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Mortality and morbidity of newly diagnosed heart failure with preserved systolic function treated with β-blockers: A propensity-adjusted case–control populational study

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ABSTRACT

Background: The effect of treatment with β-blockers on the prognosis of patients newly diagnosed with heart failure with preserved systolic function (HF-PSF) is unknown.
Objectives: To analyze the relationship of commencing treatment with the β-blockers bisoprolol or carvedilol (CT-βB) with the mortality and the morbidity of newly diagnosed HF-PSF.
Methods: Prospective propensity-adjusted cohort study over 5 years on 1085 adults diagnosed with HF-PSF for the first time, in an integrated university-based health organization in Spain. The independent relationship between CT-βB and mortality and morbidity was analyzed, stratifying patients for comorbidity, after a multivariable adjustment for potential confounders.
Results: The 378 patients (34.8%) who CT-βB were more frequently older women, with more cardiovascular comorbidity. Of the total patients 554 (51.0%) died, and 711 (65.5%) were hospitalized. Using an intent-to-treat approach, CT-βB was associated with a lower risk of mortality (all-cause: RR [CI 95%] 0.37 [0.21 to 0.50], and cardiovascular: 0.31 [0.18 to 0.45]), and a lower age- and sex-adjusted hospitalization rate (per 100 persons/year), 13.6 vs. 19.2, ($P<0.001$ in all cases), even after adjustment for the propensity to take β-blockers, or other medications, comorbidities, and other potential confounders.
Conclusions: In this observational study, commencing treatment with the β-blockers bisoprolol or carvedilol is associated with a reduced mortality and morbidity of patients with newly diagnosed heart failure with preserved systolic function.

1. Introduction

β-blockers (bisoprolol, metoprolol, and carvedilol) improve prognosis in patients with all grades of symptomatic heart failure with depressed systolic function (HF-DSF). Recent evidence suggests that β-blockers are equivalent to angiotensin-converting enzyme inhibitors as initial drugs in treating HF-DSF [1]. Nevertheless, the role of β-blockers in the treatment of heart failure with preserved systolic function (HF-PSF) has not been established by randomized clinical trials, and the effect of β-blockers on the prognosis of newly diagnosed HF-PSF has not been studied.

With the objective of determining the association, if any, between therapy with β-blockers and the prognosis of newly diagnosed non-systolic, we put forward the present prospective propensity-adjusted case–control study over 5 years on 1085 patients diagnosed with HF-PSF for the first time (in the community and after admission to hospital), who commenced treatment with the β-blockers bisoprolol or carvedilol.

2. Methods

2.1. Design

Prospective study of a cohort of 1085 adult patients (≥14 years) diagnosed for the first time with HF-PSF during a period of 5 years (1 January 2001 to 31 December 2005), according to the Framingham criteria [2]. The patients included are residents of a community of 87,106 inhabitants in the south of Spain, served by the University Hospital of Puerto Real (HUPR), Cadiz. Diagnosis was made either in the community, by consultation between specialists in internal medicine and family doctors (976 patients), or after admission to the hospital (109 patients). The system organized for consultation between specialists in internal medicine and family doctors (CIMF) has been described previously [3]. Patients aged less than 14 years and those not permanently resident in the community of reference have been excluded. This study has been undertaken with the informed consent of the patients, and with the approval of the Committee for Ethics, Research and Clinical Assays, of the University Hospital of Puerto Real.

2.2. Collection of data

The data collected provide information on: Sociodemographic and clinical parameters, tests requested, previous treatment, definitive diagnoses, treatment established, scheduled or emergency outpatient visits, and hospitalizations. These data were recorded not only at the time of the inclusion of the patients in the study but also during the 5 years of monitoring. Further, we have recorded data corresponding the 12 months prior to the inclusion of those patients for whom these date were available to us (from the data bases of the HUPR and of the Family Doctor).

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We classified kidney function using the Modification of Diet in Renal Disease equation for estimated glomerular filtration rate based on outpatient determinations of serum creatinine [4]. We categorized glomerular filtration rate (in units of mL/min per 1.73 m^2) as 60 or greater, 45 to 59, 30 to 44, 15 to 29, less than 15 not requiring dialysis, and receiving maintenance dialysis [5]. Categories of 60 mL/min per 1.73 m^2 or greater were not delineated given the higher degree of error in estimating the glomerular filtration rate above this level [6].

The echocardiogram was analyzed following the guidelines of the American Society for Echocardiography [7–9]. The limit for considering the left ventricular ejection fraction "normal" has been very variable, between 40 and 50% [7–11]. The criterion that we have chosen to define normal systolic function (LVEF ≥ 50%) is that customarily utilized in previous studies [10,11]. At least one valid echocardiogram had been performed in each patient.

2.3. β-blocker therapy and other medication exposure

We included in the study group all patients commencing treatment with bisoprolol or carvedilol. Mean daily doses of β-blockers were 7.78 ± 1.15 mg for bisoprolol and, 39.74 ± 4.69 mg for carvedilol. Patients treated with β-blockers other than bisoprolol or carvedilol (24 patients taking atenolol), had been excluded. Absolute contraindications to β-blocker therapy were systolic blood pressure < 100 mm Hg, sinus bradycardia < 50/min, and greater than first-degree atrioventricular block. We considered that patients were taking β-blockers (bisoprolol or carvedilol) or other drugs when they had commenced this treatment up to 120 days before, or up to 7 days after the index date. To monitor patient compliance with treatment with β-blockers or other drugs (diuretics, digoxin, angiotensin-converting enzyme inhibitors, angiotensin II receptors blockers, calcium channel blockers, spironolactone, eplerenone, amiodarone, vasodilators, nitrates, statins, and other lipid-lowering agents), we utilize the prescription data bases of the corresponding family doctors, or of the HUPR pharmacy (recombinant erythropoietin). When the patient was admitted for a non-fatal condition, the time of hospitalization (in days) was added to the period of prescription, because patients do not usually take their own medication during the period of admission.

2.4. Outcomes

Patients were prospectively included from January 1, 2001, and censored at the end of follow-up on December 31, 2005. Primary outcomes included death from any cause, death from a cardiovascular cause, hospitalizations for heart failure, and visits for any cause (emergency services or outpatient). To confirm mortality and morbidity, the histories of the patients (hospital or health center) were monitored weekly during the period of study. Death was identified from national health service and family practitioners' databases and, deaths that occurred in the emergency department or hospital. When the cause of death was not clear, the physician certifying death was contacted. The patients admitted with heart failure were identified by weekly review of the 9th revision of the International Classification of Diseases (ICD-9-CM). The codes of the ICD-9-CM included are those previously utilized in other studies: 428, 402.01, 402.11, 425, 429.3, 514, 402.9, 404.01, 404.11, 404.90, 398, 416, and 429. When the health status of a patient was not known from their history, they were contacted by telephone.

2.5. Statistical analysis

No losses of patients initially included in the study were recorded. All the analyses were performed using SPSS for windows 14.0 (SPSS, Chicago, Inc.). Mean values of the continuous variables were compared using the *t* or ANOVA tests, and the categorical variables have been analyzed by contingency tables and χ^2 tests. When variables do not present a normal distribution, the Mann–Whitney *U* test was employed to assess for differences between groups. Significance was defined as $P<0.05$. The 95% confidence intervals (CIs) were calculated.

The standardized risk of mortality or morbidity was calculated as the product of the overall mortality or morbidity by the relative risk, employing a method of indirect standardization [12]. In analyzing hospitalizations for heart failure and visits (outpatient and emergency department), a sandwich variant estimator was applied in the calculation of the 95% confidence intervals to account for multiple hospitalizations or visits by the same patient [12]. Survival rates were calculated by the Kaplan–Meier method, using data from both groups of patients. Age- and sex-adjusted rates of death and hospitalization were calculated using Poisson regression with generalized estimating equations to account for repeated measures within individuals.

The Kaplan–Meier method with comparisons by means of the long-rank test was employed to calculate the survival curves of the patients in function of the treatment with β-blockers.

The associations between variables were analyzed, as appropriate, by ANOVA, the Kruskal–Wallis test, the χ^2 test, or Fisher's exact test. We have employed logistic regression analysis to evaluate the degree of association of the dichotomous dependent variables. The relationships of each dependent variable have been analyzed by means of Cox proportional hazards regression, utilizing as inclusion criterion a $P<0.01$ for at least one of the dependent variables, calculating the odds ratio and the relative risk, with their 95% CI [13]. For binary variables (e.g. sex) and categoric variables (e.g. functional class of the NYHA), appropriate test (*dummy*) variables have been utilized. The quantitative variables (e.g. cardiac frequency) were adjusted as simple continuous measurements, except where there was evidence of non-linearity, as occurred with age, LVEF and body mass index. The statistical predictive power of each variable is expressed as χ^2 with one degree of freedom (a higher χ^2 corresponds to a lower *P* value).

We analyzed the independent association between commencement of β-blocker use and outcomes using extended Cox regression with time-dependent covariates. Given that certain patients may stop taking the medication (β-blockers or other) in the final phases of life, and in order to avoid an optimistic estimation of the results of the treatment, performing an intent-to-treat-like approach, we have considered the patients who commenced the pharmacological treatment as having complied with the treatment through the follow-up period even if they did not collect their monthly prescriptions. A secondary analysis incorporated time-varying estimates of therapy (β-blocker and other) and assigned exposure status at the time of an outcome event based on our medication exposure algorithm. As the β-blockers (and other drugs: ACEIs, statins, etc.) have shown benefit in secondary prevention, we performed stratified models on patients who, at the time of inclusion, did or did not present comorbidities: coronary heart disease, stroke, peripheral arterial disease, chronic renal disease, diabetes mellitus, and hypercholesterolemia.

We also adjusted for the likelihood of receiving therapy (β-blocker and other), by using a continuous propensity score [13–15]. Our propensity score logistic model (*c* statistic = 0.79) considered candidate variables shown in Table 1. We identified the most likely predictive variables within each category by backward steps selection, with the variables with probabilistic value > 0.01 being eliminated from the model. The variables with predictive significance were combined and pre-established covariables were added, in the event of not having been considered in the model, such as age, sex, LVEF, etiology of the HF, arterial pressures, etc. These covariables were identified by bivariate analysis, or by previous studies [16], or by virtue of the theoretical likelihood of their association with the prognosis, or by being considered clinically important for the prediction of morbidity and mortality.

We examined the strength and shape of the relationships of continuous variables with the log odds of death, re-admissions or, visits using cubic spline plots. These functions were used to develop and refine the multivariable regression models as used previously [13–15].

3. Results

3.1. Baseline characteristics of the patients

We studied 1085 adults with newly diagnosed HF-PSF, of whom 378 (34.8%) commenced treatment with β-blockers (192 with bisoprolol [50.8%], and 186 with carvedilol [49.2%]), and 707 did not receive this treatment. The patients who commenced treatment with β-blockers (CT-βB) were preferentially older women, with greater prevalence of HF-PSF of ischemic etiology, but without significant sociodemographic or clinical differences (Table 1). The most important differences in the baseline characteristics between the two groups of patients were a greater prevalence of previous vascular events (coronary heart disease and stroke), dyslipemia, smokers, obesity, COPD, and chronic renal insufficiency in those not receiving treatment with β-blockers, without differences in the prevalence of peripheral arterial disease, diabetes mellitus, arterial hypertension, left ventricular hypertrophy, chronic hepatopathy, dementia, anemia, hyponatremia, systemic malignancy, or thyroid dysfunction. Those who CT-βB presented higher levels of total cholesterol and LDL cholesterol, but with no differences in the levels of HDL, triglycerides or hemoglobin. There were no significant differences in the prevalence with which both groups of patients were treated with drugs different from β-blockers. The patients who did not receive β-blockers presented a larger number of hospitalizations and visits, and less follow-up time (higher mortality).

3.2. Relationship between therapy with β-blockers and morbidity and mortality

During the median follow-up of 909. 3 days (interquartile range, 559.2–1303.4) 554 patients (51.0%) died and 711 patients (65.5%) were hospitalized for HF. The patients with HF-PSF who CT-βB presented a survival significantly longer than that of the patients not taking βB (RR of death [CI 95%]: 0.37 [0.21 to 0.50]) (Fig. 1).

The patients who CT-βB showed a mortality due to cardiovascular cause significantly lower than that of the patients not taking βB (RR of death [CI 95%]: 0.31 [0.18 to 0.45], $P<0.001$; Fig. 1), a lower rate of precocious re-admissions (within 30 days after discharge) (RR [CI 95%]: 0.66 [0.54 to 0.78], $P<0.001$) (data not shown), and a lower number of visits (outpatient and emergency) (RR [CI 95%]: 0.81 [0.75 to 0.88]; $P<0.01$) (data not shown).