

Original article

Differences in Outcome of Heart Failure With Preserved or Depressed Systolic Function in Patients Older Than 70 Years Who Receive Beta Blockers

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ABSTRACT

Introduction and objectives: Most studies have shown that prognosis of heart failure with preserved systolic function is as poor as that of heart failure with depressed systolic function, although these results may be biased by the fact that these types of heart failure have different characteristics (age, comorbidity, treatment), which can influence prognosis. Our aim was to determine whether short-term morbidity and mortality differed in these 2 subgroups of heart failure patients when they were comparable in terms of age, associated comorbidity, and therapy.

Methods: We analyzed 2 groups of patients aged >70 years who were candidates to receive beta blockers (preserved systolic function, 245; depressed systolic function, 374), consecutively discharged from 53 participating Spanish hospitals with a diagnosis of heart failure, and compared cardiovascular morbidity and mortality 3 months after discharge.

Results: Mean age was similar (77.5 ± 4.8 vs 78.2 ± 5.5 years). Left ventricular ejection fraction was $56.2\% \pm 8.1\%$ vs $33\% \pm 6.9\%$ ($P < .001$). The combined event rate (death, hospitalization for heart failure, acute coronary syndrome, or stroke) at 3 months after discharge was lower in patients with heart failure and preserved systolic function (13.4% vs 20.6%; $P = .026$). Depressed systolic function was an independent predictor of greater incidence of events (odds ratio=1.732; $P = .048$).

Conclusions: In patients of similar age and receiving similar treatment, short-term prognosis is better in patients with heart failure and preserved systolic function than in those with depressed systolic function.

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Diferencias en el pronóstico de la insuficiencia cardiaca con función sistólica conservada o deprimida en pacientes mayores de 70 años que toman bloqueadores beta

RESUMEN

Introducción y objetivos: La mayoría de los trabajos han puesto de manifiesto que el pronóstico de la insuficiencia cardiaca con función sistólica conservada es tan malo como el de la insuficiencia cardiaca con función sistólica deprimida, aunque estos resultados pueden estar sesgados debido a que estos dos tipos de insuficiencia cardiaca tienen características distintas (edad, comorbilidades, tratamiento) que pueden influir en el pronóstico. Nuestro objetivo es evaluar si la morbimortalidad a corto plazo es distinta en estos dos subgrupos de insuficiencia cardiaca, con pacientes homogéneos en cuanto a edad, comorbilidad y tratamiento recibido.

Métodos: Analizamos dos grupos de pacientes mayores de 70 años y que pudieran recibir bloqueadores beta, dados de alta consecutivamente tras un ingreso por insuficiencia cardiaca en 53 hospitales españoles (función sistólica deprimida, 245; función sistólica conservada, 374), y se comparó la morbimortalidad cardiovascular a los 3 meses del alta.

Palabras clave:

Insuficiencia cardiaca

Pronóstico

Bloqueadores beta

Función sistólica

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◇ The Appendix includes a list of the OBELICA study researchers.

Resultados: Las medias de edad fueron similares ($77,5 \pm 4,8$ frente a $78,2 \pm 5,5$ años). La fracción de eyección ventricular izquierda fue de $56,2 \pm 8,1\%$ frente a $33 \pm 6,9\%$ ($p < 0,001$). La incidencia del evento combinado (muerte, ingreso por insuficiencia cardíaca, síndrome coronario agudo o ictus) a los 3 meses del alta fue menor en los pacientes con insuficiencia cardíaca y función sistólica conservada (el 13,4 frente al 20,6%; $p = 0,026$). Tener la función sistólica deprimida fue predictor independiente de mayor incidencia de eventos (*odds ratio* = 1,732; $p = 0,048$).

Conclusiones: En pacientes de edad similar que reciben el mismo tratamiento, el pronóstico a corto plazo es mejor en los pacientes con insuficiencia cardíaca y función sistólica conservada que en aquellos con función sistólica deprimida.

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Abbreviations

ACEI: angiotensin converting enzyme inhibitors
ARB: angiotensin receptor blockers
HF: heart failure
LVEF: left ventricular ejection fraction

INTRODUCTION

Heart failure (HF) is a clinical syndrome of great relevance due to its high and increasing prevalence¹ and high levels of morbidity and mortality.² These problems are aggravated with age as prevalence increases exponentially with the years¹ and prognosis is worse in older patients.^{3,4} In recent decades, drugs have been developed that improve prognosis in HF. These include angiotensin converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), antialdosterone drugs, and beta blockers (BB). Their use has facilitated improved prognosis in these patients,⁵ although producing only a mildly favorable effect in the general population of patients with HF.² One reason the effect of this treatment in the general population has not been more positive is that—like electrical treatments such as resynchronization or implantable defibrillators—these drugs have only proved efficacious in patients with HF and depressed systolic function.^{6,7} No evidence exists about their usefulness to improve prognosis in patients with HF and preserved systolic function, who represent approximately half of the patients with HF.¹ In fact, several studies have shown that in recent years mortality in HF with depressed systolic function has fallen, but in HF with preserved systolic function it has not.^{8,9} Moreover, the accepted view that low left ventricular ejection fraction (LVEF) was a factor indicating poor prognosis in patients with HF has been changed by numerous studies conducted in Spain and elsewhere^{10–15} that have shown prognosis was equally poor in patients with preserved LVEF or depressed LVEF.

However, factors other than LVEF itself may influence these results. The characteristics of HF patients with preserved systolic function differ from those of patients with depressed systolic function or depressed LVEF (they are older and have more comorbidities, more of them are women, they have different etiologies and receive different treatments),^{10–16} and some of these differences, such as greater age, associated comorbidity, or less drug treatment, may unfavorably bias the final result. The objective of our study is to determine whether short-term morbidity and mortality differ in these 2 types of HF, when analyzing groups of patients in terms of age, comorbidity, and treatment received.

METHODS

To achieve our objective, we conducted a subanalysis of the recently published OBELICA study.¹⁷ This study, conducted in 2007–2008, included 627 men and women aged ≥ 70 years and diagnosed with HF according to European Cardiology Society criteria,⁷ independently of LVEF. Given that the main variable indicating efficacy in this study was the percentage of patients receiving the optimal dosage of BB at 3-month follow-up, the patients included should present no contraindications to BB use. The study was coordinated and overseen by the Spanish Society of Cardiology research agency, and conducted thanks to an unconditional grant from Menarini. Fifty-three hospitals in autonomous regional communities throughout Spain participated in the study (11 in Andalusia, 2 in the Principality of Asturias, 2 in the Balearic Islands, 7 in Valencian Community, 4 in the Canary Islands, 3 in Castile-La Mancha, 4 in Castile and León, 7 in Catalonia, 2 in Extremadura, 3 in Galicia, 5 in the Community of Madrid, and 3 in the Basque Country). Each center included 14 patients consecutively discharged following hospitalization for a principle diagnosis of HF. We defined HF with preserved systolic function as $>45\%$ LVEF and HF with depressed systolic function as $\leq 45\%$ LVEF. At 3 months, we reviewed all patients in cardiology or HF clinics. At each visit we collected demographic, clinical, and treatment data (Tables 1–3). At the final visit, at 3 months, we also collected data on events since enrollment. Nine patients were lost to follow-up, leaving 618 whose data were included in the final analysis. The principle variable in this subanalysis was the combined outcome of overall mortality and hospitalization for cardiovascular cause (HF, myocardial infarction, unstable angina, stroke, arrhythmias) during the 3-month follow-up. All events were verified by consulting patient clinical case histories for in-hospital cases and by personal or telephone contact with the primary care physician and/or family of patients who died out-of-hospital. The study was approved by the clinical research ethics committee (Hospital General de Alicante) and complied with Spanish legislation on clinical trials. Participants were required to give written informed consent.

Statistical Analysis

In 2 groups of patients with HF and preserved or depressed systolic function, we compared baseline characteristics and events at 3-month follow-up using chi-squared for qualitative variables and Student's *t* test or the Wilcoxon test for continuous variables. A value of $P < .05$ was considered statistically significant. We also performed stepwise logistic regression multivariate analysis to determine those factors independently associated with a greater rate of events at 3 months. This model included all variables showing statistical significance in univariate analysis (Table 4) and other clinically relevant parameters (history of high blood pressure, diabetes mellitus, HF etiology, treatment with ACEI, BB

Table 1

Characteristics of Patients With Heart Failure and Preserved or Depressed Systolic Function at First Visit.

	PSF (n=246)	DSF (n=372)	P
Age, years	78.2±5.5	77.5±4.8	.101
Women	130 (52.8)	125 (33.6)	<.001
Previous admission for HF	97 (39.4)	231 (62.1)	<.001
High blood pressure	204 (82.9)	267 (71.7)	.001
Diabetes mellitus	91 (36.9)	153 (41.1)	.316
Hypercholesterolemia	96 (39)	190 (51.1)	.004
Myocardial infarction	65 (26.4)	193 (51.9)	<.001
COPD	34 (13.8)	61 (16.4)	.412
Anemia	58 (23.6)	97 (26.1)	.478
Stroke	26 (10.6)	38 (10.2)	.857
Smoker	82 (33.3)	186 (50)	<.001
Previous coronary revascularization	42 (17.1)	109 (29.3)	.002
Functional class			.052
I	24 (9.8)	31 (8.3)	
II	121 (49.2)	147 (39.5)	
III	97 (39.4)	183 (49.2)	
IV	4 (1.6)	11 (3)	
Etiology of HF			<.001
Ischemic	68 (27.7)	231 (62.1)	
Hypertensive	156 (63.4)	44 (11.8)	
Idiopathic dilated cardiomyopathy	0	79 (21.2)	
Valvular heart disease	15 (6.1)	11 (3)	
Other	7 (2.8)	7 (1.9)	
Systolic blood pressure, mmHg	141±21.2	127.3±19.3	<.001
Diastolic blood pressure, mmHg	78.4±14	74.6±11.6	<.001
Body mass index	28.9±4.4	27.3±3.8	<.001
Atrial fibrillation;	91 (37)	122 (32.8)	.278
Ejection fraction, %	56.2±8.1	33±6.9	<.001

COPD, chronic obstructive pulmonary disease; DSF, depressed systolic function; HF, heart failure; PSF, preserved systolic function.

Means are compared using Student's t test or the Wilcoxon test for 2 independent samples; proportional homogeneity, using chi-squared.

Results are expressed as n (%) (for qualitative variables) and mean±standard deviation (for continuous variables).

and antialdosterone drugs) that showed no significant differences in the univariate study.

RESULTS

Baseline Characteristics of Groups

We enrolled 627 patients; 40% (n=250) with preserved systolic function and 60% (n=377) with depressed systolic

Table 2

Biochemical Parameters for Patients With Heart Failure and Preserved or Depressed Systolic Function at First Visit.

	PSF (n=246)	DSF (n=372)	P
Hemoglobin, g/l	12.9±1.8	12.6±1.8	.268
BNP, pg/ml	320.9±398.8	458.6±233.8	.108
Creatinine, mg/dl	1.2±0.6	1.3±0.6	.127
Sodium, mEq/l	139.27±3.4	139±3.6	.234
Potassium, mEq/l	4.4±0.5	4.5±0.5	.078

BNP, brain natriuretic peptide; DSF, depressed systolic function; PSF, preserved systolic function.

Means are compared with Student's t test or the Wilcoxon test for 2 independent samples.

Results are expressed as mean ± standard deviation.

Table 3

Drug Treatment of Patients With Heart Failure and Preserved or Depressed Systolic Function at First Visit and at Final Visit 3 Months After Discharge.

	PSF	DSF	P
<i>First visit</i>			
Patients	246	372	
ACEI/ARB	214 (87)	337 (90.6)	.074
Digitalis	49 (20)	101 (27.2)	.039
Beta blockers	211 (85.8)	331 (89)	.169
Statins	113 (46)	229 (61.6)	<.001
Anticoagulants	99 (40.2)	154 (41.4)	.798
Antiplatelet drugs	114 (46.3)	211 (56.7)	.013
Diuretics	208 (84.5)	334 (89.8)	.057
Antialdosterone drugs	47 (19.1)	169 (45.4)	<.001
<i>Final visit</i>			
Patients	243	358	
ACEI/ARB	217 (89.3)	326 (91.1)	.471
Digitalis	48 (19.7)	88 (24.6)	.163
Betablockers	214 (88.1)	330 (92.2)	.094
Statins	122 (50.2)	226 (63.1)	<.001
Anticoagulants	98 (40.3)	148 (41.3)	.798
Antiplatelet drugs	108 (44.45)	205 (57.3)	.010
Diuretics	191 (78.6)	314 (87.7)	.004
Antialdosterone drugs	45 (18.5)	162 (45.2)	<.001

ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers; DSF, depressed systolic function; PSF, preserved systolic function.

Proportional homogeneity is compared with chi-squared.

Results are expressed as n (%).

function. Nine patients were lost during follow-up: 4 with preserved systolic function and 5 with depressed systolic function. Hence our analysis included data on 618 patients (246 in the first group and 372 in the second). Clinical characteristics during hospitalization and the most important aspects of clinical history are in Table 1. In both groups, mean age was similar at ±78 years. The group with HF and preserved systolic function included a higher percentage of women (52.7% vs 33.7%; $P<.001$). Previous admission for HF was recorded in 62% of patients with depressed systolic function and 39.6% of patients with preserved systolic function ($P<.001$). Prevalence of high blood pressure was greater in patients with preserved systolic function; prevalence of hyperlipidemia, smoking, myocardial infarction, and coronary revascularization was greater among those with depressed systolic function (Table 1). Prevalence of atrial fibrillation, diabetes mellitus, chronic obstructive pulmonary disease, anemia, and stroke was similar in both groups (Table 1). The most frequent etiology in patients with HF and depressed systolic function was ischemic heart disease (62.1%); in patients with HF and preserved systolic function it was high blood pressure (63.4%; $P<.001$) (Table 1). LVEF was 56.2±8.1% in the group with preserved systolic function and 33±6.9% in those with depressed systolic function ($P<.001$). No relevant clinical differences were found between groups in biochemical parameters (including brain natriuretic peptide, hemoglobin, and serum creatinine) (Table 2).

Drug Treatment

Table 3 shows drug treatments received by patients in both groups at discharge, during the enrollment visit, and at 3-month follow-up, on the final visit. The percentages of patients receiving ACEI or ARB, diuretics, BB, and anticoagulants were high and similar in both groups. Patients with depressed systolic function received proportionately more antiplatelet drugs, statins, antialdosterone drugs, and digitalis (Table 3). These results changed little on the visit at 3 months after discharge (Table 3), although the percentage of patients taking BB increased slightly in both groups (88.1% in those with preserved systolic function and 92.2% in those

Table 4

Comparison of Patient Characteristics at First Visit Between Groups With and Without Events During the 3-month Follow-up.

	Cardiovascular event		P
	No (n=508)	Yes (n=110)	
Age, years	77.4±5	79.3±5.2	<.001
Women	200 (39.3)	54 (49.1)	.017
Clinical course of HF in months	29.5±36.7	38.8±46.9	.065
Previous admissions for HF	251 (49.4)	77 (70.2)	<.001
High blood pressure	389 (76.6)	82 (74.5)	.513
Diabetes	200 (39.3)	44 (40)	.965
Hypercholesterolemia	243 (47.8)	43 (39.1)	.281
Myocardial infarction	200 (39.3)	58 (52.7)	.018
COPD	75 (14.7)	20 (18.2)	.746
Anemia	120 (23.6)	35 (31.8)	.032
Stroke	50 (9.8)	14 (12.7)	.202
Smoker	226 (44.5)	42 (38.2)	.079
Previous coronary revascularization	118 (23.2)	33 (30)	.133
Functional class			<.001
I-II	290 (57.1)	33 (30)	
III-IV	218 (42.9)	77 (70)	
Etiology of HF			
Ischemic	244 (48)	55 (50)	.450
Hypertensive	172 (33.8)	28 (25.5)	.139
Other	92 (18.2)	27 (24.5)	.782
Systolic blood pressure, mmHg	133.8±21.3	127.7±19.9	.006
Diastolic blood pressure, mmHg	75.9±12.8	74.1±12.5	.199
Heart rate, bpm	77.3±16.7	76.9±16	.801
Body mass index	28.1±4.2	27.3±3.9	.087
Atrial fibrillation	163 (32)	50 (45.5)	.046
Ejection fraction, %	47.5±13.6	39.3±12.3	.023
HF with preserved systolic function	213 (41.9)	33 (30)	.026
Hemoglobin, g/l	12.8±1.8	12.3±1.9	.015
BNP, pg/ml	404.2±326.1	426.9±234.8	.463
Creatinine, mg/dl	1.2±0.6	1.5±0.8	.007
Sodium, mEq/l	139.4±3.4	138.5±4.4	.047
Potassium, mEq/l	4.4±0.5	4.5±0.5	.213
Treatment			
ACEI/ARB	455 (89.6)	96 (87.3)	.126
Digitalis	122 (24)	28 (25.4)	.894
Beta blockers	446 (87.8)	96 (87.2)	.568
Anticoagulants	196 (38.6)	57 (51.8)	.036
Antiplatelet drugs	268 (52.8)	57 (51.8)	.929
Diuretics	437 (86)	105 (95.4)	.011
Antialdosterone drugs	178 (35)	38 (34.6)	.759

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blockers; BNP, brain natriuretic peptide; COPD, chronic obstructive pulmonary disease; HF, heart failure.

Means are compared with Student's t test or the Wilcoxon test for 2 independent samples; proportional homogeneity is compared with chi-squared. Results are expressed as n (%) (for qualitative variables) and mean ± standard deviation (for continuous variables).

with depressed systolic function), and the percentage of patients receiving diuretics fell, particularly in the group with preserved systolic function (Table 3). No differences were found in the percentages of patients reaching the optimal or maximum tolerated dose of BB (39.6% in the group with HF and preserved systolic function and 46.8% in the group with HF and depressed systolic function; $P=.08$). Incidence of secondary effects caused by BB was also similar (7.7% vs 10.9%; $P=.19$).

Events During Follow-up

Figure 1 shows mortality and the cardiovascular event rate during the 3-month follow-up in both groups. Patients with HF

and preserved systolic function presented lower incidence of death and/or cardiovascular-cause admission (13.4% vs 20.6%; $P=.026$). The mortality rate was three times less in this group (1.3% vs 3.9%), although this was not statistically significant, probably due to the low number of deaths. There were no differences in other events (admissions for decompensation of HF, acute coronary syndrome, stroke, and other causes). Days of hospitalization during the 3 months were also similar (8.0 ± 5.9 vs 8.7 ± 8.5 ; $P=.412$). A greater percentage of patients with HF and preserved systolic function were in New York Heart Association (NYHA) functional class I or II at 3-month follow-up (88% vs 74%; $P<.001$). Table 4 compares patients who presented events during the 3-month follow-up and those who did not. The proportion of patients with HF and preserved systolic function was greater in the subgroup with no

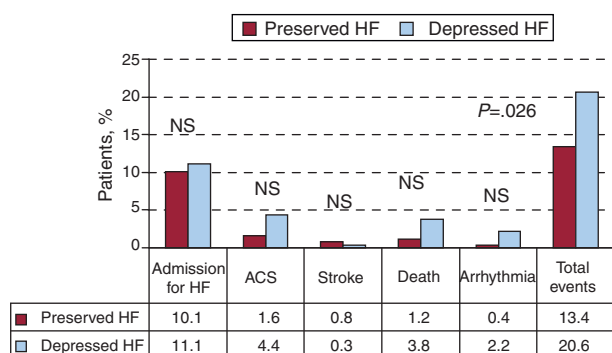


Figure 1. Incidence of events at 3-month follow-up in our patients. ACS, acute coronary syndrome; HF, heart failure; NS, not significant.

events (41.9% vs 30.2%; $P=.026$). In multivariate logistic regression analysis, HF with depressed systolic function was an independent predictor of events at 3 months (odds ratio [OR]=1.732; 95% confidence interval, 1.080–3.061; $P=.048$), as were NYHA functional class III–IV, age, female sex, previous myocardial infarction, and prior admission for HF (Table 5).

DISCUSSION

In the last 10 or 15 years, the question of whether the prognosis of patients with HF and preserved systolic function was similar to that of patients with HF and depressed systolic function has provoked controversy. Although depressed LVEF has traditionally been considered a factor in poor prognosis in HF,¹⁸ most recent studies,^{10–15,19,20} but not all,⁹ have indicated that prognosis in HF with preserved systolic function is similar or equally poor as in HF with depressed systolic function. However, these studies also show that demographic, clinical, and treatment characteristics of these 2 groups of patients differ, and that some of them can bias the prognosis in one direction or the other. In effect, patients with HF and preserved systolic function are older, present greater associated comorbidity, and receive proportionately fewer drugs shown to improve prognosis in patients with HF and systolic dysfunction, like ACEI, antialdosterone drugs, and BB. These factors can make the prognosis of patients with preserved systolic function seem worse than it would be if more homogeneous groups of patients were compared. In some of these studies, the prognosis for the 2 HF sub-types does remain similar after adjusting for some of these variables, but the most precise analytical approach is to compare 2 groups in which potentially confounding variables are equally distributed. The OBELICA study design has enabled us to compare 2 wide-ranging groups of patients with HF and preserved or depressed systolic function who are all of a similar age—quite old, in fact. Comorbidity rates are also the same, as, by and large, is treatment received, with a high proportion—close to 90%–95%—taking ACEI/ARB and BB.¹⁷ Only use of antialdosterone drugs, statins and antiplatelet drugs was significantly greater in patients with HF and depressed systolic function (Table 3). The results of our analysis—even with such a short 3-month follow-up after admission for decompensation of HF—indicate cardiovascular morbidity and mortality were significantly lower in patients with HF and preserved systolic function (13.4% vs 20.6%; Fig. 1). Even overall mortality was 3 times less in the group with preserved LVEF (1.2% vs 3.8%), although this was not statistically significant, probably due to the low number of deaths associated with the short follow-up. At 3 months, functional class was

Table 5

Independent Predictors of Events During 3-month Follow-up. Results of Logistic Regression Analysis.

Variable	OR (95%CI)	P
Functional class III–IV	3.295 (1.231–4.235)	.024
Previous myocardial infarction	1.932 (1.183–3.458)	.028
Age	1.060 (1.008–1.114)	.021
Depressed HF	1.732 (1.080–3.061)	.048
Previous admissions for HF	1.786 (1.052–3.032)	.031
Female gender	1.675 (1.013–2.770)	.044

95%CI, 95% confidence interval; HF, heart failure; OR, odds ratio.

also better in the group with HF and preserved LVEF: 87.6% of patients with HF and preserved systolic function and 74.4% of those with HF and depressed systolic function ($P<.001$) were in class I or II.

In the previously mentioned studies,^{10–15,19,20} lower age and less comorbidity in patients with systolic dysfunction could have reduced morbidity and mortality in these patients, improving their prognosis so that it approached that of patients with preserved LVEF. Our study has not wholly eliminated the comorbidity bias as patients with HF and depressed systolic function presented greater prevalence of smoking, myocardial infarction, or coronary revascularization. However, we have substantially reduced it. Moreover, in the stepwise logistic regression multivariate model, HF with depressed systolic function remained an independent predictor of a greater rate of events. Furthermore, the percentage of patients receiving ACEI or ARB and, above all, BB, was very high and similar in our 2 study groups. This contrasts with the findings of most other studies, in which patients with HF and depressed systolic function received proportionately more BB. Although there is no evidence from controlled clinical trials to show the beneficial effect of these drugs on patients with HF and preserved LVEF^{21,22}—hence, probably, they are less frequently used in patients with preserved systolic function—some non-randomized studies indicate BB use may be associated with improved prognosis in these patients.^{23,24} Beta blockers can benefit patients with HF and preserved systolic function, either through their negative chronotropic effect or their control of high blood pressure and ischemic heart disease (the principle causes of this problem). In the SENIORS study,²⁴ which also included patients with HF and preserved systolic function, BB had a similar effect in patients with depressed and preserved LVEF. In our study, approximately 90% of patients in both groups received ACEI or ARB and BB, as shown in Table 3.

Limitations

Our study has certain limitations—principally the short, 3-month follow-up due to the design of the original study.¹⁷ For the same reason, we excluded from analysis in-hospital deaths prior to discharge. However, the rate of events in patients discharged for HF is greater in the first months of follow-up^{8,10,20–22} and progressively falls later, so these data do not affect the validity of our study. The curves of events in HF studies would normally be expected to separate gradually over the follow-up period, with the initial trend being accentuated. Consequently, the differences we found probably would have been greater in a longer follow-up. Another limitation, which we have already discussed, is BB use. We do not know their real effect in prognosis of HF with preserved LVEF since no controlled

studies have been done, but they may well be beneficial.^{23,24} In our study, we eliminated bias due to possible differences derived from proportionately different use of these drugs in one or the other group of patients with HF. Finally, we only enrolled patients treated in cardiology services and excluded those admitted in internal medicine, who usually present greater comorbidity. However, the high mean age of our patients—78 years—reduces this bias.

CONCLUSIONS

From our results, it can be concluded that the prognosis of patients with HF and preserved systolic function appears better than that of patients with HF and depressed systolic function, at least in the short term. When we eliminate potentially confounding factors in patient characteristics that may influence prognosis—eg, age, comorbidity, and treatment received—morbidity and mortality are significantly lower and the trend in overall mortality is 3 times lower at 3-month follow-up. Studies with these characteristics and longer follow-up are needed to confirm these data.

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CONFLICTS OF INTEREST

None declared.

APPENDIX

Principal Investigators, OBELICA Study:

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