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Does the target dose of neurohormonal blockade matter for outcome in Systolic heart failure in octogenarians?

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ABSTRACT

Background: In elderly patients with chronic heart failure (CHF), a gap exists between widespread use of lower doses of angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin-receptor blockers (ARBs) and β-blockers (BBs) and guideline recommendations. Therefore, the aim of the present study was to investigate whether patients receiving ≥50% target dose outperform those receiving <50% target dose, despite maximum up-titration, and whether the target dose outperforms all other doses.

Methods and Results: Patients (n = 185) aged ≥80 years with CHF and left ventricular ejection fraction ≤40% referred (between January 2000 and January 2008) to two CHF outpatient clinics at two university hospitals, were included and retrospectively studied. Of the study population, 53% received the target dose of ACEIs/ARBs, whereas 26% received <50% of the target dose. Half received <50% of the target dose of BBs and 21% received the target dose. After ≥5 years of follow-up, all-cause mortality was 76.8%. Patients who received the target dose of ACEIs/ARBs had higher survival rates from all-cause mortality than those receiving <50% of target dose (HR = 0.6, 95%CI 0.4-0.9, $P = 0.033$), but those receiving ≥50% of target dose did not statistically differ from those who achieved target dose. This dose-survival relationship was not the case for BBs.

Conclusions: Target dose of ACEIs/ARBs is associated with reduced all-cause five-year mortality in very old patients with systolic heart failure, despite that this was achievable in only about half of the patients. However, the clinical outcome of BB therapy is independent of BB dose when the target heart rate is achieved.

1. Introduction

First-line pharmacotherapy in systolic heart failure (HF) consists of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) if the patient is intolerant to ACEIs, and β-blockers (BBs). According to guidelines, these medications should be commenced at a low dose and up-titrated to the target dose [1–3]. However, doses recommended by guidelines are often not achieved in daily clinical practice, and regularly cannot be achieved in the elderly. Available studies demonstrate that only around one third of chronic heart failure (CHF) patients receive the target dose of either BBs or ACEIs/ARBs [4–6] despite tolerability of target dose in up to 80% of study patients [7,8,17].

The relationship between dose and effect of ACEIs/ARB and BBS in HF were inadequately studied [17,8,9,12–14]. In available CHF trials, only pre-specified target doses determined by trial investigators were used. Therefore, it remains disputable whether higher doses of ACEIs/ARBs or BBs are more effective than lower doses, and whether the target dose outperforms other doses.

Moreover, there is increasing number of studies showed that in terms of BBs; target heart rate appears to be more critical than target dose in CHF patients [15]. Therefore, achieving an optimal heart rate with BBs may be more important than the target dose in maximizing the benefits of BBs in this setting [16,18,19].

Guidelines for treatment of CHF in the adult give a general treatment recommendation irrespective of age) [1–3]. In view of the gap between the widespread use of lower doses of ACEIs/ARBs or BBs in clinical practice in elderly patients with CHF and the target dose recommended by guidelines, there is a fundamental issue; which dose level is optimal in the elderly; an individualized, highest tolerable dose as we use in our daily clinical practice, or a target dose as recommended by the guidelines? Does it differ between ACEIs/ARBs and BBs? Optimal dose-ranging studies in patients with systolic CHF have not been performed in this age group.

Therefore, the aim of the present study was to take the advantage of our well established and dedicated HF outpatient clinics to investigate whether patients receiving ≥50% target dose outperform those receiving <50% target dose, despite maximum up-titration, and whether the

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target dose outperforms all other doses, regardless of whether it is ≥50% or <50%, in an representative elderly CHF population.

2. Material and methods

2.1. Study cohort

Of three specialized outpatient CHF clinics at Sahlgrenska University Hospital (SU), SU/Sahlgrenska and SU/Östra, participated this study. Both were established more than 30 years ago. These clinics are mainly nurse-based. Consecutive patients referred to these clinics who were aged ≥80 years at referral were included (n = 185) between January 2000 and January 2008, and retrospectively studied from January 2 to May 30, 2013. The time-period chosen allowed for a follow-up period of at least five years. Long term outcome is more robust in particular regarding efficacy of pharmaceutical therapy. Patients were included if they had established systolic HF according to the ESC guidelines including evidence of left ventricular systolic dysfunction with EF ≤40% on trans-thoracic echocardiography [1–3]. The study conformed to the principles outlined in the 1964 Declaration of Helsinki. The study was approved by the Regional Ethical Review Board of Gothenburg University.

2.2. Up-titrations of HF medications

Up-titration to either the maximum tolerated dose or a target dose based on guideline recommended CHF medications were done by our HF-specialized nurses according to a prespecified schedule and after discussion with a cardiologist, over a 3–6 month time period. Up-titration was stopped after reaching the target dose, or otherwise the highest tolerable dose. The criteria for reaching the highest tolerated dose were based on a comprehensive clinical assessment and in combination with some of following vital signs:

(1) heart rate <55/min, (2) systolic blood pressure <100 mmHg, and (3) an increase in serum creatinine of >40% or serum potassium >5.5 mmol/L. Determination of the highest tolerable dose was first determined by a HF-specialized nurse then confirmed by a HF specialist (cardiologist) responsible for the patient. Target doses for ACEIs, ARBs, and BBs were based on the European Society of Cardiology guideline recommendations. After a final control after the last up-titration, patients were followed as usual at the outpatient clinic or referred to the primary care units.

2.3. Definition of groups according to doses

The study cohort was divided into three different groups according to the doses of BBs and ACEIs/ARBs. The target doses of BBs and ACEIs/ARBs were defined according to the European Society of Cardiology guidelines [1], (Table 1). In case of BBs the cohort was accordingly divided to: the low dose group included those with BB dose < 50% of the target dose; intermediate dose group included those with a BB dose of ≥50% of the target dose to less than the target dose; and the highest dose group included those with target doses. The same strategy was used for the ACEIs/ARBs.

Table 1
Target doses of neurohormonal blockers.

β-blockers and prescriptions (%)	Target daily doses (mg)
Metoprolol Succinate, (84)	200
Bisoprolol, (12)	10
Carvedilol, (4)	50
ACEIs/ARBs	
Ramipril, (56)	10
Enalapril, (24)	20
Candesartan, (13)	32
Losartan, (7)	100

Abbreviations: ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers.

2.4. Baseline characteristics

Parameters covering social, functional, and medical domains were entered into a database. Demographic and clinical characteristics from medical charts including age, gender, medical history, previous treatments, New York Heart Association (NYHA) functional class, laboratory and diagnostic tests, and therapies are presented in Table 2. Clinical data such as NYHA, blood pressure, rhythm, heart rate, electrolyte status (serum sodium, serum potassium,), and creatinine were available before and after up-titration.

2.5. Laboratory analyses

All laboratory variables were analyzed, as routine protocol, by the Clinical Chemistry Laboratory at Sahlgrenska University Hospital. The estimated glomerular filtration rate (eGFR) was calculated using the Cockcroft-Gault formula.

2.6. Clinical outcome data

The primary outcome was all-cause mortality after ≥5 years and the secondary outcomes were; 5-year cardiac mortality and hospitalization due to worsening heart failure. Data on causes of death were obtained from the death registry of the National Board of Health and Welfare in Sweden. The causes of death were classified according to the 10th revision of the International Statistical Classification of Disease and Related Health Problems.

The Automated Classification of Medical Entities system was used to select the underlying cause of death. Cardiac mortality was defined as the underlying cause of death when categorized as I11, I13, I20-I25 and I30-I52. Data on readmissions were obtained from hospital records.

2.7. Statistics

The results are presented as percentages and means ± standard deviation (SD). For continuous variables, statistical analyses were performed using One-way analysis of covariance. For categorical variables, cross tabulation with Chi-square test was used. Cox proportional-hazard survival model was used for mortality analysis. The hazard ratios (HR) with confidence intervals (CI) and *p*-values are presented. The PASW Statistics 18 (USA) statistical package was used for all analyses. A value of $p < 0.05$ was regarded as statistically significant. To adjust for the underlying clinical parameters and to analyze for probable association between the three different doses of each agent and survival, the cohort was analyzed using Cox proportional hazards regression analysis. Kaplan-Meier analysis and univariable Cox proportional-hazard regression analysis were used to build multivariable models. Parameters with significant results ($p < 0.05$) from univariable Cox regression analyses and without crossing Kaplan-Meier curves were included in the multivariable models built individually for the three doses of each agent: BBs and ACEIs/ARBS. Cox models were assessed for proportional hazard assumption for covariates, graphically with Cox adjusted log minus log curves and statically using Schoenfeld global test. Parameters of clinical importance and data completion were used in the analyses including gender; baseline ejection fraction; mitral valve regurgitation, grade ≥2 (scale 0.5-4); tricuspid valve regurgitation, grade >2 (scale 0.5-4); aortic valve stenosis, with a mean transvalvular pressure gradient of at least 10 mm Hg; atrial fibrillation at admission or on history; history of coronary artery disease; hypertension; prior stroke; chronic obstructive airway disease (COPD);