Long-Term Trends in Drug Prescription for Hospitalized Patients With Congestive Heart Failure. Influence of Type of Dysfunction

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Introduction and objectives. To evaluate changes in drug prescription during 1991-2002 in patients hospitalized for congestive heart failure (CHF) with preserved or depressed left ventricular (LV) systolic function.

Patients and method. A total of 1252 CHF patients (mean age, 69.4±11.7 years; 61.3% male) hospitalized in a cardiology department were studied. Ischemic heart disease was present in 616 (49.2%), hypertension in 693 (55.4%), and diabetes in 335 (26.8%). Some 498 (39.8%) had preserved LV systolic function, defined as an echocardiographically determined ejection fraction ≥50% at admission. Pharmacotherapy at hospital discharge was recorded for all patients.

Results. The changes in drug prescription observed in CHF patients with preserved LV systolic function paralleled those in patients with depressed LV systolic function. Change was influenced by the publication of major clinical trials on CHF and depressed LV systolic function. Consequently, the use of angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, beta-blockers, and spironolactone progressively increased during follow-up for both types of CHF. Diuretics were prescribed for more than 70% of patients, with the rate being higher in those with depressed LV systolic function. Digoxin use decreased markedly in patients with preserved LV systolic function.

Conclusions. An increase in the prescription of drugs with proven effects on mortality and morbidity in patients with CHF was observed. Nevertheless, beta-blocker and spironolactone use remains suboptimal. The trend seen after hospitalization in CHF patients with preserved LV systolic function was similar, though slightly less marked.

Key words: *Congestive heart failure. Left ventricular systolic function. Pharmacological management.*

Evolución a largo plazo de la prescripción de fármacos en pacientes hospitalizados por insuficiencia cardíaca congestiva. Influencia del patrón de disfunción

Introducción y objetivos. Evaluar a largo plazo (1991-2002) la prescripción de fármacos en pacientes hospitalizados por insuficiencia cardíaca con función sistólica (FS) ventricular izquierda conservada y deprimida.

Pacientes y método. Se ha evaluado a un total de 1.252 pacientes ingresados en el servicio de cardiología por insuficiencia cardíaca con una edad media de 69,4 ± 11,7 años y 767 (61,3%) varones. El 49,2% (616) de los enfermos presentaba cardiopatía isquémica; el 55,4% (693), hipertensión arterial, y 335 (26,8%), diabetes. La FS ventricular izquierda estaba conservada en 498 enfermos (39,8%) (fracción de eyección determinada ecocardiográficamente durante el ingreso ≥ 50%). En todos los pacientes incluidos en el estudio se ha evaluado el tratamiento prescrito en el alta hospitalaria.

Resultados. Se ha observado un patrón paralelo en la prescripción de fármacos en pacientes con insuficiencia cardíaca con FS ventricular izquierda conservada y deprimida, cuya evolución ha coincidido con la publicada en amplios ensayos clínicos de insuficiencia cardíaca con FS ventricular izquierda deprimida. Así, la prescripción de inhibidores de la enzima de conversión de la angiotensina, bloqueadores de los receptores de la angiotensina II, espironolactona y bloqueadores beta se incrementó progresivamente en ambos patrones de disfunción. Más del 70% de los pacientes utilizaba diuréticos, con más frecuencia en el grupo con FS ventricular izquierda deprimida; la utilización de digital mostró una marcada reducción en el grupo con FS ventricular izquierda conservada.

Conclusiones. Hemos asistido a un incremento del empleo de fármacos con efecto probado sobre la mortalidad y morbilidad de pacientes con insuficiencia cardíaca congestiva; sin embargo, el empleo de bloqueadores beta y espironolactona es aún limitado. Hay una tendencia paralela, aunque ligeramente inferior en el grupo de FS conservada, en el empleo de estos fármacos después de la hospitalización de los pacientes con insuficiencia cardíaca.

Palabras clave. *Insuficiencia cardíaca congestiva. Función sistólica ventricular izquierda. Tratamiento farmacológico.*

INTRODUCTION

Congestive heart failure (CHF) is a leading cause of mortality, morbidity, and health expenditure. Moreover, it is one of the areas of medicine where the greatest effort in clinical research has been made in the last 25 years. The results from clinical trials in this field have provided the basis for the current recommendations for pharmacological therapy in CHF. Blockage of the renin angiotensin system with angiotensin-converting enzyme (ACE) inhibitors and the use of beta-blockers are currently the main pillars of pharmacological treatment available to CHF patients, prescribed with the aim of prolonging survival, improving the quality of life and reducing the need for hospitalization due to cardiovascular causes. According to the recommendations of clinical practice guidelines, when there are no formal contraindications, these drugs should be included in therapeutic strategies for patients with asymptomatic ventricular dysfunction and CHF in its various phases of severity.[1-5] In the RALES study, aldosterone receptor antagonists (specifically spironolactone) administered with ACE inhibitors provided benefits similar to those seen with the use of beta-blockers and ACE inhibitors in patients with advanced CHF.[6] In addition, findings from recent clinical trials involving angiotensin II receptor antagonists (ARA II) indicate that these agents should be administered in patients intolerant to ACE inhibitors, and could be considered in combination with ACE inhibitors and beta-blockers in patients who tolerate these drugs.[7,8]

The use of loop diuretics is the basis for symptomatic treatment of patients with CHF. Although studies on long-term prognosis are not available, these agents should be included in the therapeutic approach for CHF patients to relieve the congestive symptoms. Along this line, digitalis treatment has been shown to improve the patients' clinical situation. In the Digitalis Investigation Group (DIG) study, the use of digoxin resulted in a reduction in the total number of hospitalizations and in hospitalizations due to worsening of CHF.[9]

This accumulated data is derived from studies in patients with CHF and impaired systolic function (SF).

The information on therapy in CHF patients with preserved SF is much more limited and there are no clinical trials providing sufficient clinical evidence on the approach to pharmacological treatment in these patients. Moreover, the current clinical practice guidelines[10,11] for CHF are quite speculative when referring to treatment in this important patient population, which now comprises 30% to 50% of hospitalized CHF patients.[12] It has even been suggested that the same therapeutic strategies could be used for both pathophysiological patterns of CHF.

Although reports are available indicating the situation of pharmacological treatment for CHF[13-17] in both hospitalized and ambulatory patients in Spain, the studies have a cross-sectional design and there is little information on this type of treatment in patients with CHF and preserved SF.

The objective of our study was to analyze the trends in the prescription of medication among hospitalized patients with CHF and preserved or impaired SF in the cardiology department of a teaching hospital over the last 12 years, and to assess the impact of current scientific evidence on clinical practice in these patients.

PATIENTS AND METHODS

Patients Studied

This study included all consecutive patients admitted for CHF to the cardiology department of a tertiary hospital between 1 January 1991 and 31 December 2002. Congestive heart failure was defined according to the modified Framingham criteria as follows[18]: the major criteria included paroxysmal nocturnal dyspnea, orthopnea, pulmonary rales, jugular venous distention, presence of a third heart sound, and radiologic signs of pulmonary congestion and cardiomegaly; the minor criteria included dyspnea on exertion, peripheral edema, hepatomegaly, and pleural effusion. The diagnosis was considered positive when at least 2 of the major criteria, or 1 of the major criteria and 2 of the minor criteria were present, or when echocardiographic assessment of the ejection fraction (EF) at the time of hospitalization was consistent with inclusion in the study. In patients who were rehospitalized, only the first admittance coinciding with the study period was considered.

Variables Analyzed

The demographic data, clinical situation, results from additional tests, and the treatment prescribed at hospital discharge were assessed. The cut-off point defining CHF with impaired SF on echocardiography was established at an EF value of <50%. The echocardiographic data compiled were obtained at the time of hospital admission; echocardiographic results at discharge were not considered in this study.

The selection of candidates for inclusion in the analysis and data collection from the cardiology department clinical records was carried out in 2003 by 2 cardiologists with considerable experience in CHF.

The changes occurring in the prescription of the various therapeutic drug classes were assessed yearly from 1995 on. Due to the significantly smaller number of patients admitted during the first years of the study, data from the period encompassing 1991 to 1994 was combined for the evaluation.

Statistical Analysis

Dichotomous variables were compared using the χ^2 test and expressed as a percentage. Continuous variables were expressed as the mean ± standard deviation (SD). Linear regression was used to calculate *P*-values with a linear trend. Statistical calculations were done with SPSS, version 11.5, and *P*-values <.05 were considered statistically significant.

RESULTS

Characteristics of the Study Population

A total of 1252 patients were assessed; 767 were men (61.3%) and the mean age was 69.4±11.7 years (Table). In 616 (49.2%) patients, ischemic heart disease had been diagnosed, 693 (55.4%) had hypertension, and 335 (26.8%) had diabetes. At the time of admission, 70.4% (n=881) of the patients were New York Heart Association (NYHA) functional class III or IV and 33.9% (n=424) had atrial fibrillation. Systolic function was preserved in 498 patients (39.8%).

Changes in Drug Prescription in the Total Group

In general, the changes in drug prescription for these patients have followed three well-differentiated patterns (Figure 1). Some medications have shown a significant trend to higher use, mainly the ACE inhibitors, ARA II, beta-blockers, and spironolactone. This was also true for the anticoagulants and calcium channel blockers. In contrast, the prescription of digitalis compounds has decreased. Lastly, the application of diuretics, the most widely used medication in our patients, antiplatelet agents, and nitrates has not shown statistically significant changes over the 12-year period reviewed.

The highest increase over the years was seen in the use of beta-blockers (linear trend, *P*<.001). Prescription of these drugs rose from 5.4% of the cases in 1991-1994 to more than half of the patients (54.0%) with CHF discharged from the hospital in 2002, the final year of the study. With regard to ACE inhibitors and/or ARA II, peak use was reached in 1999 with prescription of these drugs recorded in the discharge records of 78.0% of the patients; since then their use has remained virtually stable.

TABLE. **Clinical Characteristics of the Total Population of Patients Admitted for Heart Failure Between 1991 and 2002 and the Subgroups With Either Preserved or Impaired Systolic Function***

Variable	Total Group (n=1252), n (%)	EF<50% (n=754), n (%)	EF≥50% (n=498), n (%)	P†
Mean age, years	69.4±11.7	67.4±12.2	72.3±10.2	<.001
Mean stay, days	14.4±12.1	15.0±12.0	13.6±12.3	.047
Males	767 (61.3)	522 (69.2)	245 (49.2)	<.001
Etiology				<.001
Ischemic heart disease	616 (49.2)	409 (54.2)	207 (41.6)	
Valvular disease	260 (20.8)	95 (12.6)	165 (33.1)	
Dilated cardiomyopathy	116 (9.2)	116 (15.4)	0	
Other heart disease	260 (20.8)	134 (17.8)	126 (25.3)	
HT	693 (55.4)	389 (51.6)	304 (61.0)	<.01
DM	335 (26.8)	210 (27.9)	125 (25.1)	NS
DYS	419 (33.5)	256 (34.0)	163 (32.7)	NS
NYHA III or IV	881 (70.4)	553 (73.3)	328 (65.9)	<.001
Pulmonary rales	958 (76.5)	572 (75.9)	386 (77.5)	NS
Peripheral edema	401 (32.0)	231 (30.6)	170 (34.1)	NS
Alveolar edema	152 (12.1)	118 (15.6)	34 (6.8)	<.001
Pleural effusion	243 (19.4)	151 (20.0)	92 (18.5)	NS
Atrial fibrillation	424 (33.9)	232 (30.8)	192 (38.6)	.005
LBBB	196 (15.7)	159 (21.1)	37 (7.4)	<.001

*EF indicates ejection fraction; HT, arterial hypertension; DM, diabetes mellitus; DYS, dyslipidemia; NYHA, New York Heart Association functional class; LBBB, left bundle branch block; NS, non-significant.
†Statistically significant difference between the 2 subgroups with EF<50% or ≥50%.

	Linear Trend, P	R^2
ACEI	.057	0.425
ACEI or ARA II	.030	0.514
Beta-Blockers	<.001	0.883
Spironolactone	.001	0.813
Diuretics	.269	0.171
Digitalis	.005	0.701
Antiplatelet Agents	.524	0.060
Anticoagulantes	.012	0.617
Calcium Channel Blockers	.010	0.635
Nitrates	.183	0.237

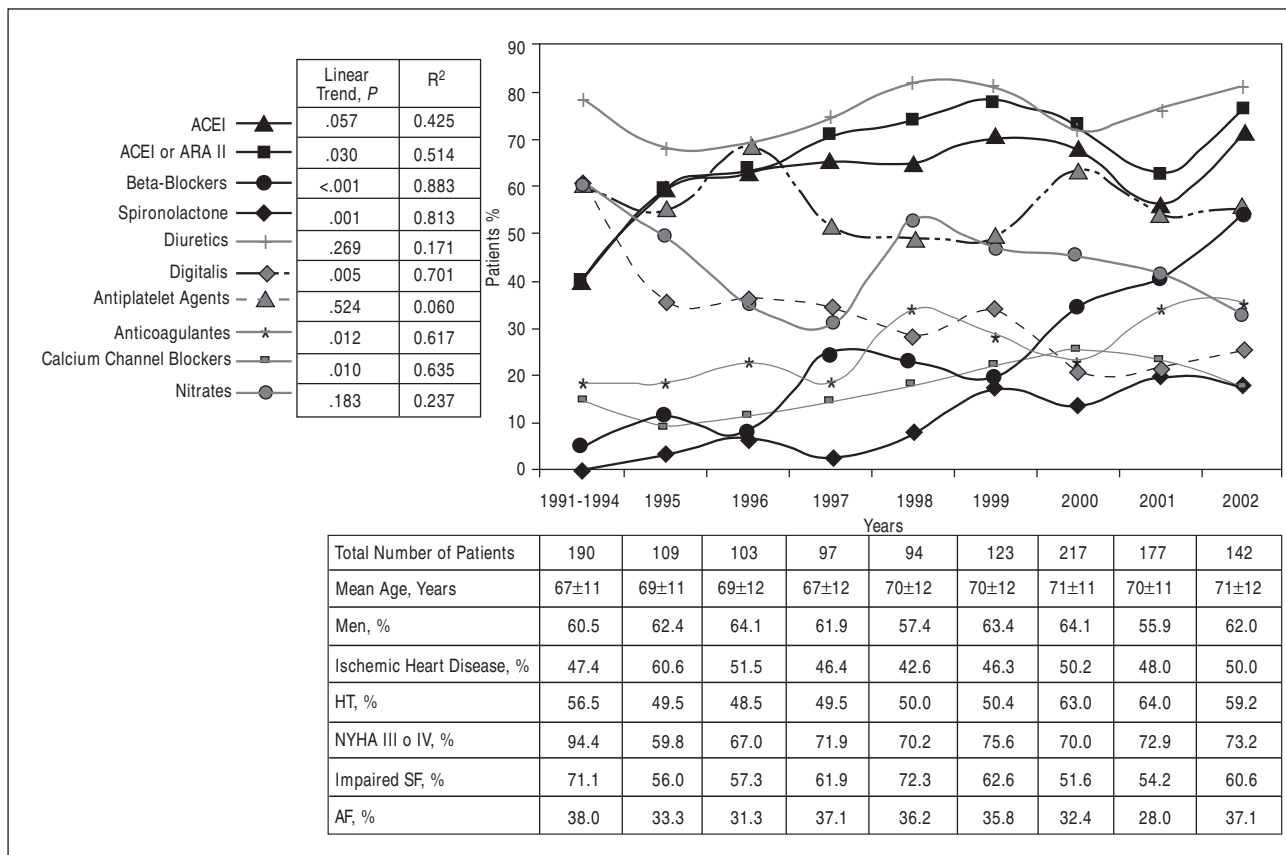| Years	1991-1994	1995	1996	1997	1998	1999	2000	2001	2002
Total Number of Patients	190	109	103	97	94	123	217	177	142
Mean Age, Years	67±11	69±11	69±12	67±12	70±12	70±12	71±11	70±11	71±12
Men, %	60.5	62.4	64.1	61.9	57.4	63.4	64.1	55.9	62.0
Ischemic Heart Disease, %	47.4	60.6	51.5	46.4	42.6	46.3	50.2	48.0	50.0
HT, %	56.5	49.5	48.5	49.5	50.0	50.4	63.0	64.0	59.2
NYHA III o IV, %	94.4	59.8	67.0	71.9	70.2	75.6	70.0	72.9	73.2
Impaired SF, %	71.1	56.0	57.3	61.9	72.3	62.6	51.6	54.2	60.6
AF, %	38.0	33.3	31.3	37.1	36.2	35.8	32.4	28.0	37.1

Figure 1. Changes in drug prescription in patients with heart failure, occurring between 1991 and 2002
ACEI indicates angiotensin converting enzyme inhibitors; ARA II, angiotensin II receptor antagonists; HT, arterial hypertension; NYHA, New York Heart Association functional class; SF, left ventricular systolic function; AF, atrial fibrillation; R2, the slope of the change in drug prescription.

Changes in Drug Prescription in Patients With CHF and Preserved or Impaired Systolic Function

The main differences between the groups with preserved or impaired SF include younger age in the impaired group (67 vs 73 years), a higher prevalence of ischemic heart disease (54% vs 42%) and more advanced NYHA functional classes (73% vs 66%) (Table). In contrast, atrial fibrillation was more frequent in patients with preserved SF (39% vs 31%).

The trends in the use of ACE inhibitors and ARA II in the preserved and impaired SF groups were found to be parallel, although prescription of these drugs was higher in patients with impaired function. In the year 2000 a more highly significant difference was reached between these groups with changes also detected in the use of beta-blockers and spironolactone, again with higher application in the group with EF<50%. Up to 1996, the prescription of beta-blockers and spironolactone had been higher in patients with preserved SF, with a significant difference for both pharmacological classes during that year (Figure 2).

The prescription of diuretics and antiplatelet agents was more constant over the 12-year period. Whereas the use of diuretics was slightly higher in the group with impaired SF, there were no differences in antiplatelet use between the 2 patterns of ventricular dysfunction.

Except for the first 4 years when its use was nearly three-fold higher in the patients with impaired SF, the prescription of nitrates has also followed a parallel pattern with a slight predominance in patients with systolic dysfunction that has been lost in the last 2 years.

Digoxin use has decreased notably in the group with preserved SF, dropping from 73.9% in the period of 1991-1994 when it surpassed the prescription in impaired SF, to 17% in 2002. The use of these drugs in patients with EF<50% has shown a much more homogeneous pattern over the last 12 years, although there is also a decreasing trend.

In CHF patients with preserved SF, there has been a linear rise in the prescription of anticoagulants since 1997. This increase went beyond that of the impaired SF group in 2000 and reached a significant difference in 2004.

In contrast to the changes seen in the aforementioned pharmacological agents, the use of calcium
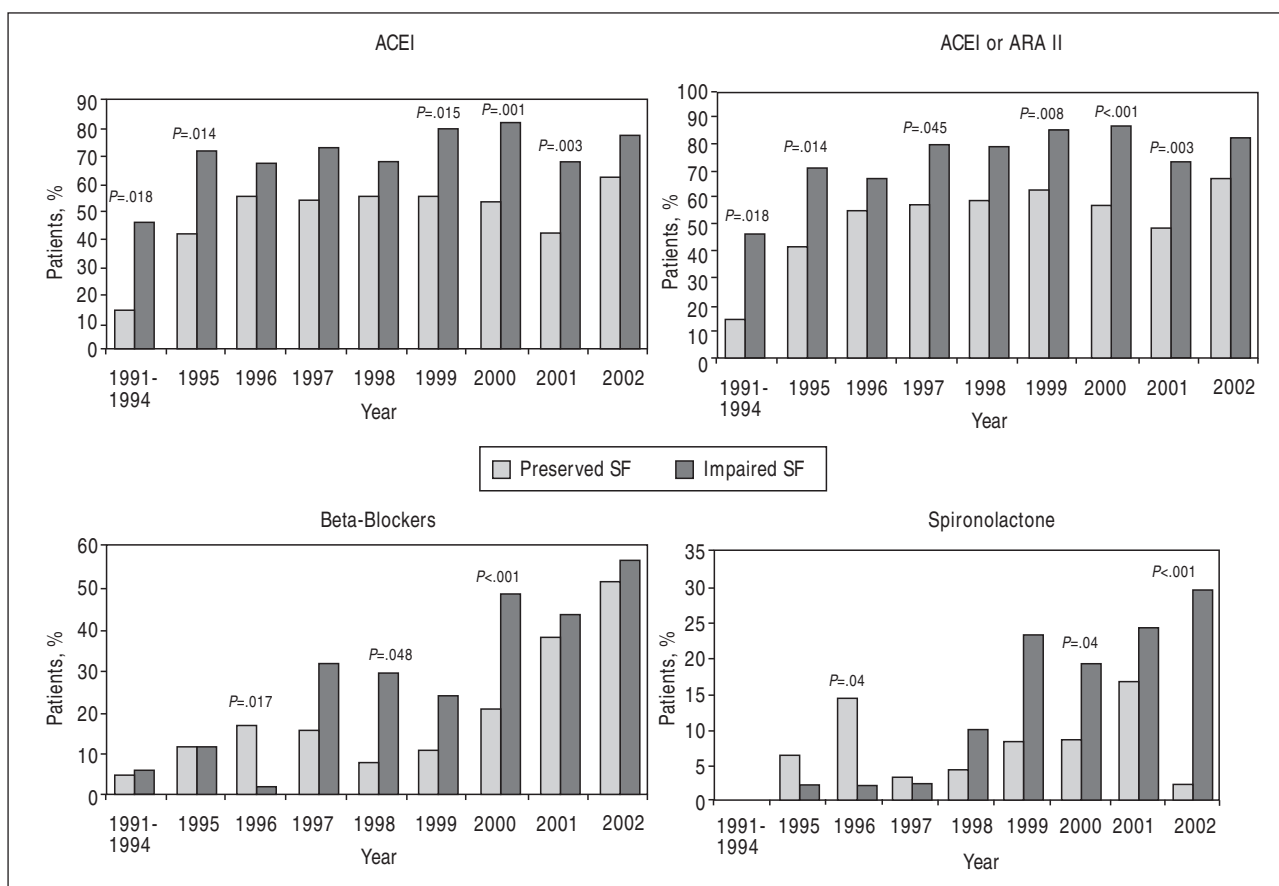
Figure 2. Changes in the prescription of drugs indicated for heart failure in patients with this disease and preserved or impaired left ventricular systolic function (statistically significant differences in the prescription of drugs between the groups with preserved or impaired systolic function are shown with the respective *P*-values).

channel blockers has been constantly higher, and almost always significantly higher in patients without systolic dysfunction. There was a rising trend in its use up to 1999 and since that time it has remained stable (Figure 3).

DISCUSSION

Over the 12 years analyzed in this study, there have been considerable changes in the pharmacological treatment of patients with CHF, as is reflected in recommendations from the guidelines of several scientific societies, which are the reference for the use of these agents in clinical practice. To the best of our knowledge, this is the first study that analyzes the changes in pharmacological treatment of CHF patients without, and particularly with, preserved left ventricular systolic function, performed in a large patient population and over a lengthy observational period. The parallel patterns in the prescription of the majority of therapeutic drug classes in these 2 CHF patient populations is noteworthy, and is an aspect about which we have little information.

The changes in the prescription of ACE inhibitors is

related to the published results of large clinical trials, which have demonstrated the clinical and prognostic benefits of these drugs in patients with chronic CHF, and CHF with post-myocardial infarction ventricular dysfunction.[1,2] It should be highlighted that in the last years of observation, ACE inhibitors were prescribed in more than 60% of the patients, a higher proportion than has been reported in other studies performed inside and outside Spain, both in ambulatory and hospitalized patients.[13,19,20] This percentage was complemented with ARA II use. Taken together, pharmacological blockade of the renin-angiotensin system with ACE inhibitors or ARA II was prescribed in 80% of the patients, a figure indicating close adherence to the recommendations in the related clinical practice guidelines. According to the pattern of dysfunction (CHF, with preserved or impaired SF) there were significant differences in the frequency with which ACE inhibitors and ARA II were prescribed, being higher in CHF with systolic dysfunction. This fact is unquestionably related to the scientific evidence supporting the efficacy of these drugs in this group of patients.

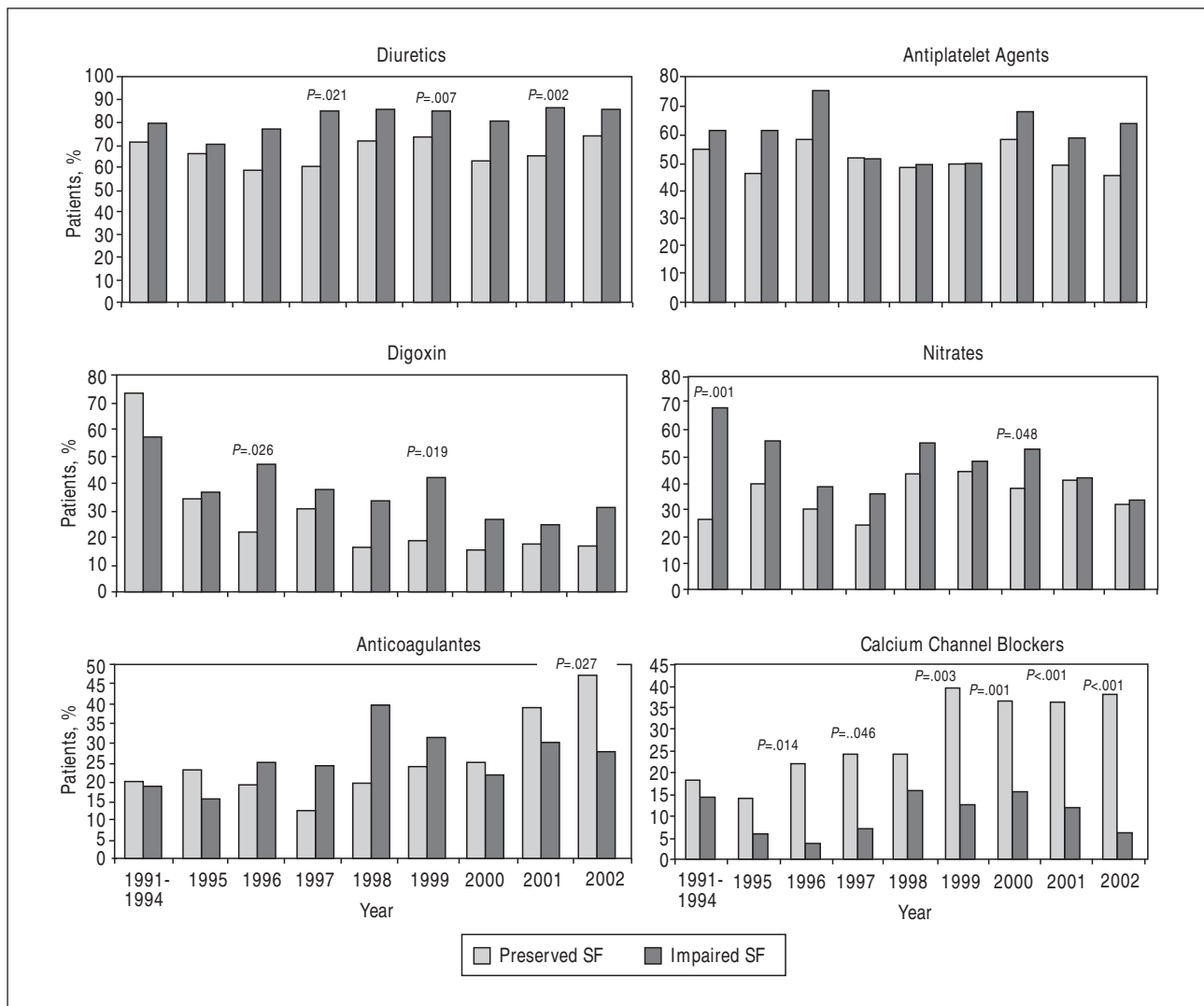Although to a lesser extent, the use of renin-

Figure 3. Changes in the prescription of drugs that are not indicated as first-line therapy in heart failure in patients with this disease and preserved or impaired left ventricular systolic function (statistically significant differences in the prescription of drugs between the groups with preserved or impaired systolic function are shown with the respective *P*-values).

angiotensin system blockers in patients with preserved SF has also been very frequent, with almost 70% of patients prescribed these agents at hospital discharge in 2002. This fact is justified by the effectiveness of these drugs in lowering blood pressure and their capacity to induce regression of left ventricular hypertrophy and fibrosis. Adequate blood pressure control and improvements in structural and functional cardiac alterations are important factors to take into account when planning the therapeutic approach for patients with CHF and preserved SF.[21] In addition, recent data have indicated that these drugs may promote atrial electric stability and contribute to maintaining sinus rhythm,[22] which improves ventricular filling and favors relief of pulmonary congestion.[23] The progressive increase in the use of spironolactone is not consistent with the guideline recommendations which, after the results of the RALES study, have established that

spironolactone should be used in patients with advanced CHF (NYHA functional classes III/IV).[6] Although these results are similar to those reported in other recent studies,[24,25] they should make us reflect on the need for enhancing the use of a medication with an excellent cost-benefit ratio.[26]

In recent years there has been a considerable increase in the prescription of beta-blockers, related to the publication in 1999 of the main clinical trials with these agents in CHF patients. In the last year of observation in the present study, 50% of patients were given this medication. The use of beta-blockers in our series was higher than that observed overall in Spain[16] and was similar to the reported rates in hospitalized patients in Europe and North America.[27] It should be kept in mind that a significant percentage of elderly patients with CHF do not tolerate treatment with beta-blockers, and in many cases difficulties are encoun-

tered when starting these drugs during hospitalization, particularly in the population requiring elevated doses of diuretics. Nevertheless, we believe that efforts should be made to include these agents in as many patients as possible. Physicians other than cardiologists who are responsible for the clinical follow-up of CHF patients may have more difficulties in establishing the treatment, and this would deprive patients of important benefits in terms of survival and quality of life.[13,14,19] Between 1997 and 2000 in the present study, the use of beta-blockers was higher in the group with impaired SF; nevertheless, in the last 2 years the prescription has equalized in the 2 cardiac dysfunction patterns. The reasons may be the same as in the case of ACE inhibitors and ARA II. Moreover, the heart-slowing effect of this drug, which improves the filling conditions of the heart and can contribute to the patients' clinical stability, should be taken into account.

The reduced use of digoxin in our series seems to be highly influenced by the results of the DIG study published in 1997, in which this agent showed a neutral effect on mortality in CHF patients.

Current clinical practice guidelines do not justify the use of calcium channel blockers in CHF patients, and they contraindicate verapamil and diltiazem in patients with CHF and impaired SF.[28,29] In addition, the guidelines indicate that the use of long-acting dihydropyridines may be safe in CHF patients who need additional treatment for the control of angina or hypertension. Nondihydropyridine calcium channel blockers could be useful in patients with CHF and preserved SF due to their heart-slowing, antianginal and antihypertensive actions.[21] We observed a slight decrease in the frequency of calcium channel blocker prescription in the last 3 years. In addition, the use of these agents was statistically more frequent in patients with CHF and preserved SF.

To our knowledge this is the first study assessing drug therapy prescription in patients with CHF at long term in Spain; in other related publications performed in our country the periods analyzed are shorter. In a study similar to ours by Ojeda et al[17] comparing drug prescription for patients with cardiac dysfunction (systolic or diastolic), the rates of ACE inhibitor, ARA II and beta-blocker use are similar to those found in our series. The prescription of spironolactone is, however, higher in Ojeda' s study, probably because that series had a higher prevalence of patients in advanced NYHA classes. In contrast, the prescription of drugs with a demonstrated indication in CHF was considerably lower in a series of 256 patients studied by Permanyer et al,[16] in which 54% received ACE inhibitors or ARA II and only 4% were treated with beta-blockers. It should be taken into account that most of the patients included in the study were hospitalized in departments other than cardiology, and this low rate may reflect a certain difficulty for specialists other than

cardiologists to establish these drugs in this type of patient. This fact is also reflected in the INCARGAL study, which analyzed the influence of the hospital department where the CHF patient is admitted on the use of diagnostic and therapeutic resources.[14]

LIMITATIONS

This study is limited to an analysis of the changes in the prescription of the different pharmacological groups in patients admitted to the cardiology department at a single center, with specific clinical and management characteristics that may be different from other departments and hospitals. Hence, extrapolation of the results should be made with caution.

In addition, the results of our study only reflect the pharmacological treatment used at the time of hospital discharge; the percentage of patients who discontinued the treatment or were started on other drugs during follow-up is not known.

CONCLUSIONS

Over the study period in our hospital there has been an increase in the use of drugs with a proven effect on mortality and morbidity in patients with CHF. Nevertheless, beta-blocker and spironolactone use is still limited. There was a parallel, although slightly lower trend in the use of drugs with beneficial effects among patients with preserved SF.

Efforts should be made in our setting to develop systems that identify the reasons why there is a disassociation between guideline recommendations and clinical practice and to implement corrective measures. These strategies are particularly relevant, since the specialized medical activity used in hospitals exerts an important influence on the follow-up of patients by other groups of medical professionals.

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