Metoprolol-induced functional benefit in dilated cardiomyopathy is sustained over four years and favorably influences outcome

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Key words:
Beta-blockers; Dilated cardiomyopathy; Heart failure; Prognosis; Ventricular function.

Background. **Beta-blockers improve survival and ventricular function in patients with heart failure. We evaluated the long-term persistence of metoprolol-induced improvement and its impact on prognosis in idiopathic dilated cardiomyopathy.**

Methods. **Two hundred and four of 586 patients enrolled in a registry on the natural history of idiopathic dilated cardiomyopathy survived 4 years without transplantation; 98 of them were on standard heart failure treatment, whereas 106 took metoprolol in addition. We analyzed the effects of treatment using beta-blockers in terms of changes in left ventricular ejection fraction (LVEF), NYHA functional class and left ventricular end-diastolic diameter index (LVEDDI) after 1, 2 and 4 follow-up years in order to elaborate an improvement score that was related to the subsequent outcome over 60 months after the 4-year follow-up visit.**

Results. **Greater LVEF increases and NYHA functional class and LVEDDI decreases were observed in patients submitted to metoprolol vs standard treatment at all stages of follow-up. Changes (delta vs baseline) for LVEF (p = 0.02), NYHA functional class (p = 0.0001) and LVEDDI (p = 0.004) were maximal during the first year (10 ± 11 vs 6 ± 12 units, -0.72 ± 0.77 vs -0.23 ± 0.81, -3.5 ± 5 vs -1.6 ± 3.5 mm), persisted at 2 (12 ± 12 vs 8 ± 12 units, -0.80 ± 0.70 vs -0.37 ± 0.87, -4.2 ± 5 vs -2.3 ± 4 mm) but showed a trend to decline at 4 years (11 ± 12 vs 8 ± 13 units, -0.54 ± 0.90 vs -0.24 ± 0.91, -4.3 ± 5 vs -2.3 ± 5 mm) of follow-up. Improvement at 4 years was associated with a better transplant-free survival (81 vs 52%, p = 0.0005, odds ratio 0.36, 95% confidence interval 0.18 to 0.74).**

Conclusions. **In idiopathic dilated cardiomyopathy, the more significant improvement in symptoms and left ventricular function and size, that is observed following treatment using metoprolol, translates into a better outcome. These benefits peak within the first 2 years of start of treatment but may begin to fade thereafter.**

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Introduction

In view of their antagonism with respect to a hyperactivated adrenergic nervous system, beta-blockers have gained widespread acceptance in the treatment of heart failure and are thought to prolong survival[1-5]. Many studies[1,6-16] report a striking short- and medium-term improvement in left ventricular function: using beta-blockers the left ventricular ejection fraction (LVEF) is increased by about 5 absolute percent points over 3 to 6 months and the improvement was reported to persist as long as 12 to 24 months[7]. Reverse remodeling with a decrease in left ventricular end-diastolic and end-systolic volumes was also observed[17]. Symptoms improved in some studies[1,2,7-11] but not in others[16]. Using beta-blockers the maximal improvement may be delayed in onset[12] and further benefits may be expected after 12-18 months, even in patients who have been submitted to long-term standard therapy.

Despite this impressive body of evidence, there are no controlled studies on the effects of long-term therapy (> 2 years) using beta-blockers on symptoms and left ventricular dimensions and function and their prognostic impact in patients with idiopathic dilated cardiomyopathy (IDC). Nor is this gap likely to be filled with results from the large randomized trials that were successful in showing a relatively short-term survival benefit using beta-blockers and were con-

sequently terminated prematurely[2-4]. Furthermore, in the subgroup of patients with primary dilated cardiomyopathy[3] or non-ischemic heart failure[4] the evidence on survival benefits appears less compelling, with very large confidence intervals (CI) for data regarding the effects of treatment.

Metoprolol improves long-term prognosis[1,4,18]. We reasoned that insight into the mechanisms and course through which this survival benefit is achieved might be useful to tailor disease monitoring in the clinical setting. Therefore, in order to determine whether metoprolol-induced functional improvement is maintained in the long term and in order to evaluate its prognostic impact, we investigated, in stable patients with IDC, the course of changes in symptoms and left ventricular dimensions and function according to beta-blockade with metoprolol during 4 years and their relation to patient outcome during an extended follow-up over the subsequent 5 years.

Methods

Study population. This report deals with a subgroup of IDC patients enrolled between January 1986 and October 1995 into a multicenter prospective registry. Details on the registry inclusion criteria and on methodology have been previously published[18]. In all registry patients IDC had been confirmed invasively[19,20] by demonstrating: 1) absence of significant coronary artery disease (> 50% luminal diameter reduction of a major coronary artery branch) at coronary angiography, 2) absence of specific myocardial disease or active myocarditis at endomyocardial biopsy. The transplant-free survival rates of the overall registry population were 91, 83 and 71% at 1, 2 and 4 years of follow-up respectively[18].

As the aim of the present study was to describe the long-term functional course of IDC, from the whole registry population we selected only patients who, since their enrolment into the study, had a transplant-free survival of at least 4 years, i.e. the time lapse from inclusion of the last patient till study closure. At baseline, all patients presented with evidence of left ventricular dysfunction, as expressed by a LVEF ≤ 0.40, measured at contrast left ventricular angiography or radionuclide ventriculography or echocardiography, and/or a previous documented episode of symptomatic heart failure. Functional status was assessed according to the New York Heart Association (NYHA) classification. The left ventricular end-diastolic (LVEDDI) and end-systolic diameter indexes were measured at M-mode echocardiography under two-dimensional guidance in the parasternal long-axis view, as the average of three beats. The LVEF for follow-up assessment was obtained by two-dimensional echocardiography from the apical 4-chamber view using the single plane area-length method; intra and interobserver variability were 3 ± 4 and 7 ± 3%, respectively.

Patients were submitted to standard therapy for heart failure or left ventricular dysfunction, on the basis of clinical judgment. Treatment included ACE-inhibitors in 98% of patients (captopril in 75 patients, mean dose 83 ± 41 mg/day, enalapril in 110, mean dose 19 ± 11 mg/day, lisinopril in 7 patients, mean dose 18 ± 13 mg/day, other ACE-inhibitors in 7 cases). Digitalis was administered to 90% of patients, while diuretics were also used in 84% of cases to relieve congestive symptoms. When indicated, amiodarone (n = 67, 33%, average daily dose 228 ± 69 mg) was administered for the treatment of complex symptomatic ventricular arrhythmias or for the control of heart rate in case of atrial fibrillation. In one of the study centers, according to a local protocol, patients were treated, since their enrolment into the registry, with the immediate-release metoprolol formulation. Having achieved stabilization using conventional medical therapy, patients received a test dose of metoprolol (5 mg bid for 2 to 7 days) and underwent stepwise titration over 7 weeks[18] till achievement of a resting heart rate of 60 ± 10 b/min or unless signs of intolerance (worsening heart failure or conduction disturbances) developed. Metoprolol was increased to > 150 mg/day if heart rate was persistently higher than the quoted target in the absence of worsening heart failure. Thus the beta-blockade group was treated with metoprolol for 4 years since enrolment into the registry.

Follow-up data were obtained during regular visits at each institution. Clinical and echocardiographic evaluation, including assessment of the NYHA functional class, echocardiographic LVEF and LVEDDI, was repeated at 1, 2 and 4 years. At each follow-up interval, patients were considered improved if, with respect to baseline, they presented two of the three following criteria: 1) at least one decrease in NYHA functional class, 2) at least a 10% decrease in LVEDDI, 3) at least a 10 unit increase in LVEF.

This two of three criterion permitted the assessment of improvement even in patients who were in NYHA class I at baseline. At follow-up, the finding of a LVEF ≥ 0.40 in the absence of symptoms (NYHA class I) was considered as an optimal response to treatment. The other patients were classified as non-improved; among these, we identified a subgroup of patients with deteriorating cardiac function, who, with respect to baseline, presented with two of the three following criteria: 1) at least one increase in NYHA functional class, 2) at least a 10% increase in LVEDDI, 3) at least a 10 unit decrease in LVEF.

As the study population included only patients who had survived at least 4 years, study endpoints, i.e. death due to any cause of heart transplantation, were assessed starting from the 4-year follow-up visit, i.e. 4 years since enrolment into the registry. Death was classified as: 1) due to progressive heart failure; 2) sudden and unexpected, when it occurred within 1 hour of new symptoms or during sleep in patients in NYHA classes I-III; 3) non-cardiac. Causes of deaths occurring out of hos-

pital were investigated during a telephone interview to the patient's relatives or attending physician. Heart transplantation was indicated when patients, with or without intravenous inotropic support, were hospitalized because of refractory heart failure or in the presence of a peak oxygen consumption < 14 ml/kg/min.

The study was terminated on September 30, 1999. During a mean period of 35 ± 24 months (range 0-92 months) from the 4-year follow-up visit, i.e. 7 years on average since enrolment into the registry, 47 of 204 patients (23%) presented with an unfavorable outcome. Twelve were submitted to heart transplant (26% of total endpoints), 6 (13%) died of refractory heart failure, and 26 (55%) died suddenly. Non-cardiac death occurred in 3 patients (6%).

Statistical analysis. The study was an observational cohort investigation that aimed to evaluate the extent and time course of functional changes in a subgroup of cases selected from our prospective registry. All analyses were performed according to the originally assigned treatment. Metoprolol-treated cases were compared to patients on conventional therapy alone using the unpaired Student's t-test for continuous variables and the χ^2 test with Yates correction for categorical variables. The NYHA functional class, LVEF and LVEDDI at follow-up were compared as absolute mean values and as mean changes from baseline at different time intervals by one-way analysis of variance for repeated measures. Significance was assessed for the effect of treatment, of time and for the treatment-time interaction. A two-sided p value < 0.05 was considered to indicate statistical significance.

Survival curves were plotted according to Kaplan and Meier; differences between curves for patients on standard treatment and those for patients on metoprolol were preliminarily assessed using the log-rank test; to evaluate the transplant-free survival in an acceptable number of patients, the assessment was extended till at least 15% of enrolled patients remained at risk[21]. Factors predicting improvement according to the global improvement score or optimal response to treatment at the 4-year follow-up visit were identified by multiple logistic regression analysis.

Results

Comparison of standard treatment and metoprolol cohorts. The study group included 204 (35%) 4-year survivors out of 586 patients enrolled in the registry; 106 (52%) of these late-survivors were treated with metoprolol from the time of enrolment into the registry onwards. One patient originally assigned to metoprolol, who, owing to worsening heart failure, did not tolerate the test dose, has been included in the metoprolol cohort. After titration to the maximum tolerated levels, the average daily dose, including the intolerant patient, was 127 ± 42 mg (range 0-200 mg); 36 patients (34%) were receiving ≤ 100 mg daily (mean dose 76 ± 26 mg), and 70 (66%) > 100 mg daily (mean dose 153 ± 16 mg); in 7 cases included in the latter group the final daily dose was > 150 mg (range 175-200 mg).

Metoprolol was continued, until the end of follow-up, in all but one patient in whom treatment was interrupted after 1 month at a dose of 50 mg/day because of worsening heart failure. In 2 other cases metoprolol was temporarily withdrawn in the first and second follow-up year respectively because of symptomatic bradycardia or worsening heart failure. Therapy was restarted later on. In 19 patients the dose of metoprolol was tapered to a lower level during follow-up but never suspended. Conversely metoprolol was further uptitrated in 53 cases; in 8 of these, however, it was subsequently necessary to return to the previous dose. For patients actually receiving metoprolol, the mean daily dose was 147 ± 53 mg at 1 year (range 25-300 mg), 152 ± 55 mg at 2 (range 10-300 mg) and 144 ± 55 mg at 4 years (range 25-300 mg).

The standard treatment cohort consisted of 98 patients (48%) and included 14 patients who started metoprolol after enrolment: 4 during the first year, 8 during the second and 2 during the fourth year.

Table I shows the baseline clinical and laboratory characteristics in the two groups of patients. Prior to enrolment into the registry, metoprolol-treated patients had a longer duration of symptoms and were more often treated with digitalis than the standard treatment cohort. On the other hand, amiodarone therapy was less frequent.

Functional changes in standard treatment and metoprolol cohorts. The NYHA functional class, LVEF and LVEDDI during follow-up are shown in table II as mean values and in figure 1 as mean differences from baseline.

The prevalence of long-term improvement at the different stages of follow-up was determined on the basis of the presence of two of the three criteria defined in the Methods section; the distribution of criteria did not differ between the two treatment groups at any time. The time course of improvement according to the global score was as follows: at 1 year 25 of 93 standard treatment (27%) and 49 of 102 metoprolol patients (48%) had improved (p = 0.004); 9 patients in the standard treatment group (vs 3 at baseline) and 32 in the metoprolol cohort (vs 2 at baseline) respectively had reached a LVEF ≥ 0.40 and NYHA class I (p = 0.0004). At 2 years, 35 of 98 standard treatment (36%) and 64 of 106 metoprolol patients (60%) had improved (p = 0.0009); 21 and 54 patients respectively presented with an optimal response to treatment (p = 0.00002). At 4 years, the differences in the global improvement score were no longer significant: 40 of 98 standard treatment (41%) and

Table I. Baseline clinical and laboratory findings in the two study groups.

	Standard treatment (n=98)	Metoprolol (n=106)	p
Male gender	80 (79%)	83 (77%)	NS
NYHA class I	24 (25%)	21 (20%)	NS
NYHA class II	43 (44%)	54 (51%)	
NYHA class III	26 (26%)	27 (26%)	
NYHA class IV	5 (5%)	4 (4%)	
ACE-inhibitors	95 (97%)	104 (98%)	NS
Digitalis	82 (84%)	103 (97%)	0.002
Diuretics	82 (84%)	90 (85%)	NS
Amiodarone	40 (41%)	27 (26%)	0.03
Atrial fibrillation	9 (9%)	3 (3%)	NS
Left bundle branch block	39 (40%)	37 (36%)	NS
Age (years)	45 ± 11	44 ± 12	NS
Symptom duration (months)	17 ± 24	27 ± 34	0.02
Heart rate (b/min)	82 ± 13	79 ± 13	NS
Systolic blood pressure (mmHg)	124 ± 14	122 ± 13	NS
Left ventricular end-diastolic diameter (mm/m^2)	39 ± 4	38 ± 5	NS
Left ventricular end-systolic diameter (mm/m^2)	33 ± 5	33 ± 5	NS
Left ventricular ejection fraction (%)	28 ± 8	28 ± 9	NS
Mean aortic pressure (mmHg)	90 ± 15	86 ± 12	NS
Mean pulmonary artery pressure (mmHg)	19 ± 10	19 ± 9	NS
Mean pulmonary wedge pressure (mmHg)	13 ± 9	12 ± 7	NS
Ventricular ectopic beats (n/h)	105 ± 211	104 ± 197	NS
Ventricular pairs (n/h)	1.03 ± 5	2.23 ± 7	NS
Ventricular tachycardia episodes (n/h)	0.11 ± 0.8	0.12 ± 0.28	NS

Table II. Functional variables at follow-up according to metoprolol treatment and dose.

	Metoprolol (all doses)	Standard treatment	Metoprolol ≤ 100 mg/day	Metoprolol > 100 mg/day
LVEF (units)				
Baseline	28 ± 9	27 ± 8	30 ± 11	27 ± 8
Year 1	39 ± 11	34 ± 10	36 ± 11	40 ± 11
Year 2	40 ± 12	36 ± 12	38 ± 12	41 ± 11
Year 4	39 ± 11	36 ± 11	36 ± 11	41 ± 11
p for treatment		0.003	0.006	
p for time		0.0001	0.0001	
p for treatment-time interaction		0.04	0.006	
LVEDDI (mm/m^2)				
Baseline	38 ± 5	38 ± 4	39 ± 6	38 ± 4
Year 1	34 ± 6	37 ± 5	35 ± 5	34 ± 6
Year 2	34 ± 5	36 ± 5	35 ± 6	33 ± 5
Year 4	34 ± 5	36 ± 6	35 ± 6	33 ± 5
p for treatment		0.01	0.004	
p for time		0.0001	0.0001	
p for treatment-time interaction		0.015	0.01	
NYHA functional class				
Baseline	2.1 ± 0.8	2.1 ± 0.8	2.1 ± 0.8	2.2 ± 0.7
Year 1	1.4 ± 0.6	1.9 ± 0.5	1.6 ± 0.6	1.3 ± 0.5
Year 2	1.3 ± 0.6	1.8 ± 0.6	1.4 ± 0.6	1.3 ± 0.6
Year 4	1.6 ± 0.7	1.9 ± 0.7	1.6 ± 0.8	1.6 ± 0.7
p for treatment		0.0001	0.0003	
p for time		0.0001	0.0001	
p for treatment-time interaction		0.0001	0.0001	

LVEDDI = left ventricular end-diastolic diameter index; LVEF = left ventricular ejection fraction.

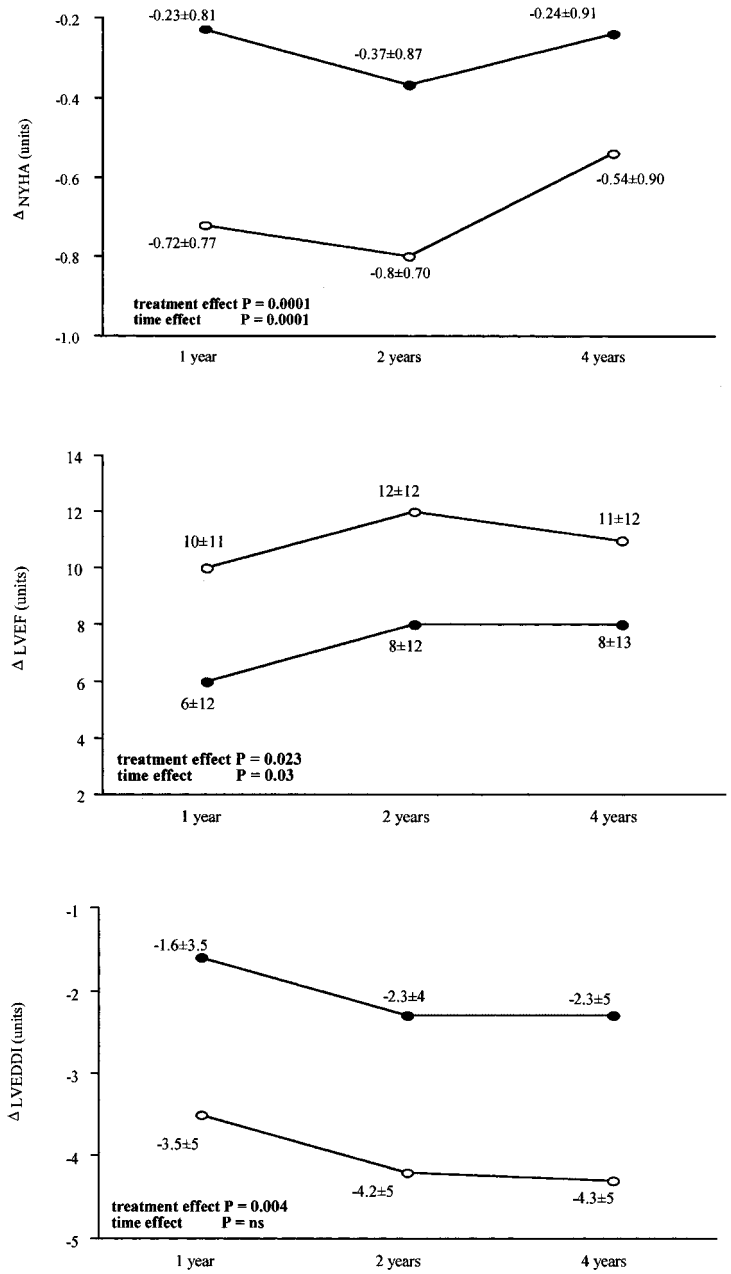

Figure 1. *Changes from baseline ± 1 SD in NYHA functional class* (upper panel), *left ventricular ejection fraction (LVEF)* (middle panel), *and left ventricular end-diastolic diameter index (LVEDDI)* (lower panel) *at 1, 2 and 4 years of follow-up in patients on standard treatment* (closed circles) *and metoprolol* (open circles).

49 of 106 metoprolol patients (46%) had improved (p = 0.49) with respect to baseline. However, the percentage of patients presenting with an optimal response was still higher in the metoprolol-treated group (39 vs 22%, p = 0.02). The administration of digitalis or of amiodarone did not seem to influence the global improvement score or the frequency of an optimal response to treatment.

Conversely, deterioration, as defined in the Methods section, was observed in 5 and 6% of standard treatment patients at 1 and 2 years of follow-up respectively but in none of those on metoprolol (p = 0.05 and p = 0.01). However, at 4 years, 7% of patients on standard treatment and 5% of those on metoprolol had deteriorated with respect to baseline (p = NS).

Functional changes and metoprolol dose. As stated above, 36 patients in the metoprolol-cohort took ≤ 100 mg daily of metoprolol and 70- > 100 mg. The former group, albeit older (48 ± 12 vs 42 ± 11 years, p = 0.01), did not significantly differ from the latter for any other variable. The NYHA class decreased more in both metoprolol groups than in standard treatment patients (Fig. 2, upper panel). Increasing metoprolol doses determined greater effects on LVEF (Fig. 2, middle panel) and this effect was maintained over time. The LVEDDI al-

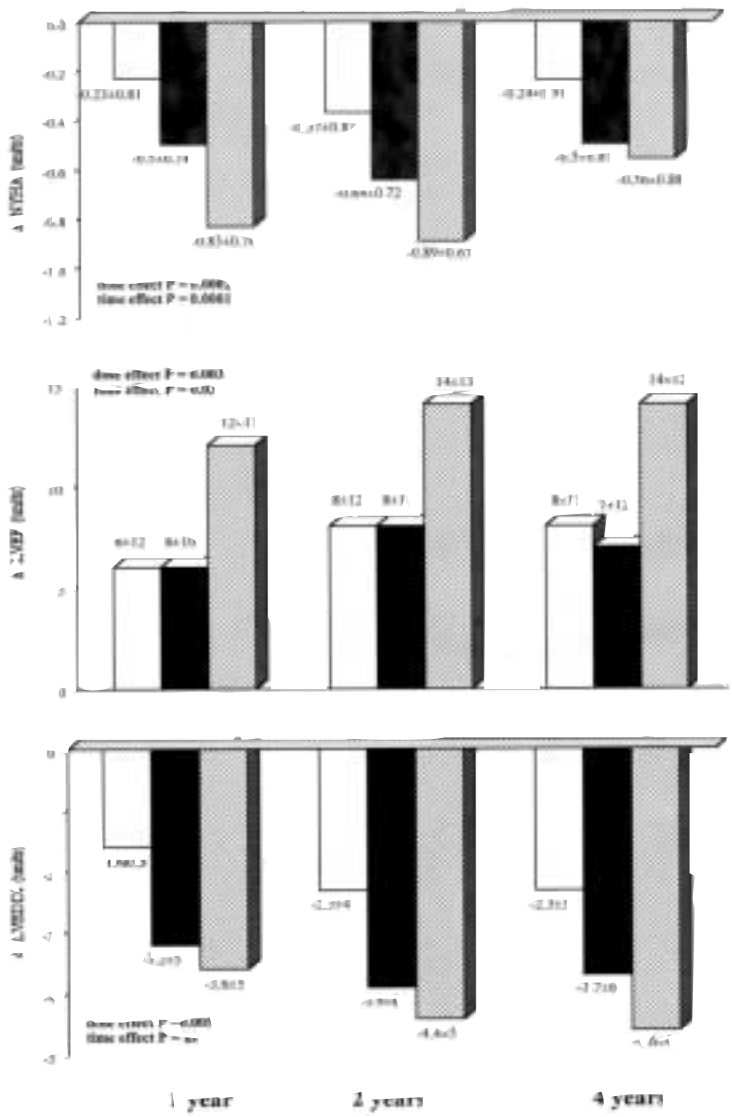

Figure 2. *Changes from baseline ± 1 SD in NYHA functional class* (upper panel), *LVEF* (middle panel), *and LVEDDI* (lower panel) *at 1, 2 and 4 years of follow-up in patients on standard treatment* (open bars), *patients on ≤ 100 mg/day of metoprolol* (solid bars) *and patients on > 100 mg/day of metoprolol* (hatched bars). *Abbreviations as in figure 1.*

so decreased significantly (Fig. 2, lower panel) according to metoprolol treatment and dose (p = 0.005), but not according to time (p = NS) or the time-dose interaction (p = NS).

Although patient improvement was not dose-dependent at 1 (39% for metoprolol doses ≤ 100 mg/day vs 52% for doses > 100 mg/day, p = NS) and 2 years (47 vs 67%, p = 0.08), significantly less patients on low doses had improved at 4 years (31 vs 54%, p = 0.03).

Functional changes, prediction of improvement and outcome. To determine the independent predictors of functional improvement or of an optimal response to treatment at 4 years, patient data at baseline, at 1 and at 2 years were analyzed using multivariate logistic regression analysis. The single best predictor was the change in LVEDDI observed at 2 years of follow-up (odds ratio 0.88, 95% CI 0.84 to 0.91, p = 0.0001).

Product-limit survival was evaluated in the 204 patient series after the 4-year follow-up visit, when all patients were still alive and none had undergone heart transplant; the transplant-free survival rates were 85% at 2 and 68% at 5 years.

To determine the effect of improvement at follow-up on outcome, we analyzed the transplant-free survival over the subsequent 5 years according to patient status at the 4-year follow-up visit. Patients who, according to the global score, had improved or who presented with an optimal response to treatment (n = 102) had a significantly better prognosis than non-improved patients (n = 102): the 5-year transplant-free survival was 81 vs 52%, (p = 0.0005, Fig. 3, odds ratio 0.36, 95% CI 0.18 to 0.74). When patients were further stratified according to metoprolol treatment and improvement, no differences in outcome were observed among improved patients on metoprolol vs standard treatment (77 vs

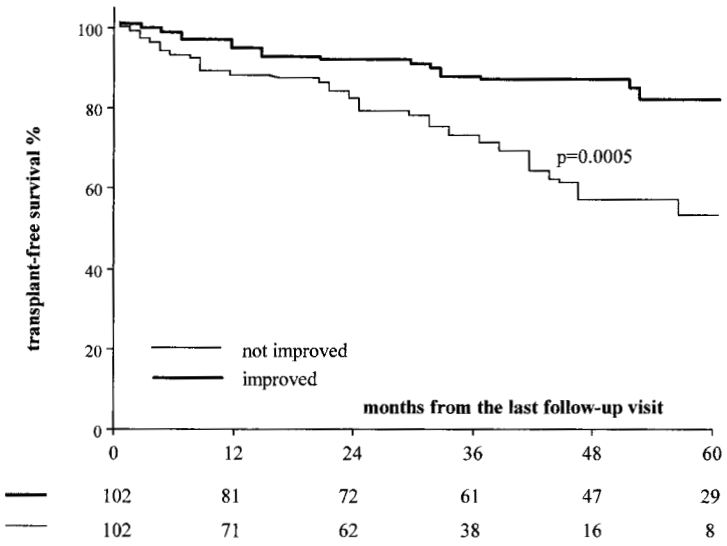

Figure 3. *Five-year transplant-free survival rates according to the global improvement score or the achievement of an optimal response to treatment (left ventricular ejection fraction ≥ 0.40 and NYHA functional class I) observed 4 years after enrolment into the registry and start of beta-blockade. Numbers below the x-axis are patients alive at each time interval.*

86%, p = NS, odds ratio 1.43, 95% CI 0.44 to 4.6). A trend to better survival was found among non-improved patients on metoprolol (54% metoprolol vs 47% standard treatment, p = 0.08, odds ratio 0.27, 95% CI 0.11 to 0.68).

Discussion

This study was designed to assess the impact of the addition of metoprolol on functional changes and their relation to prognosis in long-term IDC survivors on standard treatment. Long-term metoprolol had a persistent beneficial effect on patient symptoms and on left ventricular function and dimensions. Benefits increased during the first year, peaked at 2 and persisted following 4 years of treatment, although with a trend towards attenuation. Documented improvement after 4 years of therapy was associated with a positive outcome during the subsequent extended follow-up.

Functional changes and long-term beta-blockade. This, to our knowledge, is the first controlled, although not randomized, study including long-term data and evaluating the functional effects of 4 years of therapy using beta-blockers in patients with IDC. Many controlled studies have shown a consistent improvement in ventricular function, as assessed by LVEF, after a minimum of 3 months of beta-blocker treatment[6-16]; the duration of most of these reports was 6 to 12 months. The increase in LVEF averaged 5 units, even though changes of greater magnitude were reported using vasodilating beta-blockers[9-11], in particular carvedilol[22]. These beneficial effects were observed in patients already on optimal standard treatment for heart failure, including ACE-inhibitors. A treatment benefit, consisting of an increase in LVEF averaging 2 to 3 units, had been reported to persist for up to 3 years using the ACE-inhibitor enalapril[23].

In the present retrospective analysis of prospectively enrolled and treated patients, data are consistent with those of previous randomized trials on beta-blockers and even with those of more recent studies evaluating the functional changes observed during metoprolol treatment[24]. Although in the present study, even patients on standard therapy presented with a significant improvement in LVEF averaging 5 units, the magnitude of the observed changes and the level of ventricular function attained were at all stages greater in metoprolol-treated patients (Table II). Just as for carvedilol[14], even in the present study, the increase in LVEF was related to the dose of metoprolol. Benefits increased during the first year and peaked during the second. This improvement in pump function is indirectly confirmed by the increase in the average dose of metoprolol administered at 1 year (from 127 to 142 mg daily). Subsequent follow-up showed that these beneficial effects were largely maintained at 4 years, although with a trend towards deterioration (Table II, Fig. 1).

The results of trials on the effects of beta-blockers on symptoms in heart failure have been conflicting[1,7,9,11,15,25]. Our series includes only long-term survivors and so, probably less advanced cases. Hence, the probability of symptomatic remission was higher. Moreover, patient status was evaluated for the first time following 12 months of therapy. This time lapse may have been long enough to permit recovery from the initial worsening in symptomatic status which has been consistently reported following beta-blocker up-titration[3]; the beta-blocker-related improvement in left ventricular function may have, by 1 year, fully translated into symptomatic relief. Conversely, the trend to deterioration in functional class at 4 years mirrored the decrease

in LVEF observed at this stage of follow-up compared to that at 2 years.

The favorable effects of beta-blockade on left ventricular remodeling have been demonstrated in various studies[6,9,12,16,17]. We, as others, used the left ventricular end-diastolic diameter[16,25], a parameter better suited to a long-term observational study. Just as for other long-term findings in previous studies[12,17], even in the present registry the decrease in the above parameter was more marked in patients submitted to metoprolol treatment and reached a nadir at 2 years of follow-up. The course of these changes confirms that beta-blockers induce a positive effect on left ventricular size. This benefit persists longer than the improvement in pump function.

Metoprolol, improvement and outcome. In a previous observational cohort study[18] that included the whole population of our registry, metoprolol treatment significantly improved prognosis. In the present subgroup analysis the response to treatment, as assessed by an improvement score or by the achievement of a LVEF ≥ 0.40 in the absence of symptoms, significantly influenced the subsequent outcome. A persistent beneficial effect of treatment, even in this stable population with mild to moderate heart failure, was in fact associated with a better prognosis at an average of 7 years of follow-up. In the present report the benefits of metoprolol are probably even underestimated. This, in view of the fact that, in the original registry series[18], the proportion of non-transplanted survivors was higher in the metoprolol than in the standard treatment cohort.

Outcome stratification by improvement and beta-blockade together hinted to a positive effect of metoprolol on transplant-free survival, even in those patients who, according to the composite score, did not improve. This suggests that it might be clinically worthwhile to treat with metoprolol all patients who are able to tolerate it. This survival benefit in non-improved metoprolol-treated patients might be due to a protective effect of beta-blockade from sudden death. However, the small number of cases in the different subgroups included in the present study precludes meaningful analyses regarding the mechanisms of death. Actually, in large-scale trials both bisoprolol[3] as well as metoprolol[4] significantly reduced the incidence of sudden death by about 40%.

Limitations of the study. Although this retrospective analysis including prospectively enrolled patients was neither blinded nor randomized, its strong points are the presence of a control group on standard treatment and the average long-term follow-up (7 years between enrolment into the registry and endpoint occurrence or study closure), which would be difficult to achieve in a randomized clinical trial. Moreover, the findings during the initial period of observation indicate changes of the same magnitude and in the same direction as those previously shown and are consistent with reports of randomized blinded studies. This lends support to the validity of the results at late follow-up.

Although all registry patients had a history of heart failure including significant left ventricular dysfunction, only 4-year survivors were included in this report. This, in order to assess the long-term persistence of the beneficial effects of beta-blockade; furthermore, the mean age was much lower than that of other studies on beta-blockade in heart failure. Therefore, our results may not be extrapolated to older patients or to those with more advanced or unstable heart failure. On the other hand, this study provides information on a subgroup of patients that has not been directly assessed in recent trials.

Clinical implications. The course of the functional changes during 4 years of metoprolol treatment demonstrates that beta-blocker-induced improvement is largely complete within 2 years. The clinical stability at 48 months, as well as the prognosis over the ensuing 5 years, may be predicted by the level of ventricular remodeling reached at 2 years of follow-up. Patients who improve in the first and second follow-up year may be considered at low risk of deterioration, while those who do not improve have an unfavorable long-term outcome. At 4 years a trend towards a decrease in treatment benefits becomes evident with respect to the peak improvement. This suggests an escape phenomenon and possibly initial clinical deterioration and disease progression. Therefore, following this period, stricter surveillance may be advisable. This trend has not been previously described and should be confirmed in larger studies with a long-term follow-up.

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Appendix

Centers participating in the SPIC (Italian Multicenter Cardiomyopathy Study)

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