Pre-discharge initiation of beta-blocker therapy in elderly patients hospitalized for acute decompensation of chronic heart failure: an effective strategy for the implementation of beta-blockade in heart failure

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Key words:
Aging; Beta-blockers; Congestive heart failure; Management in cardiology; Prognosis.

Background. **Current guidelines recommend beta-blockers in patients with heart failure and left ventricular systolic dysfunction. These agents, however, are largely underused in elderly patients because of the perception of up-titration complexity and the fear of side effects.**

Methods. **We prospectively assessed the feasibility, safety, tolerability, and 1-year outcome of the in-hospital initiation of carvedilol in elderly patients admitted for worsening heart failure.**

Results. **Among 164 eligible subjects (age > 70 years, left ventricular ejection fraction < 40% and no sign of congestion), 120 (73%) received carvedilol, on average 4.5 days after admission. The drug was permanently withdrawn in 10 out of 116 survivors (9%) at 60 days: 5 did not tolerate the starting dose because of worsening heart failure (n = 1), bradycardia (n = 1), and bronchospasm (n = 3). Two discontinued carvedilol during the in-hospital dose titration phase because of increasing premature ventricular beats and transient second degree atrioventricular block. The remaining 3 dropouts (fatigue in 2 and symptomatic bradycardia in 1 case) occurred after discharge. During the period between 60 days and 12 months, carvedilol was discontinued in 2 patients because of a depressive syndrome and symptomatic bradycardia. In no case these adverse events lead to death or were life-threatening, required hospitalization or resulted in any disability. The 1-year tolerability was 89%, the mortality was 17.5%, the frequency of hospitalization for worsening heart failure was 21%.**

Conclusions. **Thus, our results show that the in-hospital initiation of carvedilol is feasible and well-tolerated in elderly patients with recent worsening heart failure, and allows rapid identification of the most intolerant patients. The proportion of subjects taking carvedilol after 1 year from discharge was very high. This unconventional approach could significantly modify the use of beta-blockers in clinical practice.**

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Introduction

Randomized controlled trials, international guidelines and statements on quality of care recommend beta-blockers as standard treatment for chronic congestive heart failure due to systolic dysfunction since they have been shown to reduce mortality, morbidity and costs of illness[1-8]. Nevertheless, there is growing evidence that in the "real world" these agents are considerably underused, particularly in elderly patients[9-13]. The major causes responsible for the incomplete application of treatment guidelines in clinical practice in these patients are related to the unjustified perception of up-titration complexity, the fear of adverse events and the lack of short-term benefits[14-16]. These misperceptions represent unsuitable barriers to the effective management of heart failure patients and inevitably lead to the development of strategies for the implementation of beta-blocker use in the broad heart failure population. The practice of starting beta-blocker therapy during hospitalization may overcome these obstacles and, besides, provide a closer patient monitoring during the initial titration phase and increase the patient's compliance. This approach may prove particularly useful in

frail elderly patients for whom the reluctance of community physicians regarding the introduction of beta-blockers is further strengthened by the presence of major comorbidities and multiple drug regimens.

Accordingly, we performed this observational prospective study to evaluate the feasibility, safety and 60-day tolerability of starting beta-blocker therapy during the recovery phase of hospitalization for worsening heart failure in a cohort of elderly patients with left ventricular systolic dysfunction. We also assessed the proportion of subjects taking beta-blockers after 1 year from discharge and their long-term outcome.

Methods

Study population. Eligible subjects for this observational study were patients > 70 years of age with a left ventricular ejection fraction < 40% admitted for worsening heart failure diagnosed on the basis of the modified Framingham criteria[17]. Patients were consecutively recruited between January 2000 and December 2001 in 4 Italian Heart Failure Units and prospectively followed up for 12 months. Patients with the following conditions were not considered for beta-blocker treatment: hospitalization in an intensive care unit; active treatment (or treatment required within the previous 48 hours) with an intravenous positive inotropic agent; refractory pulmonary or systemic edema; second or third degree atrioventricular blocks or sick sinus syndrome or bradycardia (defined as a resting heart rate < 60 b/min) unless a permanent pacemaker was present; hypotension (systolic blood pressure < 100 mmHg); a history or clinical evidence of wheezing, bronchial asthma or related bronchospastic conditions; severe chronic obstructive pulmonary disease defined as a mean forced expiratory volume in 1 s < 50% measured by the spirometric test; peripheral arterial disease with symptoms at rest; severe systemic disease reducing the 1-year life expectancy; pre-existing treatment with any beta-blocker. Patients with a recent history (during the previous 3 months) of unstable angina or acute myocardial infarction and those with a history of percutaneous transluminal coronary angioplasty or coronary artery bypass grafting during the previous 6 months were also excluded.

Study protocol. The study patients were approached with an intensive unloading therapy (intravenous furosemide, sodium nitroprusside) and, if required, positive inotropic agents, in order to stabilize their clinical status. This condition was defined as the absence of fluid overload after 2 days of diuretics at a fixed dose and weaning from continuous intravenous vasodilators and/or inotropic agents. In this early stage of hospital stay, digitalis, low-dose spironolactone and angiotensin-converting enzyme (ACE)-inhibitors were always administered, unless contraindicated. After 48 hours, in case of achievement of clinical goals, patients were weaned from intravenous treatment and switched to oral therapy.

Once their clinical conditions had stabilized, all patients underwent a complete clinical and echocardiographic evaluation. The Charlson's index was calculated in all patients to identify the presence and the weight of prognostic comorbidities[18]. The clinical status was evaluated using the New York Heart Association (NYHA) functional classification and patients were grouped in two cohorts: patients with persistent NYHA class IV heart failure and patients with NYHA class < IV heart failure. At standard transthoracic echocardiography, the left ventricular volumes and ejection fraction were computed from the apical 2- and 4-chamber views in all patients using the area-length method[19]. Mitral regurgitation was diagnosed by means of color Doppler and quantified using a 1-4+ grading system[20].

Carvedilol was administered in accordance with current guidelines (3.125 mg twice daily at the beginning, then doubling the dose every 2 weeks up to 25 mg twice daily) when the patient's clinical conditions became stable and any sign of pulmonary or systemic congestion had disappeared. The starting dose was administered at least 48 hours before discharge. On the day when the test dose was given, patients remained rested for the subsequent 4-hour monitoring period. Their blood pressure, heart rate and symptoms were checked every 6 hours. If the patient tolerated the starting dose, continuous therapy with carvedilol was then given at an increasing dosage according to his/her tolerability and clinical conditions.

The 2-week up-titration intervals were varied if deemed appropriate in order to reach the target dosage of 50 mg/die or when the patient presented with symptoms and signs indicative of "effective" beta-blockade defined as clinical stability on a fixed diuretic dosage, a heart rate comprised between 60-70 b/min and a systolic blood pressure comprised between 100-120 mmHg. During this time, a temporary dose reduction was prescribed for those patients who did not tolerate an increase in the dose of carvedilol.

At discharge, diuretics were administered at the lowest dosage needed to control fluid retention and ACE-inhibitors at the highest tolerated dose. ACE-inhibitors could be replaced by angiotensin receptor blockers in case of side effects. Intensive educational issues such as the early recognition of symptoms, physical activity, diet, the flexible use of diuretics and the need of frequent controls of body weight and blood pressure were discussed with patients and their caregivers. Seven days after discharge the patients received the first outpatient clinical examination and thereafter were re-evaluated at 2 and 12 months. In all patients a complete echocardiographic examination was repeated at the end of follow-up.

The protocol of this study was approved by the local Institutional Ethics Review Boards. Informed consent was obtained from each eligible subject.

Protocol-specified endpoints. The data from the present observational study were analyzed mainly with the aim of evaluating the feasibility, tolerability and safety of beta-blocker therapy managed as inpatient care of heart failure. Tolerability was based on percent drug discontinuation and was evaluated at the short (60 days from discharge) and long term (1-year follow-up). Death, hospitalization for worsening heart failure and permanent withdrawal from carvedilol were considered as outcome measures. Causes of drug discontinuation as well as of hospitalization were accurately identified and reported on the study database. The secondary endpoints of the present study were the number of patients treated with beta-blockers at 1 year from discharge, the changes in the clinical and echocardiographic variables and the frequency of death and hospitalization at that time.

Statistical analysis. The variables chosen for analysis were presented as mean value ± 1 SD (parametric variables) or as median and quartiles (non-parametric variables). Differences between continuous variables were evaluated with one-way analysis of variance. Discrete variables were summarized by frequency percent and compared using the χ^2 test. The paired Student's t-test was used to measure the variations of the parameters documented during follow-up in the individuals taking carvedilol. Multiple logistic regression analysis by a stepwise forward-conditional procedure was carried out, using the Systat 8.0 Release (Systat Software Inc., Point Richmond, CA, USA), to identify the independent factors associated with permanent discontinuation of beta-blocker therapy. Kaplan-Meier cumulative survival curves were constructed for patients in NYHA functional class IV and those with less symptomatic cardiac syndromes at the initiation of beta-blocker therapy, to compare the risk of death or hospitalization due to cardiovascular causes. The differences between the curves were tested for significance using the Mantel-Cox log-rank test. A p value < 0.05 was considered as statistically significant.

Results

Feasibility. During the enrolment period, 164 patients consecutively admitted to our Centers were considered as being eligible for the present study. Beta-blocker therapy with carvedilol was started in 120 of them (73%). The reasons for exclusion from beta-blocker usage in the remaining 44 patients are listed in table I. The clinical characteristics of the patients who received carvedilol compared with those excluded from this therapy were markedly different (Table II). There were also some significant differences in the pharmacological therapy between the two groups of patients at entry and during the early phases of hospital stay (Table III).

Table I. Exclusion criteria from beta-blocker therapy.

Variables	No. patients
Severe COPD	17 (39%)
Hypotension	9 (20%)
Poor functional status	3 (7%)
Bradycardia	3 (7%)
Symptomatic peripheral artery disease	1 (2%)
No clinical contraindication	11 (25%)
Total	44

COPD = chronic obstructive pulmonary disease.

Carvedilol was started 4.5 ± 2.5 days after admission (range 2-16 days). The mean hospital stay in the carvedilol group was 10.3 ± 7.0 days, no longer than 10.1 ± 2.5 days for the patients who did not receive beta-blocker therapy (p = NS). The mean daily dose of carvedilol at discharge was 10.1 ± 3.2 mg.

Safety and tolerability: 60-day follow-up. In the cohort of 120 patients who started beta-blocker therapy no in-hospital death occurred. After discharge, during the 60-day titration period, 4 patients (3%) died suddenly (carvedilol was well tolerated in all of them before the fatal events) and 3 (2.5%) were re-hospitalized for worsening heart failure. In all these cases a relevant concomitant factor (severe anemia, new onset atrial fibrillation and pneumonia) was identified. Carvedilol was temporarily discontinued during the early phases of hospitalization in all patients and up-titrated again at discharge. The tolerability of study drug was evaluated in the 116 survivors. Among these subjects, carvedilol was permanently withdrawn in 10 (9%) at 60 days. Seven dropouts (70%) occurred during hospitalization: 5 patients did not tolerate the starting dose because of worsening heart failure (n = 1), bradycardia (n = 1) or acute bronchospasm (n = 3). Two patients discontinued carvedilol during the in-hospital dose titration because of a significant increase in premature ventricular beats in one case and for the development of an asymptomatic transient second degree atrioventricular block in the other. The remaining 3 dropouts (30%) occurred after discharge: in 2 patients the administration of the study drug was interrupted because of fatigue and in 1 because of symptomatic bradycardia. In no case these adverse events lead to death or were life-threatening, required hospitalization (or prolonged stay for in-hospital patients) or resulted in any disability. Table IV shows the characteristics of the patients who discontinued carvedilol in comparison with those of the patients who did not.

Outpatient long-term follow-up. During the period between 60 days and 12 months following the initiation of beta-blocker therapy, carvedilol was discontinued in 2 patients: the reasons were the occurrence of a depressive syndrome in 1 case (after 3 months), and sympto-

Table II. Principal characteristics of the study patients.

	Whole population (n = 164)	Carvedilol (n = 120)	No carvedilol (n = 44)	p
Male gender	100 (61%)	75 (62%)	25 (57%)	NS
Age (years)	76 ± 6	76 ± 6	78 ± 7	0.04
Body weight (kg)	66 ± 15	66 ± 14	68 ± 16	NS
Systolic blood pressure (mmHg)	125 ± 20	127 ± 21	122 ± 17	NS
Diastolic blood pressure (mmHg)	76 ± 9	76 ± 8	77 ± 11	NS
Atrial fibrillation	42 (26%)	27 (22%)	15 (34%)	NS
Diabetes	51 (31%)	39 (32%)	12 (27%)	NS
NYHA functional class (score 1-4)	2.9 ± 0.7	2.8 ± 0.7	2.9 ± 0.7	NS
NYHA functional class IV	24 (15%)	15 (13%)	9 (20%)	NS
Acute pulmonary edema as a cause of hospitalization	14 (9%)	6 (5%)	8 (18%)	0.04
Heart rate (b/min)	78 ± 14	78 ± 15	77 ± 13	NS
Arterial hypertension	121 (74%)	93 (77%)	28 (64%)	NS
Mild-moderate COPD	49 (30%)	29 (24%)	20 (45%)	0.01
Charlson's comorbidity index	2.2 ± 1.5	2.2 ± 1.5	2.1 ± 1.4	NS
Onset of symptoms of HF (months)	14 (3-24)	13 (2-24)	18 (6-24)	NS
Hospitalization for worsening HF in previous years				
No. patients	69 (42%)	56 (47%)	13 (30%)	NS
No. admissions	74 (45%)	61 (52%)	13 (30%)	NS
Admissions per patients	0.45	0.51	0.29	0.02
Etiology of HF				NS
Ischemic	85 (52%)	61 (50%)	24 (55%)	
Non-ischemic	79 (48%)	59 (50%)	20 (45%)	
Serum creatinine (mg/ml)	1.3 ± 0.5	1.2 ± 0.5	1.4 ± 0.5	0.03
Serum sodium (mmol/l)	138 ± 5	138 ± 5	139 ± 6	NS
Left ventricular ejection fraction (%)	30 ± 8	29 ± 8	32 ± 8	0.04
Left ventricular end-diastolic volume (ml/m^2)	103 ± 38	103 ± 40	102 ± 33	NS
Mitral regurgitation (score 1-4)	1.6 ± 1.0	1.6 ± 1.1	1.8 ± 10	NS

COPD = chronic obstructive pulmonary disease; HF = heart failure.

matic bradycardia in the second (after 4 months of therapy). During this time, 17 patients died (only 1 patient had discontinued carvedilol before the event). Thus, in the entire period of observation 21 patients died (the overall mortality was 17.5%). The long-term tolerability was analyzed in the 99 patients who were alive at the 12-month final evaluation. At that time, 88 patients (89%) who had started beta-blocker therapy before discharge were still on carvedilol: the mean daily dose was 25 ± 15 mg (range 6.25-50 mg), 45 patients (51%) taking 25 mg/day or more and 18 (20%) the target dose of 50 mg/day. During long-term follow-up the frequencies of hospitalization because of all causes, cardiovascular reasons and worsening heart failure were 30, 23 and 16% respectively (Fig. 1). In comparison with less symptomatic patients, those in NYHA functional class IV at the time of the initiation of carvedilol had a higher 1-year mortality (36 vs 17%, p = 0.05) and a higher risk of adverse cardiovascular events requiring hospitalization (50 vs 14%, p = 0.001) (Fig. 2). By comparison of the 12-month measurements with respect to baseline it emerged that both the functional status and left ventricular systolic function markedly improved in the study group. Similarly, the left ventricular end-diastolic volume as well as the degree of mitral regurgitation significantly decreased during the follow-up (Fig. 3).

Discussion

Inpatient starting beta-blockade: an opportunity. Current heart failure guidelines recommend that beta-blockers should be started in patients with stable clinical conditions and no evidence of significant congestion, usually after a waiting period of 2-4 weeks following a hospitalization for cardiac decompensation[1,2]. The fluid retention and the transient reduction in left ventricular systolic function that may occur when starting beta-blockade render this cautious strategy reasonable. Unfortunately, considering the wide underutilization of these agents in clinical practice and the difficulty to produce appropriate changes in physician behavior[21], these suggestions may become insurmountable barriers to the effective management of heart failure patients[10-14,22]. After hospital discharge, indeed, most patients with chronic heart failure (CHF) are usually followed up by general practitioners, who are usually reluctant to initiate beta-blocker therapy perceived as a potentially harmful therapy in the community setting, and considered as a "hospital initiated thing"[23]. This is particularly true for frail elderly patients for whom the frequency of readmissions after hospitalization for worsening heart failure is particularly high[24,25], while the rate of beta-blocker prescription remains, even in

Table III. Pharmacological therapy at hospital admission, during the early phase of hospitalization and at hospital discharge administered to the study patients divided according to the beta-blocker treatment.

	Carvedilol (n = 120)	No carvedilol (n = 44)	p
Before hospitalization			
ACE-inhibitors or ARB	69 (58%)	14 (32%)	0.006
Diuretics	59 (49%)	13 (30%)	0.04
High-dose furosemide (> 40 mg/day)	51 (43%)	24 (55%)	NS
Aldosterone antagonists	11 (9%)	3 (7%)	NS
Digoxin	33 (27%)	12 (27%)	NS
Anticoagulant	39 (32%)	16 (36%)	NS
Antiplatelet agents	60 (50%)	22 (51%)	NS
Nitrates	48 (40%)	23 (52%)	NS
Amiodarone	14 (12%)	10 (23%)	NS
During the early phase of hospitalization			
Intravenous positive inotropic agents	23 (19%)	17 (38%)	0.009
Intravenous sodium nitroprusside	26 (22%)	7 (16%)	NS
Diuretics	120 (100%)	42 (95%)	NS
High-dose furosemide (> 40 mg/day)	91 (76%)	35 (79%)	NS
ACE-inhibitors or ARB	111 (93%)	39 (89%)	NS
At hospital discharge			
ACE-inhibitors or ARB	109 (91%)	34 (77%)	0.04
Daily dose of ACE-inhibitor (equivalent of enalapril)	10 ± 8.5	8.7 ± 7.1	NS
Diuretics	111 (93%)	39 (89%)	NS
High-dose furosemide (> 40 mg/day)	54 (45%)	24 (55%)	NS
Aldosterone antagonists	62 (52%)	19 (43%)	NS
Digoxin	72 (60%)	32 (73%)	NS
Anticoagulant	36 (30%)	17 (39%)	NS
Antiplatelet agents	59 (49%)	22 (50%)	NS
Nitrates	49 (41%)	32 (73%)	0.0001
Amiodarone	14 (12%)	10 (26%)	0.03

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blockers.

Table IV. Baseline clinical variables which were different between patients who discontinued beta-blocker therapy during the first 60 days of treatment and those who did not.

	Group who discontinued carvedilol (n =10)	Group who maintained carvedilol (n = 106)	p
Univariate analysis			
Mild-moderate COPD	6 (60%)	23 (22%)	0.007
Mitral regurgitation (score 1-4)	1.9 ± 1.0	1.1 ± 0.9	0.04
Serum creatinine (mg/dl)	1.3 ± 0.5	1.0 ± 0.3	0.02
Multivariate analysis*	*Odds ratio*	*95% CI*	
Mild-moderate COPD	9.7	64.2-1.5	0.02
Mitral regurgitation (score 1-4)	3.6	10.3-1.3	0.03

CI = confidence interval; COPD = chronic obstructive pulmonary disease. * stepwise logistic regression analysis. Independent predictors of drug discontinuation.

2003, unacceptably low[10-13]. In view of this, the inpatient phase of care is a unique opportunity for the implementation of the use of beta-blockers in these patients and an exceptional teaching method to familiarize the out-of-hospital primary healthcare providers with beta-blockade in heart failure.

Initiation of carvedilol during hospitalization. In line with McDonald and Ledwidge[22], who stressed the need of complementing the relevant advances in outpatient management programs for heart failure by focusing on the in-hospital phase of care, in this investigation we evaluated the chance of commencing beta-blocker treatment before discharge in a cohort of elderly patients hospitalized for worsening heart failure. We chose carvedilol, i.e. the only available beta-blocker agent in Italy during the period of the study, indicated for CHF therapy with commercially available flexible dosage packages. In accordance with the guideline recommendations, we initiated beta-blocker treatment

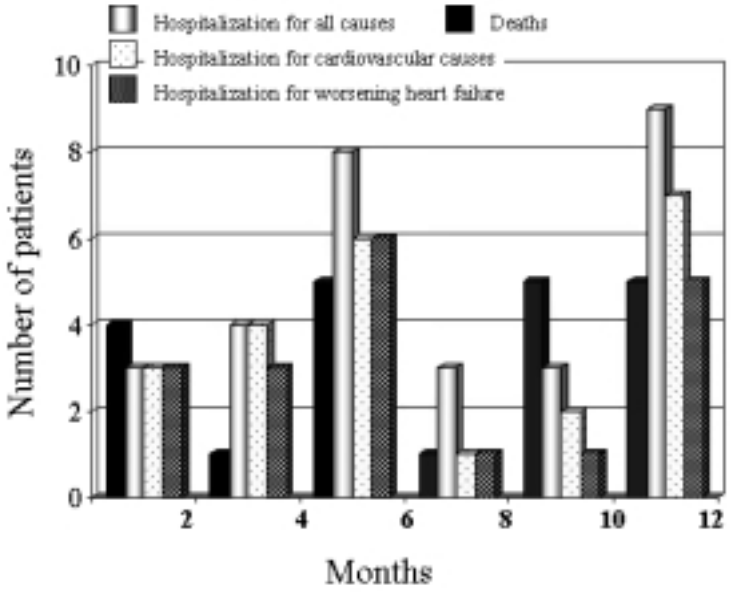

Figure 1. *Two-monthly frequency of the major adverse events (deaths, hospitalization for all causes, for cardiovascular causes and for worsening heart failure) that occurred during follow-up in the patients recruited into the study.*

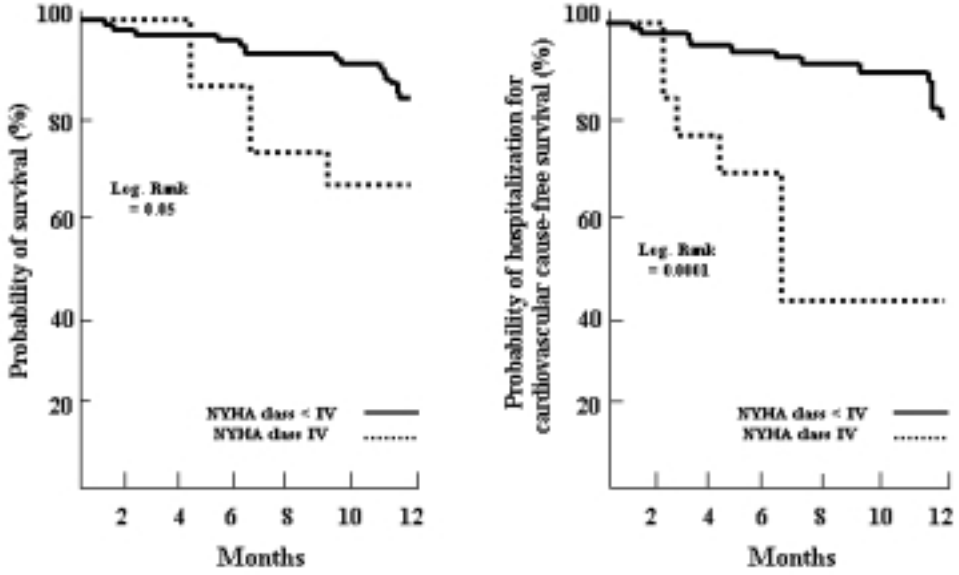

Figure 2. *Kaplan-Meier analysis of the cumulative risk of death* (left panel) *and of hospitalization for cardiovascular causes* (right panel) *in patients stratified according to their baseline NYHA functional class (NYHA classes < IV have been analyzed as a single group).*

with carvedilol once the signs of pulmonary or systemic congestion disappeared and having discontinued intravenous positive inotropic agents, but we did not wait neither for the achievement of a totally symptomless condition or for a prolonged stable dose of diuretics and vasodilators. Using this unconventional approach, we could start carvedilol in about three quarter of patients eligible for beta-blocker therapy and maintain active treatment for 1 year in 89% of the survivors. These percentages are far higher than those reported in recently published heart failure studies which targeted the implementation of beta-blockers in clinical practice[10-13].

Tolerability. Contrary to the experience of Baxter et al.[16] conducted on elderly patients treated with bisoprolol and showing a rate of withdrawal twice that previously reported in younger patients, the data of the present study showed that carvedilol tolerability is excellent in elderly subjects both during the initiation of therapy and in the long term (91% at 60 days and 89% at 1-year follow-up). Our results also indicated that the patient's selection criteria were appropriate and that the risk of adverse events was not higher in comparison with all previous investigations that tested beta-blocker treatment in the outpatient phase of care[4-6,11,16,26]. Furthermore, none of the adverse events we observed dur-

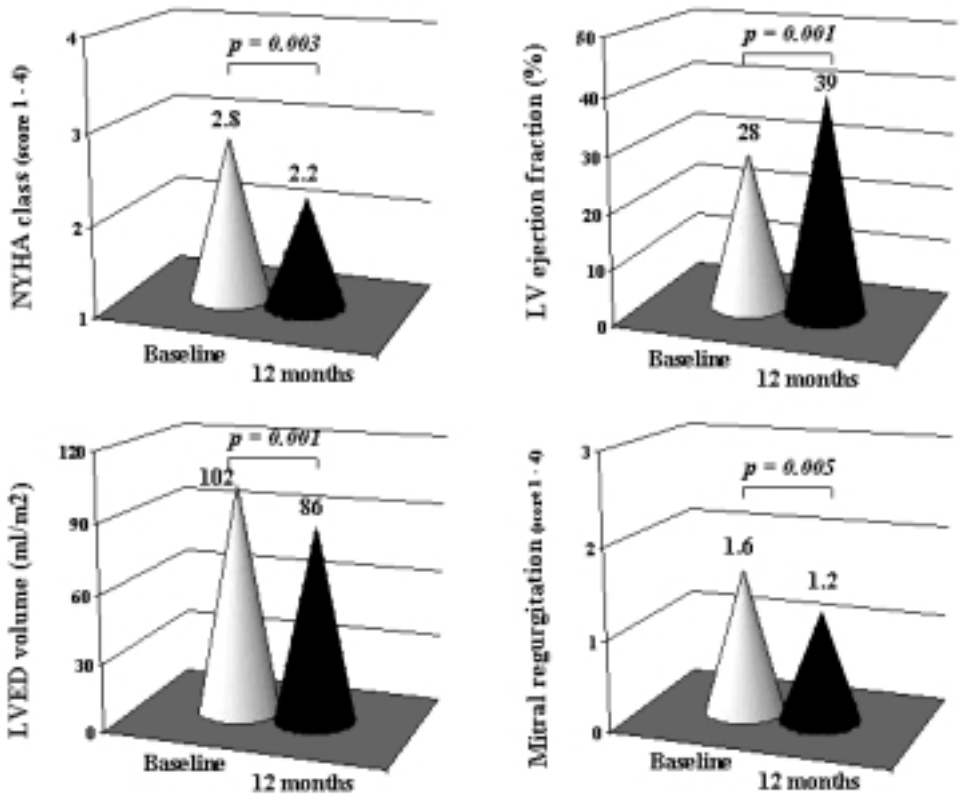

Figure 3. *Variations during the time in the NYHA functional class, left ventricular (LV) ejection fraction, left ventricular end-diastolic (LVED) volume and degree of mitral regurgitation measured at baseline and at the end of follow-up in the study patients.*

ing the study were fatal or life-threatening. All these findings are in accordance with those of the COPERNICUS trial[26] and with the data of Macdonald et al.[27] on patients in NYHA class IV which provided conclusive reassurance regarding the tolerability and safety of beta-blockers in middle-aged patients with severe heart failure.

By analyzing the frequency of adverse events which over time led to the discontinuation of carvedilol, we found that there was a higher risk of intolerance during the initial phases of drug administration in the elderly. More than four fifths of adverse reactions, indeed, occurred within 60 days following discharge. This finding is in line with the MERIT-HF experience in which there was a slight excess of discontinuation with metoprolol compared with placebo over the first months of therapy[5]. In contrast, in the COPERNICUS trial, the tolerability to carvedilol during the first 8 weeks was similar to that of the entire period of observation (10.4 months)[26]. The differences in long-term adverse events (significantly fewer in our study) and not in the excess of early drug discontinuation, may explain this discrepancy.

Low-dose carvedilol in the elderly. In our investigation we found an excellent tolerability with a relatively low dose of carvedilol. This result is in agreement with the data reported in other community studies by Rochon et al.[28] and by Sin and McAlister[29]. The maximal dosage of carvedilol we could prescribe in our elderly patients was much lower than that reported in the randomized clinical trials in younger heart failure patients[4,26,30,31]. As documented in middle-aged patients, beta-blockers in CHF have dose-related beneficial effects; however, this assertion has never been properly tested in older heart failure subjects[30,31]. Multiple lines of evidences support the idea that the efficiency of sympathetic beta-stimulation of the heart declines with aging[32]; furthermore, old patients usually present a complex heterogeneity of aging processes manifested by broad differences in terms of physical and mental health status, functional capacity and burden of physical diseases. Therefore, it is possible that an adequate inhibition of the sympathetic system could be obtained, in some old CHF patients, using lower doses of beta-blockers. We previously showed that in elderly CHF patients, once the sympathetic nervous system is adequately inhibited, low-dose carvedilol provides a significant improvement in clinical status, left ventricular systolic function and long-term outcome[33,34]. The data of the present study support these evidences and underscore the importance, when dealing with elderly CHF patients, of tailoring beta-blocker therapy on an individual basis.

Beyond the good tolerability, the COPERNICUS trial[26] demonstrated that the beneficial effects of carvedilol on outcomes became apparent as early as 2-3 weeks after the initiation of treatment and are espe-

cially observed among patients with more advanced disease. In line with these results, our patients exhibited a short-term mortality and a rate of rehospitalization (3 and 2.5% at 60-day follow-up respectively) significantly lower than those reported by any other experience involving elderly patients with heart failure on a standard approach of outpatient disease management. In both studies, patients were selected for their ability to reach adequate clinical compensation and had a relatively high systolic blood pressure.

Identikit of the older intolerant patient. The BRING-UP experience[11], designed to implement beta-blocker use in clinical practice on 3091 heart failure outpatients, identified older age, a worse functional class, lower systolic blood pressure and an ischemic etiology as independent predictors of permanent discontinuation of beta-blockers during a period of 12 months. On the other hand, no single variable emerged as an independent marker of inability to tolerate carvedilol in the retrospective investigation of Krum et al.[35] conducted on 808 middle-aged patients recruited in everyday clinical practice by hospital and private cardiologists. In our selected cohort of elderly patients, the intolerance to carvedilol was associated with the presence of chronic obstructive pulmonary disease and moderate-to-severe mitral regurgitation. As recently emphasized by Kotlyar et al.[36], the tolerability to carvedilol in patients with heart failure and concomitant mild-to-moderate chronic obstructive pulmonary disease is high and does not represent *per se* a contraindication to beta-blocker treatment. Although in the present study carvedilol was safely initiated in 80% of patients, half of the adverse events conditioning discontinuation of beta-blockade occurred in patients suffering from chronic obstructive pulmonary disease. Thus, our data suggest that in this subgroup of elderly patients, as well as in those subjects with significant mitral regurgitation (a marker of more severe heart failure and of an adverse outcome), the introduction of beta-blocker therapy necessitates close and careful clinical surveillance.

Study limitations. In our study we excluded old patients who, presumptively, would not benefit from or tolerate beta-blocker therapy such as those with irreversible physical signs of congestion and/or refractory heart failure symptoms requiring hospitalization in an Intensive Care Unit. This may imply an overestimation of the tolerability to carvedilol in the elderly population admitted for worsening heart failure. On the other hand, however, we could comment that using our enrolment criteria, the institution of beta-blocker therapy during hospitalization of high-risk elderly patients with a recent episode of cardiac decompensation is feasible and safe.

The final consideration regards costs and prognosis. We registered a similar duration of in-hospital stay in patients who started beta-blocker therapy and in those who did not receive carvedilol. The latter cohort of patients, however, does not constitute a credible control group managed with a different strategy so that we can draw any definite conclusion neither on the prognostic implications nor on the cost-effectiveness of our approach. But these were not objectives of the present study, which proposes, instead, a feasible and safe way for giving optimal therapy to elderly patients with CHF. Studies dedicated to analyzing the cost-effectiveness of the inpatient phase of care are urgently required.

Conclusions. Whilst waiting for consensus guidelines for acute heart failure and keeping in mind the results of the present study, we encourage the optimization of the pharmacological treatment of heart failure before discharge in frail elderly patients with recent worsening heart failure and uphold the concept that hospitals should not allow that quality of care is sacrificed in order to shorten the length of stay. This strategy may be an extraordinary opportunity to improve the quality of care in heart failure syndromes.

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