Clinical features and prognosis associated with a preserved left ventricular systolic function in a large cohort of congestive heart failure outpatients managed by cardiologists. Data from the Italian Network on Congestive Heart Failure

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Background. **The aim of this study was to evaluate the clinical characteristics, 1-year prognosis and therapeutic approach of heart failure with a preserved left ventricular systolic function in a large multicenter registry of patients referred to specialized heart failure clinics.**

Methods. **The study population consisted of 5164 outpatients (mean age 62 ± 12 years, 78.8% male, 28.1% in NYHA functional class III-IV) with an available left ventricular ejection fraction (LVEF) measurement at the initial evaluation for enrollment in the Italian Network on Congestive Heart Failure. A 1-year follow-up was available for 2390 patients.**

Results. **2859 out of 5164 patients (55.4%) had an LVEF < 35%, 1618 (31.3%) had an LVEF between 35 and 45%, and 687 patients (13.3%) had an LVEF > 45%. Patients with an LVEF > 45% were significantly older, more often female and presented a significantly higher prevalence of a hypertensive etiology, obesity and atrial fibrillation. The severity of the clinical picture, as indicated by a lower prevalence of NYHA class III-IV (17.2 vs 35.6%, p = 0.001) and a third heart sound (14.8 vs 33.5%, p = 0.001), was less in patients with an LVEF > 45%. The therapeutic approach differed significantly, with a larger use of calcium antagonists and beta-blockers in patients with an LVEF > 45%, while ACE-inhibitors, diuretics and digoxin were more often prescribed to those with an impaired LVEF. The 1-year mortality and morbidity (all cause and congestive heart failure worsening hospitalizations) were significantly lower in patients with a preserved left ventricular systolic function compared to those with left ventricular systolic dysfunction (8.9 vs 18.8% for mortality, p = 0.001, and 8.3 vs 16.5% for hospital readmissions due to worsening congestive heart failure, p = 0.001, respectively).**

Conclusions. **Patients with congestive heart failure and a preserved left ventricular systolic function seem to constitute a distinct population not infrequently presenting even in the clinical setting of specialized heart failure clinics. Further studies are needed to establish a definitive and standardized diagnosis and the most appropriate therapy for congestive heart failure with a normal LVEF.**

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Introduction

In developed countries congestive heart failure (CHF) is a major public health problem[1-3]. It currently affects 1 to 2% of the adult population[4], and it is the leading cause of hospitalization and a major cause of chronic disability in patients > 65 years of age[5].

In recent years, due to the widespread utilization of noninvasive techniques such as echocardiography to assess the ventricular function, evidence has accumulated that a relevant percentage of patients with CHF (ranging from 13 to 70% according to different studies) has a normal or relatively preserved left ventricular systolic function[6-20]. CHF with a preserved systolic function is often attributed to an abnormal left ventricular diastolic function and seems to be particularly common among the elderly.

Despite the fact that several studies on CHF with a preserved systolic function have been published in the literature, our knowledge of the clinical characteristics of

patients presenting with this disorder is still limited. Relatively few patients have been evaluated in most previous studies and a referral bias cannot be excluded[7-12]. Limited data are available on CHF with a preserved systolic function in an outpatient cardiology clinic[9,11]. Most data are obtained in the hospital and in community settings and have been found to be conflicting[15-20]. Furthermore, insights on morbidity and mortality and on the appropriate therapeutic strategy and prevention of CHF with a preserved left ventricular systolic function are incomplete. In view of the above, we analyzed the Italian Network on Congestive Heart Failure (IN-CHF) database, a large nationwide multicenter registry, in order to evaluate the prevalence and prognosis of CHF with a preserved systolic function, the patient's clinical characteristics, and the current therapeutic approach in the setting of heart failure outpatients managed by cardiologists.

Methods

IN-CHF registry and patients. The IN-CHF database was developed by the Working Group on Heart Failure and by the Research Center of the Italian Association of Hospital Cardiologists (ANMCO) in order to create a national registry of CHF outpatients referred to cardiological centers. In 1995 all centers of the ANMCO Working Group on Heart Failure were invited to collect the data. One hundred and thirty-three out of 192 centers (69%), highly representative of the whole country, agreed to participate and several training meetings were organized to prepare cardiologists to collect and enter data in a standardized way.

From March 1995 to January 1999, the 133 centers of the IN-CHF network collected and entered into the national database data from 8102 consecutive outpatients with CHF. Entry into this database required that the patient had a diagnosis of heart failure based on criteria reported in the European Society of Cardiology guidelines, on the presence of typical symptoms and signs and on the documentation of cardiac disease[21]. The registry is strictly observational and the physicians are not invited to do anything apart from what they feel useful for the patients. The central coordination of the project was at the ANMCO Research Center in Florence (Italy). The patients' demographic data, history and NYHA functional class, the definition of the primary etiology, the physical and laboratory examination results and drug prescription were all recorded. When multiple etiologic factors for heart failure were present, the one judged by the referring cardiologist to be predominant was identified as the primary cause. There were 1050 out of 8102 (12.9%) patients with organic valvular disease or idiopathic hypertrophic cardiomyopathy as the primary etiology; these subjects were excluded from this study. The determination of the left ventricular ejection fraction (LVEF) by means of two-dimensional echocardiography, obtained within 3 months before enrollment, was available for 5164 (73.2%) patients. At the time of the analysis, 1-year follow-up data were available for 2390 (58.8%) subjects.

Study variables. Based on the LVEF value, patients were categorized into three groups: group 1, patients with an LVEF < 35% and considered as having CHF with an impaired systolic function; group 2, patients with an LVEF > 45% and classified as having CHF with a preserved systolic function; group 3, patients with an LVEF between 35 and 45%, representing a mixed group with a moderately reduced systolic function. The variables collected in the database were: the patient's demographic data, the etiology of CHF, the NYHA functional classification, hospital admission for CHF during the previous 12 months, the patient's clinical features (heart rate, systolic blood pressure, third heart sound, ventricular or atrial arrhythmias), the presence or absence of comorbidities (diabetes, hypertension, chronic obstructive pulmonary disease, impaired renal function, obesity, vascular disease other than coronary artery disease), the use of cardiovascular medications, death (all causes), hospitalizations (for all causes, for cardiovascular events and for worsening CHF).

Statistical analysis. Continuous variables were expressed as mean ± SD and univariate analyses were performed using analyses of variances, the Student's t-test for comparison of two groups and the Bonferroni correction for multiple comparisons. Discrete variables were summarized by frequency percents and analyzed using the χ^2 test. Multivariate Cox proportional hazards regression analyses were used to identify independent predictors of death and of hospital admission. A p value of < 0.05 was considered statistically significant. All analyses were performed with the SAS system software (SAS Institute Inc., Cary, NC, USA).

Results

Clinical characteristics of the patients. The distribution of the demographic and clinical variables in the study population is shown in table I. Of 5164 patients with an echocardiographic evaluation of the left ventricular function at the initial assessment, 2859 (55.4%) had an LVEF < 35% (group 1), 687 patients (13.3%) had an LVEF > 45% (group 2), and 1618 patients (31.3%) had an LVEF between 35 and 45% (group 3). Table II compares the clinical characteristics and the baseline echocardiographic data of the patients belonging to each of the three groups. Compared with those with left ventricular systolic dysfunction (group 1), patients with a preserved left ventricular systolic function (group 2) were older, more often female, had a higher prevalence of a hypertensive etiology and a lower prevalence of coronary artery disease and dilated car-

Table I. Clinical characteristics of the patients with a known ejection fraction.

No. patients	5164
Age (years)	62 ± 12
≥ 70	1436 (27.8%)
≥ 80	231 (4.5%)
Male	4068 (78.8%)
NYHA class III-IV	1449 (28.1%)
Hospital admission for CHF during the previous year	2946 (57.1%)
Heart rate ≥ 100 b/min	533 (10.4%)
SBP ≥ 130 mmHg	1829 (35.4%)
Third heart sound	1446 (28.0%)
Primary etiology	
CAD	2347 (45.4%)
IDC	2013 (39.0%)
Hypertension	604 (11.7%)
Other	200 (3.9%)
Comorbidities	
Diabetes mellitus	808 (15.7%)
COPD	917 (17.8%)
Vascular disease	810 (15.7%)
CRF (serum creatinine > 2.5 mg/dl)*	57 (2.3%)
Obesity (BMI > 27 kg/m^2)	1836 (35.6%)
Atrial fibrillation	863 (17.4%)
Major ventricular arrhythmias**	393 (27.9%)

BMI = body mass index; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; CRF = chronic renal failure; IDC = idiopathic dilated cardiomyopathy; SBP = systolic blood pressure. * = available for 2458 patients; ** = available for 1411 patients.

diomyopathy (p = 0.001 for each characteristic). However, it is interesting to note that 203 out of the 687 patients of group 2 (29.5%) were considered as having primary dilated cardiomyopathy. There were also some significant differences regarding the clinical features: patients with a preserved systolic function compared with those with systolic dysfunction presented a better NYHA functional class and were less often hospitalized for worsening CHF during the previous year. They also presented with a higher blood pressure and a higher prevalence of obesity and of atrial fibrillation. On the other hand, a third heart sound and non-sustained ventricular tachycardia at Holter monitoring were significantly more frequent in group 1 than in the other groups. There were no significant differences between groups regarding the prevalence of comorbidities. Finally, compared to the others, group 2 patients had a significantly less dilated left ventricle as evaluated at echocardiography. Besides, severe (grade 3-4/4) mitral insufficiency was only observed in a minority of these patients (7 out of 687, 1.0% vs 317 out of 2859, 11.0% in group 1, p = 0.001).

Drug prescription. The use of medications significantly differed among the three groups of patients (Table III): there was significantly less use of ACE-inhibitors, diuretics, digoxin, nitrates, amiodarone, anti-

Table II. Clinical and echocardiographic characteristics of 5164 patients with congestive heart failure and a preserved or reduced left ventricular ejection fraction (LVEF).

Characteristics	Group 1 (n=2859)	Group 2 (n=687)	Group 3 (n=1618)	p
Age (years)§	61 ± 11	63 ± 14	63 ± 12	< 0.001
≥ 70	693 (24.2%)	235 (34.2%)	508 (31.4%)	0.001
≥ 80	85 (3.0%)	58 (8.4%)	88 (5.4%)	0.001
Female	494 (17.3%)	228 (33.2%)	374 (23.1%)	0.001
NYHA class III-IV	1018 (35.6%)	118 (17.2%)	313 (19.3%)	0.001
Hospital admission for CHF during the previous year	1824 (63.8%)	338 (49.2%)	784 (48.4%)	0.001
Primary etiology				0.001
CAD	1352 (47.3%)	212 (30.9%)	783 (48.4%)	
IDC	1252 (43.8%)	203 (29.5%)	558 (34.5%)	
Hypertension	188 (6.6%)	187 (27.2%)	229 (14.1%)	
Other	67 (2.3%)	85 (12.4%)	48 (3.0%)	
SBP > 130 mmHg	794 (27.8%)	343 (49.9%)	692 (42.8%)	0.001
Third heart sound	958 (33.5%)	102 (14.8%)	386 (23.9)	0.001
Concomitant conditions				
Diabetes	450 (15.7%)	90 (13.1%)	268 (16.6%)	NS
COPD	494 (17.3%)	124 (18.1%)	299 (18.5%)	NS
Vascular disease	448 (15.7%)	106 (15.4%)	256 (15.8%)	NS
CRF (serum creatinine ≥ 2.5 mg/dl)*	33 (2.3%)	9 (2.9%)	15 (2.1%)	NS
Obesity	883 (30.9%)	297 (43.2%)	656 (40.5%)	0.001
Atrial fibrillation	433 (15.8%)	163 (24.9%)	267 (17.2%)	0.001
VT**	279 (30.8%)	26 (22.4%)	88 (22.7%)	0.001
LVEDd (mm)§§	70 ± 17	58 ± 8	64 ± 15	< 0.001
LVESd (mm)§§	59 ± 15	41 ± 8	50 ± 14	< 0.001
MI (grade 3-4/4)***	317 (11.0%)	7 (1.0%)	74 (4.5%)	0.001

LVEDd = left ventricular end-diastolic diameter; LVESd = left ventricular end-systolic diameter; MI = mitral insufficiency; VT = ventricular tachycardia (sustained and non-sustained). Other abbreviations as in table I. * = available for 2458 patients; ** = available for 1411 patients; *** = available for 3069 patients; § = Bonferroni's t-test: group 1 ≠ group 2; group 1 ≠ group 3 (p < 0.05); §§ = Bonferroni's t-test: group 1 ≠ group 2 ≠ group 3.

Table III. Drug prescriptions.

Drugs	Group 1 (n=2859)	Group 2 (n=687)	Group 3 (n=1618)	Total (n=5164)	p
ACE-inhibitors	2531 (88.5%)	540 (78.6%)	1416 (87.5%)	4487 (86.8%)	0.001
Beta-blockers	501 (17.5%)	135 (19.7%)	331 (20.5%)	967 (18.7%)	0.043
Diuretics	2550 (89.2%)	525 (76.4%)	1313 (81.2%)	4388 (84.9%)	0.001
Digoxin	2080 (72.8%)	360 (52.4%)	985 (60.9%)	3425 (66.3%)	0.001
Nitrates	1353 (47.3%)	222 (32.3%)	709 (43.8%)	2284 (44.2%)	0.001
Calcium antagonists	215 (7.5%)	155 (22.6%)	249 (15.4%)	619 (11.9%)	0.001
Anticoagulants	879 (30.8%)	145 (21.1%)	308 (19.0%)	1332 (25.7%)	0.001
Antiplatelet agents	1071 (37.5%)	209 (30.4%)	703 (43.5%)	1983 (38.4%)	0.001
Amiodarone	702 (24.6%)	118 (17.2%)	315 (19.5%)	1135 (21.9%)	0.001
Other antiarrhythmic agents	54 (1.9%)	21 (3.1%)	37 (2.3%)	112 (2.1%)	NS

coagulant agents, and antiplatelet drugs, and more use of calcium antagonists and beta-blockers in group 2 patients compared to the other groups.

Outcomes. At the time of analysis, 2390 out of 5164 (58.8%) patients enrolled in the database had their 1-year follow-up scheduled visit. Patients who did not complete their 1-year follow-up evaluation differed from the others only in that they had a slightly lower prevalence of advanced NYHA functional classes: 443 (26.5%) of the subjects for whom the follow-up visit was not available were in NYHA functional class III and IV compared with 715 (29.9%) in the group with the 1-year scheduled visit available ($p = 0.016$).

The clinical events that occurred during follow-up are outlined in tables IV and V. During the 1 year since entry in the database, 28 (1.2%) patients underwent heart transplantation and 360 (15.2%) patients died (Table IV). Table V analyzes the hospital admissions for all causes, for cardiovascular events and for worsening heart failure. As shown in tables IV and V patients with heart failure and a preserved left ventricular systolic function (group 2) had significantly less events compared with those affected by CHF and left ventricular systolic dysfunction (group 1). At multivariate analysis the independent predictors of deaths (Table VI) were: an advanced NYHA functional class, the presence of ventricular tachycardia at Holter ECG, hospital admission for CHF during the previous year, significant left ventricular systolic dysfunction as revealed by an LVEF < 35%, atrial fibrillation, advanced age, heart rate, and a high systolic blood pressure.

Multiple logistic regression analysis (Table VII) revealed chronic renal failure (serum creatinine ≥ 2.5 mg/dl), hospital admission for CHF during the previous year, significant mitral insufficiency, an advance NYHA functional class, an ischemic etiology and the heart rate as being the factors associated with an increased risk for hospital admission during the 1-year follow-up period.

Discussion

The IN-CHF registry was initially designed with the aim of registering and following-up outpatients with CHF managed by cardiologists. The database is one of

Table IV. Clinical events among the 2390 patients of the IN-CHF database during 1 year of follow-up.

	Group 1 (n=1359)	Group 2 (n=327)	Group 3 (n=704)	Total (n=2390)	p
Heart transplantation	26 (1.9%)	1 (0.3%)	1 (0.1%)	28 (1.2%)	0.001
Death (all causes)	250 (18.8%)	29 (8.9%)	81 (11.5%)	360 (15.2%)	0.001

Table V. Hospital admissions among the 2362 patients of the IN-CHF database with an available 1-year follow-up and not submitted to heart transplantation.

Hospitalization	Group 1 (n=1333)	Group 2 (n=326)	Group 3 (n=703)	Totale (n=2362)	p
All causes	361 (27.1%)	60 (18.4%)	137 (19.5%)	558 (23.6%)	0.001
CV causes	301 (22.6%)	43 (13.2%)	105 (14.9%)	449 (19.0%)	0.001
HF destabilization	220 (16.5%)	27 (8.3%)	68 (9.7%)	315 (13.3%)	0.001

CV = cardiovascular; HF = heart failure.

Table VI. Independent predictors of all causes of death at 1 year.

Variable	OR	95% CI	p
NYHA class III-IV vs I-II	1.88	1.51-2.35	0.0001
Ventricular tachycardia (yes vs no)	1.86	1.28-2.72	0.0012
Hospital admission for CHF during the previous year (yes vs no)	1.54	1.22-1.96	0.0003
LVEF < 35% vs > 45%	1.54	1.02-2.31	0.0379
Atrial fibrillation (yes vs no)	1.35	1.04-1.75	0.0252
Age*	1.02	1.00-1.03	0.0001
Heart rate*	1.01	1.00-1.01	0.0370
Systolic blood pressure*	0.99	0.98-0.99	0.0001
Ischemic etiology (yes vs no)	1.23	0.98-1.54	0.0658
Relevant mitral regurgitation (yes vs no)	1.32	0.93-1.86	0.1119
Third sound (present vs absent)	1.17	0.93-1.47	0.1585
Creatinine ≥ 2.5 mg/dl (yes vs no)	1.26	0.55-2.88	0.5702
Sex (M vs F)	1.06	0.82-1.39	0.6239

CHF = congestive heart failure; CI = confidence interval; LVEF = left ventricular ejection fraction; OR = odds ratio. * = continuous variables.

Table VII. Independent predictors of all causes of hospital admission at 1 year.

Variable	OR	95% CI	p
Creatinine ≥ 2.5 vs < 2.5 mg/dl	2.43	1.08-5.48	0.0319
Hospital admission for CHF during the previous year (yes vs no)	1.58	1.27-1.95	0.0001
Relevant mitral regurgitation (3-4/4) (yes vs no)	1.57	1.09-2.24	0.0139
NYHA class III-IV vs I-II	1.46	1.17-1.83	0.0008
Ischemic etiology (yes vs no)	1.44	1.16-1.79	0.0009
Heart rate*	1.01	1.00-1.02	0.0014
Systolic blood pressure*	0.99	0.98-1.00	0.0535
Age*	1.00	0.99-1.01	0.1913
Sex (M vs F)	0.870	0.67-1.12	0.2921
LVEF < 35% vs > 45%	1.17	0.84-1.64	0.3423
Third sound (present vs absent)	1.56	1.09-2.23	0.4681
Atrial fibrillation (yes vs no)	1.02	0.77-1.33	0.8875
Ventricular tachycardia (yes vs no)	0.98	0.67-1.43	0.9289

Abbreviations as in table VI. * = continuous variables.

the largest multicenter cohorts of outpatients presenting with CHF and adequately represents the cardiologist's way of evaluating and treating this disease in Italy. However, there is growing evidence[22-27] that, in Italy as well as in many other western countries, the process of caring for CHF patients actively involves several healthcare figures other than cardiologists. In fact, internists, general practitioners and specialized nurses also give a helping hand. As a consequence, only a relatively small proportion of the whole CHF population, ranging in different studies from 3 to 23%, is under the direct management of cardiologists. CHF patients followed by cardiologists are generally younger, more often males, with few comorbidities and more frequently present with coronary artery disease than CHF patients observed in other clinical settings[22,25-27]. Accordingly, the mean age of the patients enrolled in our registry was 62 years, with only < 5% of the population > 80 years of age. Besides, there was a striking prevalence of the male gender (78.8%). These features are not to be underestimated when dealing with the epidemiology of CHF with a preserved systolic function, since its prevalence has been shown to be higher in the elderly and in the female sex. Therefore, the lower mean age of our patients and the lower prevalence of the female gender, compared to what observed for CHF populations in community studies[15-20], may explain the low prevalence of subjects presenting with CHF and a preserved systolic function in our database (13.3%). This prevalence is similar to those reported in other studies conducted by cardiologists (13% in the V-HeFT Trial[9] and 22% in the CHF outpatients series of the Heart Function Clinic at the University of Alberta Hospital[11]). The observation that patients with CHF and a preserved systolic function represent only a minority of CHF patients cared for by cardiologists, recently also confirmed in a national survey of heart failure in French hospitals[25], may in our opinion have relevant implications, specially when planning resource utilization in heart failure management programs.

Just as for other series of patients[9,11,17-20], even in our study CHF patients with a preserved left ventricu-

lar systolic function, compared to those with an impaired left ventricular systolic function, are significantly older, with a predominance of the female sex, a higher prevalence of a history of hypertension, and a lower prevalence of coronary artery disease. Some other clinical parameters, such as a high arterial pressure, obesity and atrial fibrillation at the time of enrollment into the database, were significantly more frequent in patients with CHF and a preserved systolic function. Conversely, the indexes of severity of CHF, such as a NYHA functional class III or IV or a third heart sound were more common in patients with left ventricular systolic dysfunction.

As expected, at echocardiographic Doppler examination CHF patients with a preserved systolic function presented left ventricular cavity dimensions which were significantly smaller, and severe (grade 3-4/4) functional mitral regurgitation was very unusual. From our registry we were unable to obtain data on the Doppler profiles of the transmitral and pulmonary venous flows. For this reason, we have no information regarding the presence and extent of diastolic function abnormalities. Although it may be hypothesized that several patients with a preserved left ventricular systolic function included in this database actually had isolated or predominant diastolic dysfunction as the pathophysiologic mechanism of CHF, it is our opinion that, at least in this study, the term "heart failure with a preserved systolic function" cannot be considered equivalent to the term "diastolic heart failure". In fact, the diagnosis of CHF secondary to diastolic dysfunction requires not only the presence of clinical signs and symptoms of heart failure associated with a normal left ventricular systolic function, but also the use of a proper evaluation protocol for the diastolic function[28-30], in order to identify the specific abnormalities which may be responsible for the clinical picture and hence necessitate appropriate treatment. Recently, Aurigemma et al.[31] showed that in the Cardiovascular Health Study among the 170 out of 2671 patients developing (and being hospitalized for) CHF during a follow-up of 5.2 years (corresponding to an incidence of 6.4%), more than one half showed a normal or borderline LVEF, with the simultaneous occurrence of abnormalities of the transmitral blood flow (expressed as the E/A ratio) at Doppler echocardiography, indicating diastolic dysfunction as being probably responsible for the onset of symptoms.

It is noteworthy that the analysis of the primary etiology of CHF in our database showed that 203 out of 687 CHF patients (29.5%) with a normal or preserved systolic function (LVEF > 45%) had a diagnosis of dilated cardiomyopathy, a clinical condition usually characterized by a primary impairment of the left ventricular systolic function, often with concomitant diastolic dysfunction. Several hypotheses can be proposed to explain the finding of a normal LVEF in patients with this diagnosis. These include severe systemic hypertension, unrecognized myocardial ischemia, the healing phase of acute myocarditis, the reverse remodeling of the left ventricle due to aggressive pharmacological treatment[32-40], etc., all these events eventually occurring, singly or in association, during the time interval between the first diagnosis and enrollment in the registry. Thus, in a recent report a significant number of patients who had a normal ejection fraction months to years following a CHF episode had a reduced ejection fraction during the CHF episode[41]. However, this phenomenon further emphasizes the need for an accurate diagnostic approach to the patient with suspected heart failure.

In patients with CHF and a preserved systolic function ACE-inhibitors were utilized in 78.6%, a proportion comparable with the 71% reported by McAlister et al.[11] in a specialized heart failure clinic. It was higher than the 63% found by Cohen-Solal et al.[25] in French hospitals where the attending physicians of patients with CHF with a preserved systolic function were mainly general practitioners and not cardiologists. It also differs from the reported rates in some US series: 31% of ACE-inhibitor prescription reported by Senni et al.[20] in patients with a first-time diagnosis of CHF assessed in the Olmsted County community, 50% reported by Dauterman et al.[42] in the California Medicare Hospitals, and 55% referred by Philbin et al.[24] in the MISCHF study performed in New York. We believe that these wide variations in the prescription rates reported in the different studies are the result of many factors such as the attitude and confidence of the attending physicians in using ACE-inhibitors for the management of CHF, the temporal trend and the implementation of therapeutic regimens including ACE-inhibitors for the care of CHF and different health policies in different nations.

However, even in our series the prescribing pattern of medications significantly differed among the various groups of CHF patients. In accordance with other studies[11,20,25], the prescription rate of ACE-inhibitors in patients with a preserved systolic function (78.6%) was significantly lower compared to that found in patients with an LVEF < 35% (88.5%). This is probably a consequence of our incomplete knowledge which, in turn, is due both to the absence in the literature of randomized clinical trials evaluating the use of these drugs in such patients and to the conflicting results of some of the available non-randomized studies[42,43].

In this large outpatients series presenting with CHF, the 1-year prognosis was better in CHF patients with a preserved left ventricular systolic function compared to that of patients in whom heart failure was associated with left ventricular systolic dysfunction. The annual mortality rate in patients with an LVEF > 45% was 8.9%, about half that of CHF patients with an LVEF < 35%. Indeed, at multivariate analysis this latter group of patients presented an odds ratio of 1.54, confirming the results reported in the Framingham CHF outpatient's cohort[15] and in studies by other authors[9,10]. These studies, which report a better prognosis for patients with

CHF and a preserved systolic function, included patients with a mean age < 65 years. Therefore, the natural history of heart failure with a preserved systolic function in younger individuals may be different to that observed in the elderly, although even in this group of patients, as in the old patients included in our series of outpatients with CHF and an LVEF > 45%, a good global functional status as expressed by a better NYHA functional class and few comorbidities associated with a preserved systolic function, are predictive of a more favorable prognosis[44-46]. In other hospital-based and community investigations[11,12,16,18-20] the mortality for CHF with a normal systolic function was similar to that reported for CHF with systolic dysfunction, probably because they included older and sicker patients. Furthermore, although at univariate analysis CHF patients with a preserved LVEF were less likely to be hospitalized, multivariate analysis did not support this datum, confirming that the morbidity of CHF patients with a preserved systolic function was not so different from that of CHF patients with systolic dysfunction.

Study limitations. The limitations of this study should be taken into account when evaluating the potential clinical implications of the results here reported. This is not an epidemiological study. Rather, it should be considered as a large nationwide database that analyzes CHF outpatients evaluated and managed by cardiologists in specific ambulatory structures at the turn of the millennium; therefore, the prevalence of CHF patients with a preserved left ventricular systolic function we reported does not at all reflect the true prevalence of this syndrome in the community. Besides a selection bias, another factor potentially contributing to the relatively benign prognosis of our CHF patients with a preserved systolic function could be the larger use by cardiologists of ACE-inhibitors[42] and other drugs usually recommended in clinical guidelines, compared to the therapeutic regimens recommended by other physicians. Finally, no specific diagnostic criteria for diastolic heart failure have been adopted in this registry, making an analysis of this specific disease (in terms of its pathophysiology and of the appropriate therapy) very difficult.

We have excluded from the study patients with etiologically relevant valvular disease; moreover, the information about the presence and the degree of mitral insufficiency was available for only 3069 out of 5164 CHF outpatients, most of them in clinically stable conditions and with an optimal unloading therapy. For these reasons, in this study the data regarding mitral regurgitation should be interpreted with caution. Nevertheless, severe mitral regurgitation was very rare in the group of patients with a preserved systolic function. Therefore, it is reasonable to expect the situation in which the LVEF may not provide an accurate indication of the severity of the systolic dysfunction as a consequence of relevant mitral insufficiency which was very uncommon in this group of patients[47,48].

Despite these limitations, this study on a large nationwide multicenter registry confirms that CHF with a preserved left ventricular systolic function is a serious and not uncommon clinical problem for the cardiologists involved in the management of outpatients with CHF. This clinical condition still leaves many unanswered questions about the proper diagnostic and therapeutic approaches to CHF with a preserved left ventricular systolic function and to diastolic heart failure. These conditions urgently require answers obtainable by means of appropriate trials[49,50].

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Appendix

Participating Centers and Investigators

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