėtiniu širdies nepakankamumu, medikamentinio gydymo ypatumus LSMUL Kauno klinikų Kardiologijos klinikoje, remiantis Europos kardiologų draugijos ilgalaikio širdies nepakankamumo stebėjimo registro duomenimis.

Tyrimo medžiaga ir metodai. 240 ambulatorinių, lėtiniu širdies nepakankamumu sergančių pacientų, buvo įtraukti į Europos kardiologų draugijos organizuojamą ilgalaikio širdies nepakankamumo stebėjimo registrą (*EURObservation Research Programme (EORP) Heart Failure Long-Term Registry*), kuriame buvo fiksuojami duomenys apie širdies nepakankamumo gydymo ypatumus. Duomenys buvo renkami nuo 2011 m. gegužės mėnesio iki 2013 m. kovo mėnesio. Statistinė duomenų analizė atlikta SPSS 22 programa.

Rezultatai. 67,1 proc. pacientų, gydytų angiotenziną konvertuojančio fermento inhibitoriais, pavyko padidinti vaisto dozę iki tikslinės. Trečdaliui pacientų (34,3 proc.), nepasiekusių tikslinės dozės, pasireiškė simptominė hipotenzija. Beta adrenoreceptorių blokatorių tikslines dozes pasiekė 82,5 proc. pacientų. Pagrindinės priežastys, dėl kurių titravimas buvo neefektyvus – simptominė bradikardija (12,7 proc. pacientų) ir simptominė hipotenzija (10,7 proc. pacientų). 52,1 proc. pacientų mineralkortikoidų receptorių antagonistai buvo sėkmingai titruoti iki tikslinės rekomenduojamos dozės. Dažniausia priežastis, dėl kurios nepavyko pasiekti tikslinės šių vaistų dozės, buvo hiperkalemija (15,4 proc. pacientų).

Išvados. Angiotenziną konvertuojančio fermento inhibitorių, beta adrenoreceptorių blokatorių ir mineralkortikoidų receptorių antagonistų dozių titravimas buvo sėkmingas – pasiektos rekomenduojamos tikslinės vaistų dozės, gydant širdies nepakankamumą. Pagrindinės priežastys, dėl kurių neurohormonų blokatorių dozių didinti iki tikslinių nepavyko – simptominė hipotenzija (vartojant angiotenziną konvertuojančio fermento inhibitorius), simptominė bradikardija (vartojant beta adrenoreceptorių blokatorius) ir hiperkalemija (vartojant mineralkortikoidų receptorių antagonistus).

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