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Relationship between different doses of beta-blockers and prognosis in elderly patients with reduced ejection fraction

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ABSTRACT

Background: Beta-blockers (BBs) remain underused in elderly patients with reduced ejection fraction (REF). Our aim was to determine the prognostic impact of different doses of BB in this setting.
Methods and results: A single-center observational study was conducted. Inclusion criteria were age ≥ 75 and EF ≤ 0.35. Six months after diagnosis, patients were divided into 3 groups depending on BB dose: no BB (NBB), low dose (<50% of the target dose) (LD), and high dose (≥50%) (HD). Two different analytical approaches were employed: multivariate Cox model and propensity-score (PS) matching. Outcomes were all-cause death and heart failure (HF) admission. We included 559 patients (134 NBB, 259 LD, and 166 HD) with median follow-up of 29.9 months. There were 212 deaths (NBB: 70 (52.2%); LD: 94 (36.3%); and HD: 48 (28.9%)) and 171 HF admissions (NBB: 42 (31.3%); LD: 85 (32.8%); and HD: 44 (26.5%)). On multivariate analysis, both LD and HD were associated with improved survival, with no differences between them (HD vs. NBB = 0.67, 95% CI = [0.46–0.98], $p = 0.037$; HD vs. LD = 1.03, 95% CI = [0.72–1.46], $p = 0.894$; and LD vs. NBB = 0.65, 95% CI = [0.48–0.90], $p = 0.009$). However, BB therapy failed to show benefits in HF admissions (p = NS, for each comparison). PS-matched analysis included 198 patients, with similar results to those mentioned above.
Conclusions: BB therapy was associated with a significant reduction in mortality among elderly patients with REF, regardless of dose. Nevertheless, it was not associated with a decrease in HF admissions. Further studies are needed to determine the optimal BB dose in these patients.

1. Introduction

Beta-blocker (BB) therapy is one of the cornerstones in the treatment of patients with reduced ejection fraction (REF), with or without overt heart failure (HF), as evidenced by the positive effect on mortality and morbidity observed in several large randomized clinical trials (RCTs) [1–3]. In spite of this effectiveness and the increased incidence and prevalence of REF in advanced ages [4,5], BB therapy seems to be underused in the elderly, as shown in real-world HF registries [6,7]; furthermore, the dose achieved in old patients tends to be lower than in younger counterparts [8]. One possible explanation for this is that less evidence has been published for this population, owing to the fact that most RCTs included few old patients, with the exception of Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with Heart Failure (SENIORS), which specifically addressed HF patients aged over 70 years, although including patients with preserved ejection fraction as well as those with REF [9]. Another factor which may limit the use of BBs in the elderly stems from concerns about the safety and tolerance of BBs in old age due to a physiological impairment in renal and hepatic clearance and the higher prevalence of comorbidities with aging [10]. Finally, older patients are more frequently managed by general practitioners than by cardiologists, which may lead to less BB prescription as well as lower achieved dose levels [10,11].

The objective of our study was to determine the impact of different doses of BBs on survival and admission for HF in a cohort of elderly patients with REF.

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2. Methods

2.1. Patients and study design

We carried out a single-center, observational cohort study. Patients were eligible if they were 75 years of age or older and had a left ventricular ejection fraction (LVEF) lower than or equal to 0.35 as measured on a 2-dimensional echocardiogram. A specific database compiled at the Cardiac Imaging Department of Hospital Fundación Jiménez Díaz (Madrid, Spain) was used to screen patients meeting both criteria. Onset of follow-up was set at 6 months after the date of diagnosis so as to allow physicians (cardiologists or general practitioners) to optimize cardiovascular treatment according to usual practice. Concerning cardiovascular treatment, we also decided to exclude patients who died or suffered a major cardiovascular event (HF admission requiring intravenous diuretics or sustained ventricular arrhythmia) within this time period, as the end-stage disease of these high-risk patients might prevent them from benefiting from BB therapy.

Data including baseline clinical characteristics, cardiovascular risk factors, comorbidities, electrocardiographic findings (rhythm, heart rate, and QRS complex width), New York Heart Association (NYHA) functional class, and type and dose of cardiovascular drugs at the onset of follow-up were collected from patients' electronic health records. Particularly, we recorded the maximal tolerated doses of those BBs with a demonstrated impact on survival in REF (carvedilol, bisoprolol, metoprolol, and nebivolol) for subsequent calculation of the ratio of maximal tolerated dose/recommended target dose (50 mg daily for carvedilol, 10 mg for bisoprolol and nebivolol, and 200 mg for metoprolol). Finally, we divided the total cohort into 3 groups based on this ratio: no BB (NBB), low dose (<50% of the recommended target dose) (LD), and high dose (≥50% of the recommended target dose) (HD).

Between January 2008 and June 2014, 784 patients aged ≥75 years and with LVEF ≤ 0.35 were assessed for eligibility in our institution, and 559 (71.3%) were finally included. The remaining patients were not included due to the following reasons: 102 (13.0%) died and 74 (9.5%) had major cardiac events during the first 6 months after diagnosis, and 49 (6.2%) were lost to follow-up.

This investigation was carried out in accordance with the principles outlined in the Declaration of Helsinki.

2.2. Outcomes and follow-up

The outcomes analyzed in our study were time to all-cause death and time to first HF admission requiring intravenous diuretics. Clinical events and death during follow-up were collected from patients' electronic health records or, if not available, from telephone interviews with patients or relatives. The same methods were used to determine the cause of death. Last follow-up was carried out in April 2015.

2.3. Statistical analysis

The main variable, BB dose group, was considered to be ordinal with 3 ordered categories (NBB, LD, and HD). Quantitative data are presented as median and interquartile range (IQR). Comparisons between groups were performed by analysis of variance (ANOVA) for quantitative variables, whereas qualitative variables were compared using linear-association $\chi 2$ test and likelihood ratio χ^2 test when appropriate. Unadjusted survival curves were obtained by applying the Kaplan–Meier method, and the log-rank test was used to compare between groups.

Because observational studies do not allow for randomization, we planned 2 different approaches in order to avoid potential confounding factors: multivariate Cox proportional hazard and propensity-score (PS) matched analysis.

Cox analysis was done in 3 steps. In the first step, we performed an univariate analysis including all potentially relevant variables and those with a p value lower than 0.2 were selected for a first multivariate analysis (second step). The final multivariate Cox model only included those variables with a p value lower than 0.2 on first multivariate analysis and served to estimate the hazard ratio (HR) and its 95% confidence interval (95% CI) for each comparison between groups.

We performed a PS-matched analysis in similar fashion. The PS was calculated with an ordered logistic regression model, taking the BB group as the dependent variable and adopting a parsimonious approach. In a first step, all the following variables were included in the univariate analysis: age, gender, hypertension, diabetes mellitus, current smoking, obesity, chronic kidney disease, chronic obstructive pulmonary disease (COPD), peripheral vascular disease, any degree of cognitive impairment, any degree of functional disability, severe osteoarthritis, ischemic origin of REF, previous HF admission, sinus rhythm, wide QRS complex, LVEF, heart rate, and NYHA class I or II (vs. III, IV, or not available) at onset of follow-up; implantable cardioverter defibrillator (ICD) or cardiac resynchronization therapy (CRT); and treatment with ivabradine, angiotensin-converting enzyme inhibitors (ACEI) or angiotensin-receptor blockers (ARB), aldosterone antagonists, loop diuretics, and digoxin. All variables with a p value lower than 0.2 were entered into a multivariate ordered logistic regression model, which served to estimate the PS of every patient. Patient-matching was performed in a 1:1:1 ratio with the nearest neighbor method (caliper = 0.2 × SD[logitPs]). Finally, HR and 95% CI were calculated using a Cox model, taking the BB group as the only independent variable.

Analysis was performed with IBM SPSS Statistics for Windows, Version 20.0 (Armonk, NY: IBM Corp).

3. Results

3.1. Overall population

Five hundred and fifty-nine patients were included in our study, with a median age of 81.3 y (IQR: 77.8–85.0), 134 of whom (24.0%) were not taking BBs, 259 (46.3%) were taking <50% of the target dose, and 166 (29.7%) were taking 50% or more of the target dose. The baseline characteristics of the 3 groups are detailed in Table 1, with significant differences in age, QRS complex width, resting heart rate, COPD, cognitive impairment, functional disability, ischemic etiology of REF, NYHA class, and in the use of ICD or CRT and ivabradine. Reported reasons for lack of BB treatment were the following: COPD (35.1%), bradyarrhythmia (13.4%), dizziness or low blood pressure (6.0%), concomitant use of sotapor (6.0%), and unknown causes (39.5%). Bisoprolol was the most frequently used BB (59.3%), followed by carvedilol (37.4%), metoprolol (2.4%), and nebivolol (0.9%).

Median follow-up was 29.91 months (IQR 16.57–48.27). Two hundred and twelve patients (37.9%) died during follow-up—70 (52.2%) in the NBB group, 94 (36.3%) in the LD group, and 48 (28.9%) in the HD group. Cause of death was unknown in 93 (43.9%) patients, 79 (37.3%) died from non-cardiac causes, 6 (2.8%) from sudden death, and 34 (16%) from non-sudden cardiac death. Regarding the second outcome, 171 patients (30.6%) were admitted due to HF, of whom 42 (31.3%) were in the NBB group, 85 (32.8%) in LD, and 44 (26.5%) in the HD group. Kaplan–Meier curves for time to all-cause death and first HF admission are shown in Fig. 1.

Table 2 shows the levels of significance for every variable on univariate and first multivariate Cox proportional hazard analysis for both outcomes. The all-cause death final multivariate Cox model included the following variables: age, diabetes, presence of significant comorbidities, resting heart rate, LVEF in addition to BB dose group, which also was an independent predictor of survival ($p = 0.025$) (Table 3). Adjusted HRs for every comparison between BB dose groups were the following: HD vs. NBB = 0.669, 95% CI = [0.457–0.978], $p = 0.037$; HD vs. LD = 1.025, 95% CI = [0.716–1.464], $p = 0.894$; and LD vs. NBB = 0.653, 95% CI = [0.475–0.897], $p = 0.009$. By contrast, the multivariate Cox