International Journal of Cardiology 167 (2013) 1217–1225

Contents lists available at SciVerse ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Depression, antidepressants, and long-term mortality in heart failure ☆

Crisanto Diez-Quevedo [a,b], Josep Lupón [a,c], Beatriz González [a], Agustín Urrutia [a,c], Lucía Cano [a], Roser Cabanes [a], Salvador Altimir [a,c], Ramon Coll [a,c], Teresa Pascual [a], Marta de Antonio [a], Antoni Bayes-Genis [a,c,*]

[a] Heart Failure Unit, Hospital Universitari Germans Trias i Pujol, Ctra Canyet s/n, 08916 Badalona, Spain
[b] Department of Psychiatry, Autonomous University of Barcelona, Ctra Canyet s/n, 08916 Badalona, Spain
[c] Department of Medicine, Autonomous University of Barcelona, Ctra Canyet s/n, 08916 Badalona, Spain

ARTICLE INFO

Article history:
Received 6 September 2011
Received in revised form 8 February 2012
Accepted 15 March 2012
Available online 14 April 2012

Keywords:
Heart failure
Depression
Antidepressants
Mortality

ABSTRACT

Background: This study was designed to assess whether depression and the use of antidepressants were related to long-term mortality in heart failure.
Methods: Heart failure outpatients (n = 1017) from a specialized tertiary unit in Spain were prospectively studied for a median follow-up of 5.4 years (IQR 3.1–8.1). Depressive symptoms were assessed using an abbreviated version of the geriatric depression scale. Survival rates during the study period (August 2001 until December 2010) and hazard ratios (HR) for mortality were adjusted by several demographic and clinical variables.
Results: Depressive symptoms were detected in 302 patients (29.7%) at baseline and 222 (21.8%) de novo during follow-up; 304 patients (29.9%) received at least one prescription of antidepressants, mainly selective serotonin reuptake inhibitors (92.8%); 441 patients (43.4%) died. In a multivariate Cox proportional hazard model, depression was associated with an increased all-cause (HR, 1.39; 95% CI, 1.15–1.68), but not cardiovascular, mortality risk after adjustment for several demographic and clinical confounders. The use of any antidepressant was not independently associated with mortality (HR, 0.89; 95% CI, 0.71–1.13), but benzodiazepines showed a protective role (HR, 0.70; 95% CI, 0.57–0.87). On the contrary, fluoxetine prescriptions, but not duration of fluoxetine treatment, were associated with increased mortality (HR, 1.66; 95% CI, 1.13–2.44).
Conclusions: Depressive symptoms are associated with long-term mortality, but the use of antidepressants and benzodiazepines is safe regarding survival in HF patients, although further research is needed considering individual antidepressants separately.

1. Introduction

Chronic heart failure (HF) is a prevalent disease in the general population, affecting 8–17% of people over 70 years of age. The average mortality rate is high, approximately 10% one year after diagnosis and increasing to 50% after 5 years [1].

Prevalence of depression in HF patients is high, ranging between 11% and 51% [2–4]. Rates vary depending on the diagnostic instrument used, the severity threshold of depressive symptoms to make the diagnosis, and the type of population assessed.

Depression has been associated with worse outcomes and higher rates of mortality in several cohorts of patients with HF, even adjusting for clinical and biological variables of HF severity [3–11]. Increased depression severity is related with higher rates of short-term mortality [12]. However, fewer studies have focused on the impact of depression on long-term mortality, with only four studies with a follow-up period of more than 5 years [13–16]. Moreover, the prognostic power of depression to predict mortality seems to increase over time [17].

Remission of depression seems to be related to an improvement on survival [18], but the benefits of antidepressant treatments on HF outcomes are not well known. Selective serotonin reuptake inhibitors (SSRIs) have been shown to inhibit platelet function, promote endothelial stabilization, and possess antiinflammatory properties, although the clinical relevance of these properties has yet to be established [19]. Nevertheless, some observations have indicated that the use of antidepressants can be associated with an increased likelihood of death or cardiovascular hospitalization [8,20,21]. Other studies have failed to find such association when controlling data for the impact of depression and other variables [4], or even have showed a

☆ Preliminary findings of this paper were presented at the Heart Failure Congress 2011, Gothenburg — Sweden, 23 May 2011, and the European Society of Cardiology Congress 2011, Paris — France, 30 Aug 2011.

* Corresponding author at: Departament de Cardiologia, Hospital Universitari Germans Trias i Pujol, Ctra de Canyet s/n, 08916 Badalona, Spain. Tel.: +34 93 465 1200; fax: +34 93 497 8843.
E-mail address: abayesgenis@gmail.com (A. Bayes-Genis).

0167-5273/$ – see front matter © 2012 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.ijcard.2012.03.143

protective role for antidepressants [22,23], and a recent double-blind trial has found sertraline to be safe in patients with HF [24].

The aim of the present study was to evaluate the effect of depressive symptoms on mortality in a cohort of chronic HF outpatients followed in a specialized tertiary unit, as well as the influence of the naturalistic use of antidepressants in this population.

2. Materials and methods

2.1. Patients

All patients with established HF, diagnosed according to the European Society of Cardiology criteria [25], regardless of etiology, aged over 18 years, and admitted to a specialized HF outpatient Unit of a University Hospital in Barcelona (Spain) between 1 August 2001 and 31 December 2009 were included in the study. At first visit, patients provided informed consent for using their clinical data for research purposes. All study procedures were in accordance with ethical standards outlined in the Helsinki Declaration of 1975, as revised in 1983, as approved by the institution's human research committee.

2.2. Procedures

Population selection, protocol management, and evaluations performed in the HF Unit are explained in detail elsewhere [26,27]. Briefly, all patients admitted to the unit were assessed at baseline and every 6 months for clinical and demographic data, and they were referred to psychiatric assessment and treatment when necessary. Patients also completed several questionnaires: the Barthel index to assess the patient's dependence in basic daily life activities [28], the Duke Older Americans Resources and Services (OARS) scale to assess autonomy in instrumental activities [29], and the Pfeiffer test to evaluate cognitive function [30]. To assess the presence of depressive symptoms, an abbreviated four-item version of the geriatric depression scale (GDS-4) [31] was administered.

Primary outcome measures were death for any cause as well as cardiovascular death during the follow-up period, which was closed on 31 December 2010. Vital status was verified using the central database of the Spanish National Health System. The use of psychotropic drugs during follow-up was assessed using clinical records from the HF Unit and from general practitioners, as well as databases of the Spanish National Health System, that cover all prescriptions received by the patient as well as the period of treatment. Recorded psychotropic drugs were any kind of antidepressants (ATC code N06A) and any kind of benzodiazepines (ATC codes N05BA, N05CD, and N05CF).

2.3. Statistical analysis

All continuous variables were tested for normal distribution using the Kolmokorov–Smirnov test. As all variables were non-normally distributed, results are presented as median and 25th–75th percentiles.

Continuous and categorical variables were described by the presence or absence of depressive symptoms according to GDS-4 scores with a cut-off point of $0/\geq 1$, and by the use of antidepressants and benzodiazepines. Statistical comparisons were made between groups using the Pearson chi-squared test for categorical variables and the Mann–Whitney *U* test or Kruskal–Wallis test for continuous variables as appropriate. To estimate the multivariate association of depression and the use of antidepressants and benzodiazepines with other variables, a multivariate logistic regression model was built. Independent variables in the analyses included sex, age, ischemic etiology, time since the diagnosis of HF, New York Heart Association (NYHA) functional class and left ventricular ejection fraction (LVEF) at baseline, therapy during follow-up with angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB) or beta-blockers, several medical comorbidities (diabetes mellitus, hypertension, hypercholesterolemia, chronic obstructive pulmonary disease — COPD-, peripheral vasculopathy, body mass index — BMI-, and creatinine clearance — CrC-calculated by Cockcroft formula), Barthel index, OARS scale, and Pfeiffer test. Changes in NYHA functional class and LVEF over the first year of follow-up were also considered. Associations were summarized using the odds ratio (OR) and its 95% confidence interval (CI).

To assess the associations between depression, antidepressants, or benzodiazepines and mortality, a Cox proportional hazard model was used. Multivariable models were fitted with the use of different demographic and clinical variables selected on the base of previous medical knowledge or significance ($P<0.10$) in univariate analyses.

A two-sided *P*-value of <0.05 was considered significant for all analyses.

Analyses were performed using IBM SPSS Statistics 19.0.0 for Windows (SPSS Inc, Chicago, Ill).

3. Results

Along the recruitment period, 1101 patients were admitted to the HF Unit. Twenty-one patients (1.9%) were excluded because of incomplete clinical data and 63 (5.7%) because of moderate to severe cognitive impairment (Pfeiffer test > 4). The remaining 1017 patients were followed for a median of 5.4 years (interquartile range 3.1–8.1 years) (Fig. 1). Ninety-eight percent of the patients were white. Table 1 shows demographic and clinical characteristics of the sample.

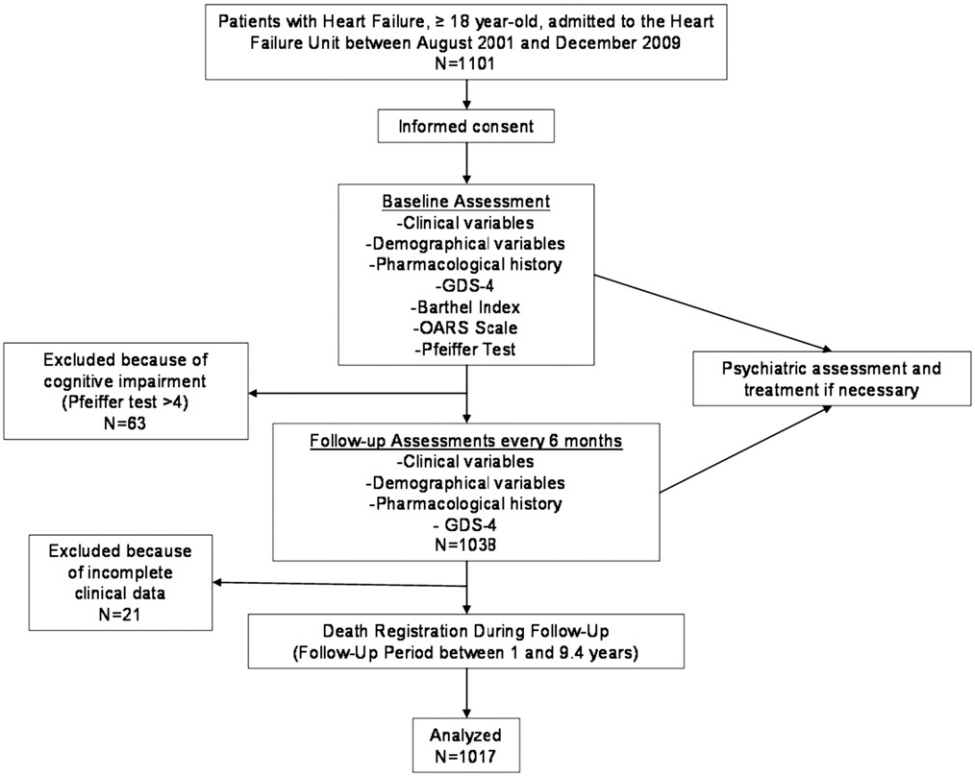

Fig. 1. Patients' flowchart.