Original articles

Patients with chronic heart failure encountered in daily clinical practice are different from the "typical" patient enrolled in therapeutic trials

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Key words:
Heart failure; Patients; Trials.

Background. **The aim of this study was to compare the clinical characteristics of patients enrolled in randomized clinical trials on congestive heart failure treatment with those of real-world patients encountered in daily clinical practice.**

Methods. **We searched the Cochrane review methodology, Medline and SilverPlatter databases to obtain the clinical characteristics of both patients enrolled in therapeutic clinical trials and real-world patients with heart failure. We selected 27 clinical trials, and 8 prospective epidemiological studies or registries published between 1987 and 2001 which enrolled 53 859 and 18 207 patients, respectively.**

Results. **On average, compared to real-world heart failure patients, patients enrolled in clinical trials were younger (63 ± 10 vs 75 ± 11 years respectively, p < 0.0001), and more likely to be male (72 vs 54% respectively, p < 0.0001). Clinical trial patients showed a lower ejection fraction (26 ± 7 vs 38 ± 15% respectively, p < 0.0001) but a lower prevalence of NYHA functional class III-IV (62 vs 75% respectively, p < 0.0001) than real-world patients. In clinical trial patients, the prevalence of ischemic heart disease (67 vs 42% respectively, p < 0.0001) and a history of previous myocardial infarction (62 vs 42% respectively, p < 0.0001) were higher than in real-world patients. Conversely, the prevalence of chronic atrial fibrillation (12 vs 31% respectively, p < 0.0001) and of diabetes (22 vs 24% respectively, p < 0.02) was lower in trial patients than in real-world patients.**

Conclusions. **Our data suggest that most clinical trials on congestive heart failure, on which the guidelines for clinical practice are based, have generally included patients who are not representative of the whole spectrum of patients actually managed in clinical practice.**

(Ital Heart J 2003; 4 (2): 84-91)

Received July 16, 2002; revision received January 7, 2003; accepted January 14, 2003.

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Introduction

In the last decades, heart failure has been the only common heart disease the prevalence of which increased in developed countries, particularly in the elderly[1]. Nowadays, it represents a major public health problem associated with a markedly diminished survival[2,3], which imposes a significant burden to patients, healthcare providers and society[4,5].

The last 13 years have seen the generation of a substantial body of evidence from randomized controlled trials on chronic heart failure indicating not only which treatments are effective in relieving symptoms but also which ones reduce morbidity and mortality, such as ACE-inhibitors[6], beta-blockers[7] and spironolactone[8]. However, as several reports point out, the relationship between evidence from randomized controlled trials and the rates of use of different drugs is weak[9-12]. In addition, the rates of different therapies vary substantially by country even for apparently similar patients[9,13,14].

Several factors may contribute to the current underuse of treatment recommendations. In some cases physicians may not be aware of them. However, those physicians who are aware of guidelines may not follow them in practice for a number of legitimate reasons: 1) concern about the safety of drugs and of dosages employed in clinical trials[15]; 2) disagreement with guidelines that are based on opinions combined with scientific evidence; 3) in contrast to conditions such as hypertension, the therapeutic goal in heart failure may be imprecise, and many physicians may consider

symptomatic improvement as the sole aim of treatment and disregard potential mortality benefits; 4) barriers related to the organization of health care and economic issues[16]; 5) objective difficulty in extrapolating clinical trial data to the individual complex patients[17].

To explore in more detail this last reason, we compared the clinical characteristics of patients with chronic heart failure enrolled in clinical trials on the results of which specific guidelines were developed with those of patients with heart failure seen in clinical practice in the real world. Our results may be important to help to plan clinical trials aimed at testing the effectiveness in the clinical arena of treatments which have been proven to be efficacious in clinical trials.

Methods

The Cochrane review methodology (www.update.software.com), Medline literature (www.ncbi.nih.gov/entrez/query.fcgi), and SilverPlatter databases (www.silverplatter.com) dating from January 1987 to December 2001 were searched using the medical subject headings heart failure (congestive), cardiomyopathy (congestive), trial, epidemiology, diagnosis, prognosis, incidence, prevalence and mortality. The criteria for consideration of the randomized clinical trials were cited in the most recent clinical guidelines for the management of chronic heart failure[18] and included detailed data about the clinical characteristics of the study patients. To identify the real-world chronic heart failure patient characteristics, we selected papers which reported multicenter prospective studies or registries on consecutive patients managed for congestive heart failure. In case registries were not yet published in full (TEMISTOCLE and IN-CHF) or reported data contained in full papers were not suitable for analysis, the search was extended using lateral references, personal communications with investigators and presentations at recent conferences. Potentially eligible studies were identified by hand searching of journals, computerized literature search, and discussion with colleagues. The IN-CHF registry was first developed to provide the Italian cardiological centers involved in the care of heart failure patients with a software package for the follow-up of these patients. This software was also aimed at creating local and national data banks concerning heart failure outpatients. A further goal was the development of a network of centers to obtain information concerning some targets such as: clinical epidemiology of heart failure outpatients, epidemiology of treatments, epidemiology of the diagnostic and therapeutic strategies, post-marketing surveillance, and cost analysis. The TEMISTOCLE (Heart Failure Epidemiological Study FADOI-ANMCO in Italian People) study was carried out through an 11-day survey to evaluate, in the Italian cardiological and internal medicine units, the typology of and the main causes of hospitalization for heart failure, the use of drugs in patients with heart failure, the appropriate use of guidelines and the in-hospital mortality for heart failure.

From each relevant study, we extracted the following data: the study population size, mean age, percentage of males, percentage of patients with a history of ischemic heart disease, myocardial infarction or diabetes, percentage of patients with chronic atrial fibrillation, percentage of patients with NYHA functional class III and IV, average left ventricular ejection fraction and percentage of patients with an ejection fraction > 40% and, for clinical trials, the duration of follow-up. Every effort was made to contact the principal investigators of eligible studies to complete those data which were not available from original reports.

Since data regarding individual patients were not available, summary data from the original reports were used. The comparison between the clinical characteristics of patients enrolled in clinical trials and actual patients was tested using the χ^2 test for categorical variables.

Results

We selected 27 randomized clinical trials published between 1987 and 2001, and 8 epidemiological studies characterizing real-world patients with chronic heart failure published between 1998 and 2002 which met the inclusion criteria (Table I)[8,19-50]. Overall, randomized clinical trials enrolled 53 859 patients, and epidemiological studies 18 207 patients. The average duration of follow-up of trial patients was 21 months (95% confidence interval 14-25 months) (Table II). With the exception of a 5-year follow-up of the DIG study[25], no trial showing benefits from drug treatment in heart failure patients had a study duration > 4 years (Table I). An important difference between real-world and trial heart failure patients is the fact that, by protocol, all trial patients have their left ventricular function assessed, whereas only about 60% of real clinical world heart failure patients have an objective assessment of their left ventricular function. In addition, the available data show that the left ventricular function of patients managed in the real clinical world was significantly higher than that found in patients enrolled in randomized trials. Three patients out of 4 enrolled in randomized trials have a left ventricular ejection fraction < 30%, and no trial patient has an ejection fraction > 40%. Conversely, one third of the patients with heart failure managed in the real clinical world have a left ventricular ejection fraction > 40%, and less than one third have an ejection fraction < 30% (Fig. 1).

Real-world patients with heart failure can be divided, according to their clinical characteristics, into two cohorts: patients who are hospitalized and patients seen in the outpatient clinic[45-50] (Table I).

Table I. Clinical characteristics of patients enrolled in the main randomized clinical trials on the pharmacological treatment of heart failure and actual patients with chronic heart failure managed in clinical practice.

Study	No. patients	Age (years)	Males (%)	IHD (%)	Previous MI (%)	Diabetes (%)	Chronic AF (%)	LVEF (%)	Follow-up (months)
Trial patients									
RALES[8]	1663	65 ± 12	73	54	NF	NF	NF	25 ± 7	24
SOLVD-Treatment[19]	2569	61 ± 7	81	71	66	26	10	25 ± 6	41.4
SOLVD-Prevention[20]	4228	59	89	83	80	15	4	28	37.4
CONSENSUS[21]	253	70	71	73	48	23	50	NF	6.8
V-HeFT II[22]	804	61	100	53	47	20	14	29	29
SAVE[23]	2231	59	83	100	100	22	NF	31	42
ELITE II[24]	3152	71 ± 7	70	79	59	24	30	31 ± 7	18.5
DIG[25]	6800	64 ± 11	22	71	65	29	0	28 ± 9	60
PROVED[26]	88	64 ± 2	85	12	NF	NF	0	28 ± 1	NF
MDC[27]	383	49 ± 12	72	0	0	0	0	22 ± 9	15
RADIANCE[28]	176	61 ± 1	77	61	NF	NF	0	27 ± 1	3
PRAISE[29]	1153	65 ± 1	76	64	NF	NF	NF	21 ± 1	13.8
ANZ[30]	415	67	80	100	90	NF	NF	29 ± 8	19
US Carvedilol[31]	1094	58 ± 12	77	31	NF	0	0	22 ± 7	6
Amiodarone[32]	1452*	62 ± 10	89	NF	51	23	–	24 ± 8	16
MERIT-HF[33]	3980	64 ± 10	78	66	49	25	17	28 ± 7	28
ATLAS[34]	3164	64 ± 10	80	65	55	20	18	23 ± 6	45.7
PROMISE[35]	1088	64 ± 11	78	54	11	NF	NF	21 ± 7	6.1
MOCHA[36]	345	60 ± 11	76	53	NF	NF	NF	23 ± 8	6
V-HeFT III[37]	450	63	100	55	NF	30	26	30	18
RESOLVD[38]	426	61 ± 11	82	69	64	25	–	29 ± 11	6
MACH-1[39]	2590	63 ± 11	79	68	63	31	14	25 ± 6	18.8
Vesnarinone[40]	3833	63 ± 12	75	57	NF	NF	NF	21 ± 6	9.5
CAPRICORN[41]	1959	63	73	86	56	22	NF	33	15
COPERNICUS[42]	2289	63	79	67	NF	NF	NF	20	10.1
BEST[43]	2708	60	78	58	NF	36	12	23 ± 7	24.3
CIBIS II[44]	2647	61	80	50	NF	0	20	28	15
Real-world hospitalized patients									
OSCUR[45]	749	76 ± 11	52	48	6	19	33	37 ± 11	
SCOOP I[46]	354	77	45	NF	NF	23	42	40	
French registry[47]	1058	76	55	33	22	19	37	NF	
TEMISTOCLE**	2127	74	53	42	43	28	34	NF	
MISCHF[48]	2184	75	56	43	NF	NF	25	35	
SCOOP II[49]	179	74	53	49	43	27	20	39	
Real-world community patients									
Olmsted County[50]	216	77	58	64	29	12	24	NF	
IN-CHF**	11 070	64	73	40	NF	NF	22	NF	

AF = atrial fibrillation; IHD = ischemic heart disease; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NF = not found. * only the results derived from trials on chronic heart failure have been considered; ** unpublished data provided by the Area Scompenso of the Italian Association of Hospital Cardiologists (ANMCO).

Table II. Summary of the data presented in table I.

Study	No. patients	Age (years)	Males (%)	IHD (%)	Previous MI (%)	Diabetes (%)	Chronic AF (%)	LVEF (%)	Follow-up (months)
Trial patients	53 859	63 ± 10	72	67	62	22	12	26 ± 7	21 ± 15
Real-world hospitalized patients	6921	75 ± 11*	54*	42*	42*	24**	31*	38 ± 15*	
Real-world community patients	11 286	64 ± 10	72	42*	NF	NF	22*	NF	

AF = atrial fibrillation; IHD = ischemic heart disease; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NF = not found. * $p < 0.0001$ vs trial patients; ** $p < 0.02$ vs trial patients.

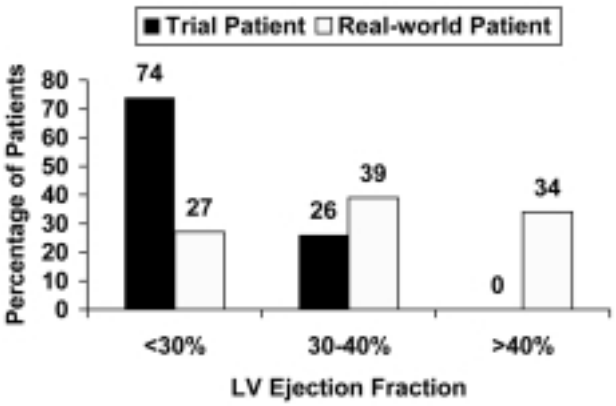

Figure 1. *Histogram showing the comparison of the left ventricular (LV) ejection fraction distribution between clinical trial and real-world heart failure patients.*

Real-world hospitalized patients. Compared to the typical patient who is hospitalized for heart failure, patients enrolled in clinical trials are approximately 12 years younger, 1.3-fold more likely to be male and 1.6-fold more likely to have a history of ischemic heart disease and previous myocardial infarction (Table II). Conversely, chronic atrial fibrillation was 2.6-fold less likely in patients enrolled in clinical trials than in actual patients hospitalized for heart failure (Table II). Diabetes was more frequent in real world patients too (Table II). In addition, despite the fact that the left ventricular ejection fraction was approximately 12% points greater in real-world patients hospitalized with heart failure than in patients enrolled in clinical trials, the former presented a more severe clinical impairment (Fig. 2). The age distribution of real-world patients hospitalized with heart failure varied between men and women so that there was a greater proportion of older women than of older men (Fig. 3). From the age distribution data shown in figure 3, it may be observed that the majority of real-world patients who are hospitalized with heart failure are comprised in age groups which are underrepresented in randomized clinical trials.

Actual outpatients with heart failure. The age and gender distributions of real-world patients with heart failure managed as outpatients were similar to those of patients enrolled in clinical trials. Similarly to real-world patients hospitalized with heart failure, outpatients showed a lower prevalence of a history of ischemic heart disease and a higher prevalence of chronic atrial fibrillation than patients enrolled in randomized trials (Table I). Data regarding the prevalence of diabetes and left ventricular ejection fraction in these patients were too incomplete for a meaningful comparison.

Discussion

The ultimate purpose of clinical trials should be to place clinicians in a position to apply the results supplied to the individual patient they meet and treat in their daily practice. To serve this purpose, patients enrolled in clinical trials and patients managed in daily practice should be comparable. Our results show that, compared to heart failure patients seen in clinical practice, patients enrolled in clinical trials are younger, are more likely to be male, show a more severe left ventricular systolic dysfunction, generally have less concomitant diseases and, finally, coronary artery disease represents the most common cause of heart failure. Although this trend would have already been clear to anyone who takes care of heart failure patients, our study is the first one specifically addressed to explore the magnitude of these differences. Hence, the present data should also help Institutions and Health Providers to plan clinical trials aimed at testing the effectiveness, in real-world chronic heart failure patients, of treatments which have been proved to be efficacious in randomized clinical trials.

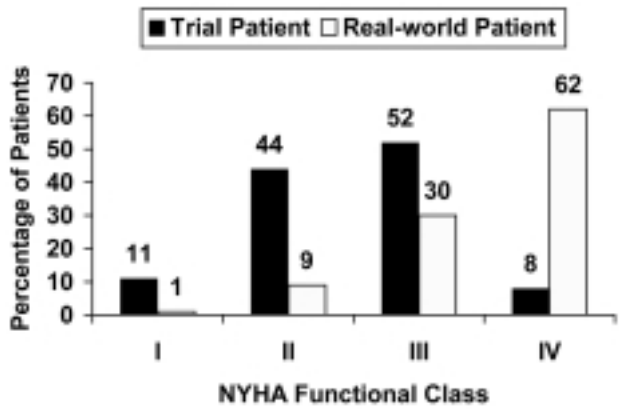

Figure 2. *Histogram showing the comparison of the NYHA functional class distribution between clinical trial and real-world heart failure patients.*

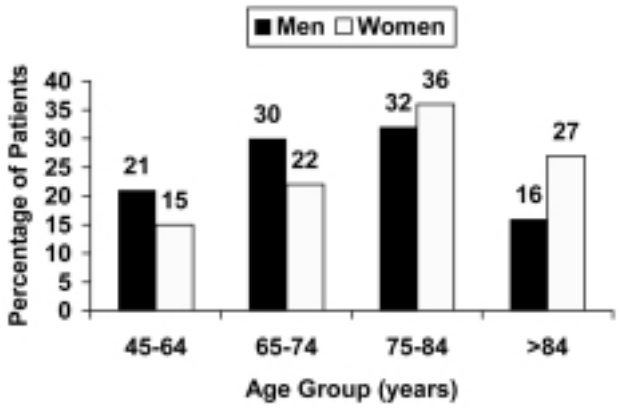

Figure 3. *Gender distribution by age group of real-world patients hospitalized with heart failure.*

Patients enrolled in clinical trials are different from patients encountered in routine clinical practice. Our data highlight once more how unrepresentative the patients enrolled in clinical trials on which guidelines are based are. With regard to age, studies aimed at evaluating the prevalence of heart failure in the general population[50-54] have demonstrated that the prevalence of heart failure progressively increases with age from approximately 1% in persons aged 50-59 years to approximately 10% in those aged 80-89, approximately doubling with each decade. In contrast, the mean age of patients enrolled in randomized clinical trials is 63 years (Table I). The reason for this selection bias is unclear since the upper age limit in the trials listed in table I ranged from 75 to 85 years. Regardless of the reason, the age-gap between trial and real-world patients is important because heart failure in the elderly is a more complex syndrome than that encountered in younger patients. Many precipitating factors may interact, the diastolic dysfunction is normally more severe[50], the pharmacokinetics is different and the necessity of multiple concomitant treatments reduces drug compliance or renders them ineffective[55,56].

With regard to gender, women represent only 28% of the global population of patients enrolled in clinical trials. Probably, the exclusion of women at least in part reflects the exclusion of older patients as women with heart failure are usually found in the upper age quartiles of the population[47,55,57,58]. Therefore, it is questionable whether clinical trial results may be extrapolated to old women encountered in clinical practice. For example, risk factors differ between the genders. Diabetes plays a greater role in the development of heart failure in women than in men[54], and ischemic heart disease plays a greater role in men, although the risk of developing heart failure after myocardial infarction is higher in women than in men[59,60].

With regard to the left ventricular systolic function, this appears to be significantly higher in real-world patients (the average ejection fraction was 38%) than that reported for clinical trial patients (the average ejection fraction was 26%). This difference is due to the selection criteria of most clinical trials in which objective (echocardiography or radionuclide ventriculography) evidence of left ventricular systolic dysfunction represented an inclusion criterion. In addition to the demographic characteristics of real-world chronic heart failure patients who are old and among whom approximately 50% are women, patient categories in which the proportion of heart failure subjects with a preserved left ventricular systolic function is relatively high[47,61] play an important role in determining the detected difference in left ventricular systolic function between real-world and clinical trial patients. These observations raise the issue of the clinical relevance of the objective evidence of left ventricular systolic dysfunction in the classical inclusion criteria of heart failure trials, and increases the expectations from the results of those trials which enroll elderly patients with a relatively preserved left ventricular systolic function or diastolic dysfunction[62,63].

Another important observation derived from the comparison between real-world and clinical trial heart failure patients is that atrial fibrillation is quite common among real-world heart failure patients (approximately 1 out of 3), suggesting that atrial fibrillation may be somewhat more than an innocent bystander in the development of heart failure. The observation that treatment of patients with symptomatic heart failure and severe left ventricular dysfunction with dofetilide was not only effective in converting atrial fibrillation and in preventing its recurrence, but also in reducing the risk of hospitalization for heart failure seems to confirm this concept[64]. Once the importance of atrial fibrillation as a cause of heart failure progression is recognized, it becomes important to determine if and how treatment can influence this condition and therefore influence clinical deterioration.

Finally, real-world heart failure patients showed a significantly lower prevalence of previous myocardial infarction and a higher prevalence of concomitant conditions such as diabetes and hypertension than clinical trial patients. The higher prevalence of previous myocardial infarction in clinical trial patients may be due to the necessity of enrolling patients with a reduced left ventricular systolic function. The necessity of enrolling patients with left ventricular systolic dysfunction, and thus more patients with a history of myocardial infarction, may also be the reason why women are underrepresented in clinical heart failure trials. A history of myocardial infarction is uncommon in 60-year-old women. On the other hand, the higher prevalence of other important concomitant conditions in real-world patients may increase both the re-admission rate and the length of hospitalization which account for a large part of the costs of the management of heart failure[55]. ACE-inhibitors[6], beta-blockers[7], spironolactone[8] and digoxin[25] have been proven to successfully decrease the rate of hospitalization in clinical trial patients, but their effectiveness in real-world complex patients with important concomitant conditions has never been tested.

Randomized, controlled clinical trials represent only the first step towards optimal patient treatment. Clinical trials can be viewed as experiments on humans, performed under conditions that are as simplified and as well defined as possible, in order to obtain a clear result. The aim of a well planned, randomized, controlled clinical trial is to assess the efficacy of a certain treatment in a well defined condition and, to reach a conclusion, confounding conditions should be reduced as much as possible. Once the efficacy of ACE-inhibitors, beta-blockers and spironolactone in reducing morbidity and mortality in chronic heart failure patients has been assessed, we need to test the effectiveness of these drugs in the complex patient seen in the real-world clinical practice. Our data can help opinion

leaders, clinical researchers, health care managers and the pharmaceutical industry to design appropriate clinical trials aimed at testing the effectiveness of these drugs in patients admitted to hospital (independently of the ward in which they are admitted). There are ongoing trials designed to test the efficacy of AT_1 receptor blockers (Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity)[62] and ACE-inhibitors (Perindopril for Elderly People with Chronic Heart Failure)[63] for elderly patients with a preserved left ventricular systolic function which will provide new insights to help to plan trials on drug effectiveness. Finally, because in any clinical trial there inevitably is case selection, it is incumbent on those who randomize patients to define, through registers, the populations from which these patients are selected. It will then be possible to describe which proportion of heart failure patients is likely to benefit from such treatments in the future.

The third step, after having proven the effectiveness of these treatments in hospitalized patients for safety reasons, should be to proceed with observational studies in order to determine whether treatments which have been proven to be effective in clinical trials are also applicable to primary care patients with chronic heart failure treated by general practitioners. The final aim is to incorporate the current scientific evidence regarding treatment into clinical practice in order to provide an optimal management for patients with heart failure in the community taking into account the epidemiological reality of the problem and the necessity of efficiently utilizing the limited health care resources.

In conclusion, our data show that the clinical characteristics of patients enrolled in clinical trials are significantly different from those of patients encountered in the real-world clinical practice. It is quite evident, therefore, that we lack an evidence base for the treatment of a sizable proportion of patients with heart failure. We need trials aimed at testing the clinical effectiveness in the real-world heart failure patient population of treatments which have been proven to be efficacious in previous landmark randomized clinical trials. It seems reasonable to hypothesize that there is much more to be gained from the more effective application of treatment measures currently available than seeking the next new breakthrough treatment.

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