Improving practice patterns in heart failure through a national cardiological network: the case of ACE-inhibitors

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Key words:
ACE-inhibitors; Chronic heart failure.

Background. **Despite the well-established benefits of ACE-inhibitors in chronic heart failure (CHF), current treatment rates and prescribed doses are lower than those proven to improve survival. We evaluated whether participation in a specialist network and the use of a common database would impact on the compliance with CHF guidelines.**

Methods. **We analyzed the rate and determinants of ACE-inhibitor use and prescribed doses among 8102 patients with CHF enrolled at 133 cardiology centers participating in a national network.**

Results. **6625 patients (82%) took ACE-inhibitors, most commonly enalapril (41%, mean dose 16 ± 9 mg), captopril (25%, mean dose 74 ± 44 mg) and lisinopril (14%, mean dose 13 ± 8 mg). The predictors of the non-prescription of ACE-inhibitors were: female gender (odds ratio-OR 1.46, 95% confidence interval-CI 1.28-1.67), older age (OR 1.01, 95% CI 1.01-1.02), valvular etiology (OR 1.87, 95% CI 1.60-2.20), NYHA class III-IV (OR 1.25, 95% CI 1.09-1.42) and creatinine levels > 2.5 mg/dl (OR 5.19, 95% CI 3.36-8.02). Conversely a left ventricular ejection fraction < 30% (OR 0.78, 95% CI 0.65-0.94) and a hypertensive (OR 0.69, 95% CI 0.55-0.86) or idiopathic (OR 0.67, 95% CI 0.57-0.78) etiology increased the rate of ACE-inhibitor prescription. Low ACE-inhibitor doses were prescribed to 26.4% of cases.**

Conclusions. **The IN-CHF database, an educational and organizational effort led by a national cardiology society, demonstrates that high rates of ACE-inhibitor treatment may be achieved in routine clinical practice in a cardiology setting.**

(Ital Heart J 2002; 3 (12): 730-737)

This study was supported in part by Merck Sharp & Dohme Italy.

Received June 11, 2002; revision received October 14, 2002; accepted October 15, 2002.

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Introduction

In patients with left ventricular dysfunction and/or chronic heart failure (CHF) ACE-inhibitors modulate neurohormonal activation, improve hemodynamic alterations and prevent ventricular remodeling[1-3]. In asymptomatic patients ACE-inhibitors decrease the occurrence of overt heart failure and the rate of hospitalization[4]; moreover, they significantly increase survival in symptomatic patients, even late in the course of the disease[5-9]. Persistent advantages in terms of mortality have been shown after 3-5 years of treatment[10,11]. ACE-inhibitor treatment is cost-effective[12,13]. For all these reasons, treatment with ACE-inhibitors is strongly recommended in all patients with heart failure and left ventricular systolic dysfunction[14,15]. ACE-inhibitors are well tolerated[1-9]: the rate of significant adverse events is generally low and the need for discontinuation of long-term treatment is no higher than 20%. However, despite the awareness of their clinical benefits, ACE-inhibitors are generally under-used or under-dosed in clinical practice in different settings[16-25].

The Italian Network on Congestive Heart Failure (IN-CHF) is a voluntary collaborative effort that was started by the Italian Association of Hospital Cardiologists (ANMCO). Its aims are to increase the quality of cardiological care in our country through educational programs and to collect epidemiological and clinical data regarding large populations of outpatients with CHF[26]. The operative tool of the IN-CHF is a specific software for the computer-assisted management of the follow-up of CHF patients. The use of the software during outpatient visits is designed to increase the clinical awareness of appropriate diagnostic tests and treatment strategies ac-

cording to guideline indications. In this study, we analyzed whether the IN-CHF cooperative effort resulted in compliance to the treatment guidelines that identify ACE-inhibitors as the cornerstone of therapy for all stages of CHF, and assessed the predictors for ACE-inhibitor under-use or under-dosing.

Methods

All centers of the ANMCO were invited to participate in the IN-CHF project and collect data on their heart failure patients; 133 centers (see Appendix), well distributed over the whole country, accepted the invitation. IN-CHF participating centers may be considered representative of the pool of national cardiology hospital centers (n = 850). Tertiary referral facilities, such as catheterization laboratories or cardiac surgery units, are similarly distributed, although a higher proportion of IN-CHF centers have a coronary care unit than non-participating centers (76 vs 56%, p = 0.0002).

Patients with CHF diagnosed by clinical cardiologists according to the criteria set by the guidelines of the European Society of Cardiology[27] were enrolled into the database. The specific software programmed by the ANMCO Research Center was designed to obtain information on the demographic data, etiology and clinical history of the enrolled population. Cardiologists collecting data at each hospital participating in the IN-CHF project were initially trained to use the software at the ANMCO Research Center. At baseline and at each scheduled control, data on symptoms, physical examination, and any performed laboratory tests (biohumoral parameters, ECG, chest X-ray, echocardiography, stress test, right and left heart catheterization, nuclear cardiology) were collected. Medical and surgical treatments, cardiovascular or non-cardiovascular events and hospital admissions were also reported in the database. In particular, pharmacological treatment at the first visit and the eventual changes in drug or dosage prescription were monitored over time. Patients were locally managed according to the clinical judgment of the attending specialists, on the basis of the indications of accepted international and national guidelines implemented in previous educational campaigns of the ANMCO. Since 1997, for the diagnostic and therapeutic aspects, the ANMCO suggested that the guidelines of the European Society of Cardiology[14,27] be followed. The use of ACE-inhibitor doses tailored on the evidence of the main clinical trials[3-9] was strongly encouraged in patients with heart failure and/or documented systolic dysfunction, even in the asymptomatic stages. Diuretics and digoxin were also suggested in symptomatic patients. The decisions regarding the use of nitrates, beta-blockers, amiodarone, antiplatelet agents and anticoagulants and the indications to interventional or surgical procedures were left to the attending cardiologist at each center. Starting from 1997, educational campaigns have also been set up to improve the rate of the use of recommended treatment in clinical practice[16].

Statistical analysis. Data were prospectively collected in all the participating centers and were periodically sent to the ANMCO Research Center by the Internet or by floppy disks for statistical analysis. Continuous data were expressed as mean values ± 1 SD and were compared using the Student's t test. Categorical values were compared using the χ^2 test. The clinical characteristics associated with the prescription of ACE-inhibitors and to under-dosing were tested by means of multivariate logistic regression analysis. Results were expressed as the odds ratios and the relative 95% confidence intervals. When data were not available for all patients, the variable was dichotomized and patients with missing values were evaluated as a separate group.

Results

From April 1995 to January 1999, the ANMCO Research Center collected data concerning the enrolment visit of 8102 outpatients followed by the 133 IN-CHF centers. The baseline clinical and laboratory characteristics of the study sample are shown in table I. The large majority of patients were male (74%, mean age 63 ± 12 years) and about one third were aged ≥ 70 years. The primary underlying etiologies were coronary artery disease in 40% and dilated cardiomyopathy in 32% of patients; the diagnosis of idiopathic dilated cardiomyopathy had been confirmed by coronary angiography in 11% of the patients.

At the baseline visit, 70% of the patients were in NYHA functional class I-II and the remaining 30% in class III-IV. A quantitative estimate of the left ventricular function as determined at echocardiography was available for 4703 patients (58%). Mean left ventricular ejection fraction (LVEF) was 34 ± 12%. A significant reduction in ventricular function (LVEF ≤ 40%) was found in 75% of this group; nearly one fourth of cases had clinical heart failure with a preserved left ventricular systolic function (LVEF > 40%). Mean heart rate was 78 ± 16 b/min.

High-risk clinical characteristics that might contraindicate ACE-inhibitor treatment were rare in this series. Mean systolic blood pressure was 130 ± 21 mmHg. Significant hypotension (systolic blood pressure < 100 mmHg) was observed in 3.6% of cases. Renal dysfunction (serum creatinine level > 2.5 mg/dl) was found in less than 3% of the 3390 patients in whom the creatinine serum level had been determined.

The pharmacological treatment prescribed after the enrolment visit is shown in table II. ACE-inhibitors were prescribed in 82% of the whole population. The prescription rate was 87% for patients with documented systolic

Table I. Clinical and laboratory findings of the study population.

	No. patients
Female gender	2110 (26.0%)
Etiology	
Ischemic	3271 (40.4%)
Dilated	2580 (31.8%)
Hypertensive	888 (11.0%)
Valvular	950 (11.7%)
Other	413 (5.1%)
NYHA class III-IV	2439 (30.1%)
Age ≥ 70 years	2658 (32.8%)
Third heart sound	2083 (25.7%)
Heart rate ≥ 100 b/min	867 (10.7%)
Systolic blood pressure (mmHg)	
< 100	292 (3.6%)
100-130	4579 (56.5%)
> 130	3231 (39.9%)
Atrial fibrillation/atrial flutter*	1667 (21.7%)
LVEF (%)**	
> 40	1169 (24.9%)
30-40	1891 (40.2%)
< 30	1643 (34.9%)
Cardiothoracic ratio > 0.55§	636 (59.0%)
Ventricular tachycardia§§	485 (28.3%)
≥ 1 hospital admissions for HF in the previous year	4608 (56.9%)
Creatinine levels > 2.5 mg/dl§§§	95 (2.8%)

HF = heart failure; LVEF = left ventricular ejection fraction. * = available in 95%; ** = available in 58%; § = available in 13%; §§ = available in 21%; §§§ = available in 42%.

Table II. Pharmacological treatment at the baseline visit in the IN-CHF database.

Treatment	No. patients
ACE-inhibitors	6625 (81.8%)
Angiotensin receptor blockers	229 (3.7%)*
Digitalis	5354 (66.1%)
Diuretics	6850 (84.5%)
Beta-blockers	1319 (16.3%)
Amiodarone	1634 (20.2%)
Oral anticoagulants	2211 (27.3%)
Nitrates	3308 (40.8%)
Calcium-channel blockers	1001 (12.4%)
Antiarrhythmic agents	191 (2.4%)
Antiplatelet agents	2847 (35.1%)

* = calculated on the basis of the number of patients enrolled since these agents became available in Italy.

dysfunction (n = 3534, LVEF ≤ 40%) and 75.5% when the systolic function was preserved (n = 1169, LVEF > 40%). Angiotensin II receptor antagonists were prescribed alternatively to ACE-inhibitors in 229 patients out of the 6158 who were enrolled from 1996 when these agents became available in our country (3.4%) and together with ACE-inhibitors in 19. Concomitant therapy mostly included diuretics (85%) and digitalis (66%). Beta-blockers and calcium-channel blockers were prescribed to 16 and 12% of patients respectively.

The rate of prescription of the different ACE-inhibitors and the mean dosages are shown in table III. Overall, the target doses of controlled clinical trials (i.e. 150 mg of captopril, 20 mg of enalapril, 20 mg of lisinopril, 20 mg of fosinopril, 20 mg of quinapril, and 10 mg of ramipril) were prescribed to 39.5% of patients. Low ACE-inhibitor doses, defined as a dose no higher than the recommended starting dose of the prescribing information sheet (< 10 mg for enalapril, lisinopril and quinapril, ≤ 10 mg for fosinopril, ≤ 50 mg for captopril, and < 2.5 mg for ramipril), were prescribed in 26.4% of cases. When compared to patients treated with other ACE-inhibitors, those who received captopril were more frequently males (p = 0.001) and ischemic (p = 0.001) and had a more severely depressed LVEF (p = 0.01) and a more advanced NYHA class (p = 0.001).

When the population was stratified by year of enrolment into the registry, the rate of ACE-inhibitor prescription remained stable over time; all the same, the number of patients treated with the target ACE-inhibitor doses significantly increased from 1995 (33%) to 1999 (48%) (p < 0.05, Fig. 1).

The predictors of either no ACE-inhibitor treatment or treatment with low doses partially overlapped. At multivariate analysis, ACE-inhibitor treatment was less frequently used in women, older patients, those with a preserved systolic function or a valvular etiology, NYHA class III-IV and renal dysfunction (Table IV). Low ACE-inhibitor doses (Table V) were more fre-

Table III. Type and dosage of ACE-inhibitors prescribed at the baseline visit in the IN-CHF database.

ACE-inhibitor	% dose available	No. patients	Mean dose (mg)	Median (mg)	Range (mg)	% on target doses	% on low doses
Enalapril	76	2723 (41.1%)	16 ± 9	20	2.5-60	51.5	19.4
Captopril	71	1645 (24.8%)	74 ± 44	75	6.25-300	16.1	41.7
Lisinopril	80	948 (14.3%)	13 ± 8	10	1.25-40	42.2	31.3
Ramipril	76	581 (8.8%)	4 ± 2	5	1.25- 25	6.7	10.1
Quinapril	74	319 (4.8%)	15 ± 9	10	2.5-60	45.3	24.4
Fosinopril	72	274 (4.1%)	18 ± 7	20	5-40	73.1	26.4
Other*		135 (2.0%)					

* = benazepril, cilazapril, delapril, moexil, perindopril, trandolapril.

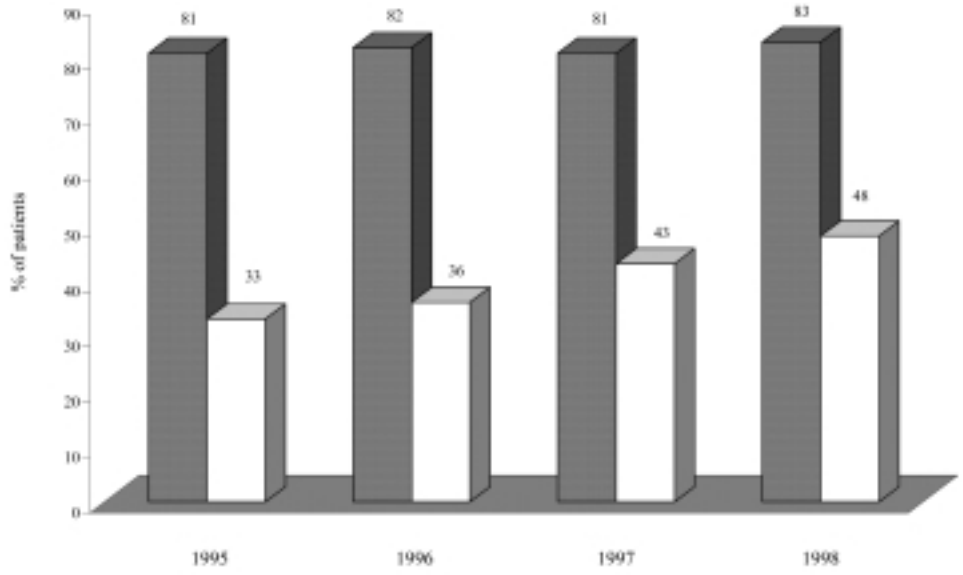

Figure 1. *Rate of ACE-inhibitor prescription* (black bars) *and proportion of patients treated with appropriate doses* (white bars) *by year of enrolment into the IN-CHF database.*

Table IV. Independent predictors of ACE-inhibitor non-prescription.

	OR	95% CI
Age (continuous)	1.01	1.01-1.02
Creatinine > 2.5 vs ≤ 2.5 mg/dl	5.19	3.36-8.02
Female vs male gender	1.46	1.28-1.67
NYHA class III-IV vs I-II	1.25	1.09-1.42
LVEF < 30 vs ≥ 30%	0.78	0.65-0.94
Etiology		
Hypertensive vs ischemic	0.69	0.55-0.86
Dilated cardiomyopathy vs ischemic	0.67	0.57-0.78
Other etiology vs ischemic	1.87	1.60-2.20

CI = confidence interval; LVEF = left ventricular ejection fraction; OR = odds ratio.

Table V. Independent predictors of a low dosage of ACE-inhibitors.

	OR	95% CI
Age (continuous)	1.02	1.01-1.02
Female vs male gender	1.20	1.02-1.41
Systolic blood pressure (continuous)	0.98	0.97-0.98
Diuretics yes vs no	0.59	0.49-0.72
Etiology		
Hypertensive vs ischemic	0.59	0.45-0.78
Other etiology vs ischemic	1.35	1.10-1.66

Abbreviations as in table IV.

quently prescribed to women, to older patients and to those with a valvular etiology; conversely a hypertensive etiology, a higher systolic blood pressure and the use of diuretics reduced the chances of receiving low ACE-inhibitor doses.

Discussion

The impressive results from controlled clinical trials make ACE-inhibitor treatment mandatory in all patients with heart failure and left ventricular systolic dysfunction, since these drugs significantly reduce the overall and cardiovascular mortality and the number of hospital admissions, even in the long term[1-11]. ACE-inhibitor treatment has been enforced by international and national guidelines[14]. Therefore, the documented variations in treatment rates are of concern. The IN-CHF database, the result of an educational and organizational effort led by a national cardiology society, demonstrates that high rates of ACE-inhibitor treatment may be achieved in routine clinical practice in a cardiology setting, although suboptimal dosing still leaves room for improvement.

ACE-inhibitor prescription in chronic heart failure. Despite the wealth of evidence, in routine clinical practice ACE-inhibitor use among patients with CHF remains below the 80-90% rates of drug tolerance documented in randomized clinical trials. Wide variations are observed depending on the treatment setting (general practice, cardiology or CHF specialists), on the case-mix and on the objective documentation of systolic dysfunction[17-26,28-33]. Even in cardiology settings, despite a tendency to a wider prescription in the last years[24,25,28], the prevalence of treated patients was still consistently low in the populations observed in 1995. It ranged from 55%[22] to 73% among patients with documented systolic dysfunction[25], to 90% in the same patient type when attended by CHF specialists[28]. Many patients who were not receiving ACE-inhibitors did not show any apparent contraindication or a history of intolerance, suggesting

that the "perceived" contraindication was the most common reason for not treating patients[29]. In the SPICE Registry[30], with an ACE-inhibitor prescription rate of 80%, the most common reason for non-use was intolerance (9%); in 5% of cases, however, no reason was given.

The IN-CHF database is one of the largest, prospective and most recent sources of data on CHF patients treated by cardiologists. The results obtained from this large outpatient sample uniformly distributed throughout the whole country clearly indicate that even in an unselected population ACE-inhibitors can be used as widely as shown in randomized trials. At the enrolment visit, 82% of patients were treated with ACE-inhibitors and over 4 years this rate of prescription did not change. Direct information on the reasons for the lack of prescription in the remaining 18% of the enrolled population was not listed in the database; however, the percentage of untreated patients overlaps with that of the main studies[3-7], suggesting a similar incidence of adverse events.

Although there is a general consensus in the literature on the attribution of ACE-inhibitor benefits to a class effect rather than to a single agent, this registry documents a larger use of the drugs tested in the major clinical trials[4-6,8]. The use of captopril in patients with advanced disease appears to be consistent with guideline recommendations[14].

Predictors of ACE-inhibitor non-prescription. The determinants of ACE-inhibitor under-prescription have been previously analyzed in the literature[25,28-32]. ACE-inhibitor under-use in clinical practice may be partially explained by the prevalence of renal impairment and of "diastolic" heart failure in the community[23,28,33].

Our study confirms most of the previous findings. A valvular etiology, NYHA class III-IV, renal dysfunction, an older age and the female gender were independently associated with a less frequent ACE-inhibitor treatment; idiopathic dilated cardiomyopathy or a hypertensive etiology and a lower LVEF reduced the risk of non-prescription.

An etiology other than ischemic, hypertensive or idiopathic is under-represented in clinical trials and this could negatively influence the prescription rate of ACE-inhibitors; moreover, cardiologists who are familiar with the post-infarction trials[3,7,8] may be more willing to use ACE-inhibitors in ischemic rather than in non-ischemic patients. Patients with a hypertensive etiology had higher blood pressure values and were probably considered as being at a reduced risk of ACE-inhibitor induced hypotension. The treatment of heart failure with a preserved systolic function is not as clearly standardized as that of heart failure associated with systolic dysfunction; in accordance with this observation, ACE-inhibitor use was higher in patients with a more severe systolic dysfunction, many of whom had dilated cardiomyopathy. Patients with severe symptoms (NYHA class III-IV) are known to have a higher likelihood of intolerance to ACE-inhibitors and present higher rates of untoward effects[9,34].

Older age is frequently characterized by under-use or under-dosing[25,30,35], even though elderly patients who are not treated with ACE-inhibitors are more likely to experience a clinical event[35,36]. Female patients with CHF are frequently older than males. Valid concerns regarding the development of hypotension and renal dysfunction in the elderly or simply the reluctance to prescribe or to complete dose titration in elderly patients may be the reasons for non-compliance with recommended guidelines.

In summary, in the literature as well as in the present series, the reasons for ACE-inhibitor under-use include a composite of a perceived high risk of adverse events and a lack of definite evidence of benefits for certain categories of patients. In some instances, however, non-prescription might be caused by an unjustified bias. In the IN-CHF database the non-prescription rate among "ideal" patients, i.e. the subset with proven systolic dysfunction, in NYHA class I to III and without hypotension or renal failure, was 12.7%.

Suboptimal dosing. In the main clinical trials with enalapril, the favorable results were obtained with a target daily dose of 20 mg[4,6] while the mean final dosages ranged from 12.7 to 16.7 mg; about 50% of patients tolerated the dosage of 20 mg well. In the CONSENSUS trial, the final achieved mean dose in severe CHF was 18.4 mg[9]. Other randomized trials had as target daily dosages 150 mg of captopril[8], 10 mg of ramipril[7] and 4 mg of trandolapril[3] respectively. Experimental[37] and clinical[38] observations reinforced the hypothesis that high-dose ACE-inhibition may be more beneficial than low-dose inhibition. However, a recent trial[39] found no significant differences between the clinical and hemodynamic variables of patients receiving standard (mean dose achieved 17.9 ± 4.3 mg) and those of patients receiving high (mean dose achieved 42 ± 19.3 mg) doses of enalapril. The recommendation to prescribe ACE-inhibitors to CHF patients on the basis of the target doses used in the placebo-controlled trials still sounds sensible.

The mean dosages of enalapril (16 ± 9 mg) and lisinopril (13 ± 8 mg) prescribed by the cardiologists participating in the IN-CHF are close to those suggested in the major trials. Although a substantial proportion of patients (26.4%) still took low doses of ACE-inhibitors, a trend towards an improvement was observed in the last years of enrolment (Fig. 1). The proportion of patients on low doses was higher for captopril (41.7%). In the SAVE trial[8], that enrolled patients on the basis of the post-infarction ventricular dysfunction, 79% of patients achieved the 150 mg target dose of captopril; conversely, in the IN-CHF population, captopril was more frequently prescribed to sicker patients, and this might explain the wide dosage gap.

In the literature, the titration to target doses appears to be dependent on specialist care[24,28], older age[36], sever-

ity of CHF and renal impairment[32]. The determinants of low-dose prescription in the IN-CHF database partially overlapped with the predictors of non-prescription, i.e. perceived high risk due to older age or hypotension, or the supposed lack of definite evidence as in the case of a valvular etiology. Surprisingly, the use of diuretics, an established factor for ACE-inhibitor-induced hypotension related to sodium and volume depletion, reduced the risk of low-dose prescription. A possible explanation for this finding is the higher rate of diuretic treatment in patients with more severe systolic dysfunction (91% for a LVEF < 30% vs 80% in patients with a LVEF > 40%, $p < 0.01$). In these patients the benefits of dose up-titration are probably perceived to be greater.

Study limitations. Although enrolment in the IN-CHF database was based on the diagnostic criteria of the European Society of Cardiology, objective documentation of ventricular dysfunction had not been obtained for all patients; thus, in a substantial proportion of cases the diagnosis of heart failure was made on clinical grounds alone.

The IN-CHF database is the result of a cooperative effort among national cardiology departments and well represents the heart failure population cared for in cardiology settings. On average, patients were relatively young, prevalently male and most of them had ischemic heart disease. Because of this inherent selection bias, caution should be employed when extrapolating these results to the whole Italian CHF population, since general practitioners or internists currently manage a large proportion of CHF patients.

In this series, ACE-inhibitor dosing at the baseline visit still appears to be suboptimal in a relatively high proportion of cases. Differences in the rate of target dose prescription seem to be mainly related to dosing indications from the prescribing information sheet of single agents, with the exception of captopril which is administered, in accordance with guideline recommendations, at lower doses to sicker patients.

Although most of the database population was stable and had long-standing CHF, further titration might have occurred during an individual patient's follow-up. This issue, along with the prognostic impact of the larger use of ACE-inhibitors in our country, should be investigated in the future.

In conclusion, the IN-CHF database depicts the real world of CHF outpatients followed by cardiologists in Italy and shows a satisfactory rate of ACE-inhibitor prescription with relatively appropriate dosages. The improvements in the therapeutic approach to CHF are the result of a policy based on the creation of a collaborative environment, a tradition of Italian hospital cardiology[40], educational programs and periodical monitoring.

The preliminary indications from the IN-CHF database suggest that this strategy points in the right direction and that the comprehensive care of CHF patients may be optimized towards the goals of an improved prognosis and cost containment. Further educational programs on CHF, involving cardiologists, general practitioners and internists and planned in collaboration with the respective medical associations, are now underway and will probably increase the adherence to guideline recommendations in terms of prescription rates and appropriate dosing of ACE-inhibitors.

Appendix

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