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Impact of Initiating Carvedilol Before Angiotensin-Converting Enzyme Inhibitor Therapy on Cardiac Function in Newly Diagnosed Heart Failure

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OBJECTIVES The purpose of this research was to evaluate the therapeutic value of initiating a beta-blocker before an angiotensin-converting enzyme inhibitor (ACEI) in the treatment of heart failure.

BACKGROUND Although ACEI and carvedilol produce benefits in heart failure, whether the order of initiation of therapy determines the impact on left ventricular (LV) function and New York Heart Association functional class (NYHA FC) has not been determined.

METHODS A single-center, prospective, randomized, open-label study was performed. We evaluated whether initiation of therapy with carvedilol either before ($n = 38$) or after ($n = 40$) perindopril therapy in newly diagnosed patients in NYHA FC II to III heart failure with idiopathic dilated cardiomyopathy, with the addition of the alternative agent after six months, determined subsequent changes in NYHA FC and LV function (echocardiography and radionuclide ventriculography). Study drugs were titrated to maximum tolerable doses.

RESULTS There were no differences in baseline characteristics between the study groups. After 12 months 11 patients died (6 in the group where the ACEI was initiated). At 12 months the group receiving carvedilol as initial therapy achieved a higher tolerable dose of carvedilol (43 ± 17 mg vs. 33 ± 18 mg, $p = 0.03$); a lower dose of furosemide ($p < 0.05$); and better improvements in symptoms (NYHA FC, $p < 0.002$), LV ejection fraction (radionuclide: 15 ± 16% vs. 6 ± 13%, $p < 0.05$; echocardiographic, $p < 0.01$), and plasma N-terminal pro-brain natriuretic peptide concentrations ($p < 0.02$).

CONCLUSIONS As opposed to the conventional sequence of drug use in the treatment of heart failure, initiation of therapy with carvedilol before an ACEI results in higher tolerable doses of carvedilol and better improvements in FC and LV function. (J Am Coll Cardiol 2004;44: 1825–30) © 2004 by the American College of Cardiology Foundation

Congestive cardiac failure is a complex clinical syndrome, the progression of which is thought to be determined, in part, by activation of neurohumoral (particularly renin-angiotensin and adrenergic) systems (1). Neurohumoral substances are capable of altering the function and structure of the heart via both direct effects on cardiomyocyte biology

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and the extracellular matrix, the consequence of which is reduced ventricular function and enhanced loading conditions (2–4). Inhibition of the renin-angiotensin and adrenergic systems has subsequently become the mainstay of contemporary pharmacologic management of patients with chronic heart failure (2,3).

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In the treatment of heart failure with pump dysfunction, beta-blocking agents are conventionally administered once optimal therapy with angiotensin-converting enzyme inhibitors (ACEI) is achieved. This approach is employed because clinical studies showing therapeutic benefits of beta-blockers (BBs) were originally conducted in patients receiving ACEI (5–7). Importantly, however, in chronic heart failure, sympathetic activation precedes that of the renin-angiotensin system (8). Moreover, the mechanisms by which beta-adrenergic receptor activation mediates detrimental effects in heart failure is thought to involve cellular pathways that are modulated by both the renin-angiotensin system (9) as well as by beta-adrenergic receptor-induced intracellular signaling pathways that are independent of the renin-angiotensin system (10). Therefore, the question arises as to whether more substantial benefits are realized when maximal doses of BBs are achieved before initiating ACEI therapy. Consequently, in the present study, we evaluated whether the order of initiation of a BB relative to ACEI therapy determines the impact of neurohumoral blockade on left ventricular (LV) function, New York Heart Association functional class (NYHA FC), and biochemical indexes of heart failure (plasma N-terminal pro-

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Abbreviations and Acronyms

ACEI	= angiotensin-converting enzyme inhibitor
BB	= beta-blocker
LV	= left ventricle/ventricular
LVEDD	= left ventricular end-diastolic diameter
LVEF	= left ventricular ejection fraction
LVESD	= left ventricular end-systolic diameter
NT-pro-BNP	= N-terminal pro-brain natriuretic peptide
NYHA FC	= New York Heart Association functional class

brain natriuretic peptide [NT-pro-BNP] concentrations [11]) in newly diagnosed patients with heart failure due to idiopathic dilated cardiomyopathy.

METHODS

Study design and patient groups. The Committee for Research in Human Subjects of the University of Witwatersrand approved the protocol. This was a single-center, prospective, randomized, open-label study conducted in 78 consecutive patients with newly diagnosed idiopathic dilated cardiomyopathy in NYHA FC II to III heart failure. The study was initiated, conducted, and analyzed by the investigators. Inclusion criteria: 1) age ≥18 and ≤70 years; 2) NYHA FC II or III congestive heart failure of unknown etiology; 3) left ventricular ejection fraction (LVEF) <40% as determined by radionuclide ventriculography; 4) sinus rhythm. Exclusion criteria: 1) chronic obstructive pulmonary disease; 2) significant valvular heart disease; 3) history or evidence of ischemic heart disease; 4) systolic blood pressure >160 mm Hg and/or diastolic blood pressure >95 mm Hg.

After initial presentation, and following a diagnosis by clinical examination and echocardiography (screening visit), all patients received treatment with digoxin and diuretics for seven days. Patients were then randomized to receive either the ACEI perindopril (ACEI-first group, n = 40) or the BB carvedilol (BB-first group, n = 38) in addition to diuretics and digoxin for a further six months. After six months, carvedilol was added to the therapeutic regimen in those receiving the ACEI, and perindopril was added to the therapeutic regimen in those receiving carvedilol. Both study drugs were titrated to maximum tolerable doses, where systolic blood pressure was maintained at >85 mm Hg, no dizziness was reported, and orthostatic hypotension did not occur. The target dose of perindopril was 8 mg daily and carvedilol 25 mg twice a day. During the course of the study, the dose of furosemide was titrated to lower values according to the presence or absence of clinical features of congestion and edema. Monthly visits were scheduled for clinical assessment and evaluation of patient's adherence to therapeutic agents. Clinical examinations, echocardiographic assessments, radionuclide studies, and plasma NT-pro-BNP concentrations were determined at baseline, and then repeated at 6 and at 12 months after randomization. The primary end point was LVEF determined by using radionuclide ventriculography. To show a 10-point difference in radionuclide LVEF between groups with 80% power after 12 months of therapy required a sample size of 23 patients in each group.

NYHA FC, echocardiography, and radionuclide studies. A physician who was unaware of the treatment assigned assessed the NYHA FC of the patients during the baseline and follow-up visits. The same physician evaluated all patients.

A multiple-gated equilibrium cardiac blood pool scintigraphic technique was used to measure LVEF (Elscint Apex 409, ELSCINT, Chicago, Illinois), and calculations of LV performance were made as previously described (12). Two-dimensional targeted M-mode echocardiography with Doppler color flow mapping was performed using a Hewlett Packard Sonos 5500 (Philips, Washington, DC) echocardiograph. All studies were performed and interpreted by the same operator and recorded on videotape. Left ventricular dimensions were measured according to the American Society of Echocardiography guidelines (13). Diastolic mitral flow was assessed by pulsed-wave Doppler echocardiography from the apical four-chamber view. The E-wave deceleration time was measured as the interval between the peak early diastolic velocity and the point at which the steepest deceleration slope was extrapolated to the zero line. The investigators that performed and interpreted the radionuclide and echocardiographic studies were unaware of the treatment assigned to patients.

Plasma NT-pro-BNP concentrations. The NT-pro-BNP plasma concentrations were determined by a commercially available enzyme-linked immunosorbent assay (Roche Diagnostics, Mannheim, Germany). The average of triplicate undiluted determinations was calculated.

Statistical analysis. Data are presented as mean values ± SD. A two-way repeated measures analysis of variance with a Tukey post-hoc test was used. To determine differences in changes from baseline, and 6 and 12 months in hemodynamics, NYHA FC and biochemical measurements analysis of covariance (ANCOVA) adjusting for baseline data was used. The relationship between the final dose of carvedilol achieved and changes in both functional and biochemical parameters was determined using ANCOVA adjusting for baseline values. An unpaired Student *t* test was used for comparison of baseline data. Significance was assumed at a two-tailed probability value of <0.05.

RESULTS

Baseline characteristics. Of the 100 patients screened, 22 were not enrolled because they did not fulfill the inclusion or exclusion criteria. Eleven patients died during the 12-month study period (6 in the ACEI-first group), and 10 patients were not available for follow-up (5 in the ACEI-first group). Patients who did not complete the study were not included in the final analysis of the data. There were no differences in

Table 1. Clinical Parameters and Left Ventricular Function at 0, 6, and 12 Months of Therapy in Patients With Heart Failure Receiving Either Perindopril (ACEI-First) or Carvedilol (BB-First Group) as Initial Therapy

Initial Therapy	ACEI-First	BB-First	ACEI-First	BB-First	ACEI-First	BB-First
Months of Treatment	0	0	6	6	12	12
Sample Number	30	27	30	27	30	27
BP (mm Hg)	115 ± 14/76 ± 11	113 ± 15/74 ± 12	121 ± 22/74 ± 16	124 ± 20*/79 ± 15	119 ± 17/73 ± 12	122 ± 19*/75 ± 14
Heart rate (beats/min^{-1})	87 ± 15	88 ± 17	85 ± 16	76 ± 18*‡	76 ± 17*	73 ± 15†
NYHA FC (I/II/II/IV)	4/12/11/1	3/9/12/3	11/11/7/1	13/7/7/0	11/10/9/0	22/3/2/0
LVEDD (mm)	65.5 ± 7.9	65.3 ± 6.8	62.4 ± 7.1	62.0 ± 8.0	62.6 ± 7.9	60.0 ± 11.6†
LVESD (mm)	56.6 ± 7.8	57.6 ± 7.8	53.2 ± 8.2	51.6 ± 10.4†	53.0 ± 8.9	48.5 ± 12.4†
Deceleration time (ms)	154 ± 93	133 ± 45	155 ± 58	207 ± 73†	167 ± 60	204 ± 55†§
E/A	1.46 ± 0.87	1.86 ± 1.25	1.34 ± 0.60	1.27 ± 0.73	1.56 ± 0.79	1.17 ± 0.63*‡

*$p < 0.05$, †$p < 0.005$ versus baseline data (Table 1); ‡$p < 0.05$, §$p < 0.01$ versus change from baseline in the ACEI- first group (analysis of covariance).
ACEI = angiotensin-converting enzyme inhibitor; BB = beta-blocker; BP = blood pressure; E/A = ratio of E wave to A wave velocity; LVEDD = left ventricular end-diastolic diameter; LVESD = left ventricular end-systolic diameter; NYHA FC = New York Heart Association functional class.

baseline hemodynamic, cardiac function, and biochemical characteristics between the groups (Table 1, Figs. 1 to 3). There were no differences between the groups in age (ACEI-first group = 51 ± 11 years, BB-first group = 48 ± 10 years) and percentage of male patients (ACEI-first group = 47%, BB-first group = 44%). There were no differences in hemodynamic, cardiac function, and biochemical or demographic characteristics between patients enrolled, completing 6 months of the study, and completing 12 months of the study (data not shown).

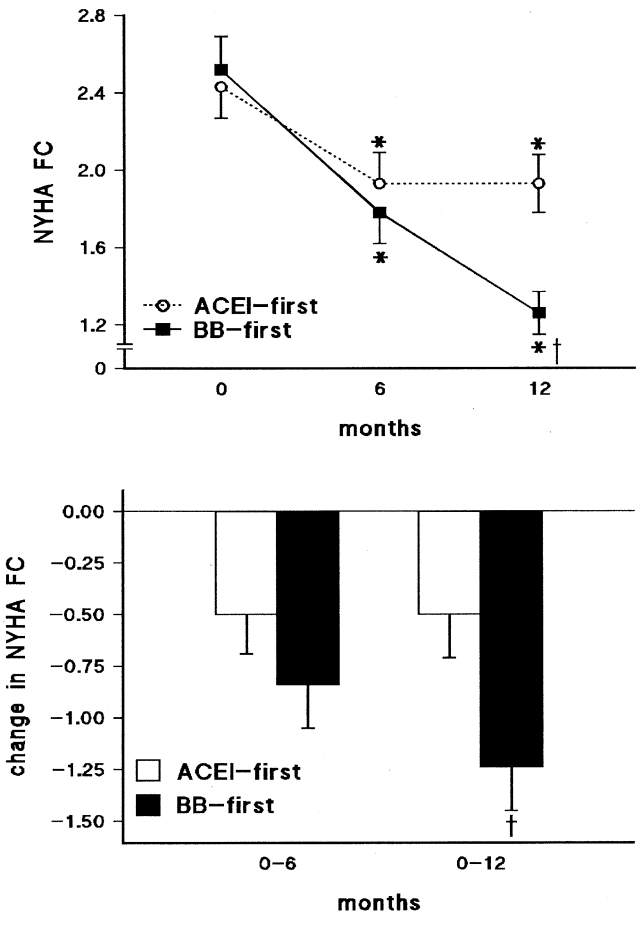

Figure 1. Impact of initiating carvedilol before perindopril therapy (beta-blocker [BB]-first group) compared with the effect of the commencement of perindopril first (angiotensin-converting enzyme inhibitor [ACEI]-first group) on New York Heart Association functional class (NYHA FC). *$p < 0.05$ versus baseline data (0 months); †$p < 0.05$ versus absolute values and change from baseline in the ACEI-first group.

NYHA FC, blood pressure, heart rate, and NT-pro-BNP. In patients in both study groups, there was an improvement in NYHA FC at 6 and 12 months (Fig. 1). In both groups most of the improvement occurred in the first 6 months with minimal additional changes noted between 6 and 12 months (Fig. 1). However, improvement in NYHA FC was consistently greater in the BB-first group (Fig. 1). Hence, NYHA FC at 12 months was lower in the BB-first group (Fig. 1).

Systolic blood pressure was increased at six months in the BB-first group (Table 1), and this change was maintained for the next six months (Table 1). In patients in whom perindopril was initiated at baseline, no alteration in systolic blood pressure was noted (Table 1).

In the BB-first group, a marked reduction in heart rate was noted at both 6 and at 12 months (Table 1). In contrast, in the ACEI-first group, a reduction in heart rate was noted at 12 but not at 6 months (Table 1). A greater decrease in heart rate at 6 but not at 12 months was noted in the BB-first group (Table 1).

LV function and dimensions. There was an increase in LVEF determined using radionuclide techniques in the BB-first group after both 6 and 12 months (Fig. 2). Although there was an increase in LVEF after 12 months in the ACEI-first group (Fig. 2), no significant change in LVEF was noted in the first six months of therapy (Fig. 2). Hence, improvement in LVEF in the BB-first group was largely attributed to the effects of carvedilol. The increase in LVEF and the final LVEF was greater in the BB-first group (radionuclide: 15 ± 16% vs. 6 ± 13%, $p < 0.05$) (Fig. 2). Similar therapeutic trends were noted for LVEF determined using echocardiography (data not shown).

There was a decrease in left ventricular end-systolic diameter (LVESD) after both 6 and 12 months (Table 1) in the BB-first group. In addition there was a decrease in left ventricular end-diastolic diameter (LVEDD) after 12

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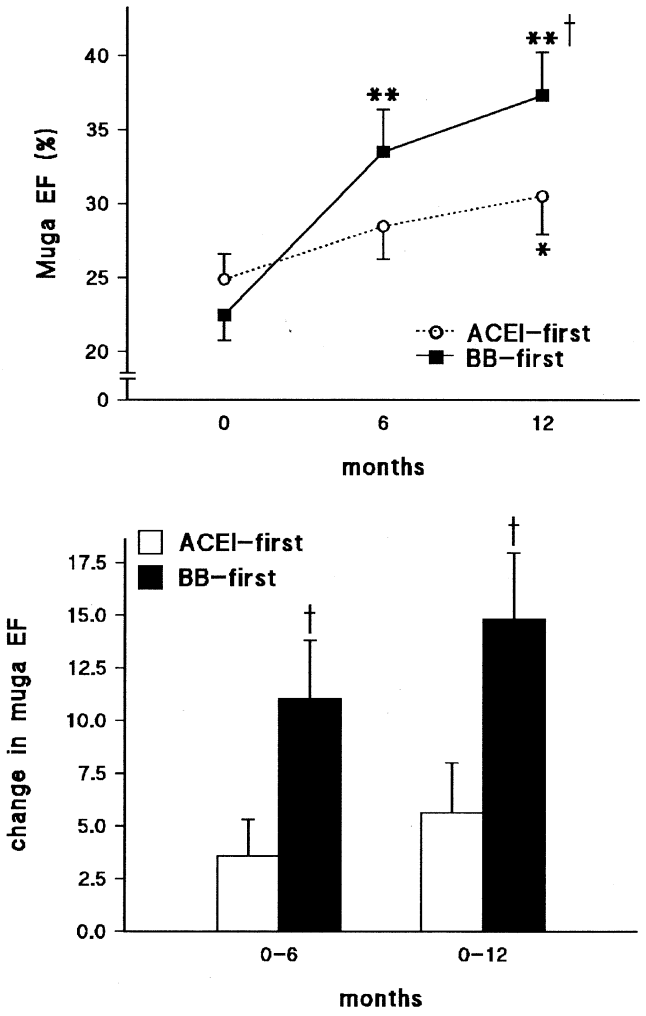

Figure 2. Impact of initiating carvedilol before perindopril therapy (beta-blocker [BB]-first group) compared with the effect of the commencement of perindopril first (angiotensin-converting enzyme inhibitor [ACEI]-first group) on left ventricular ejection fraction (EF), determined using radionuclide techniques. *$p < 0.05$; **$p < 0.001$ versus baseline data (0 months); †$p < 0.05$ versus absolute values and change from baseline in the ACEI-first group. Muga = multiple gated equilibrium cardiac blood pool scintigraphic technique.

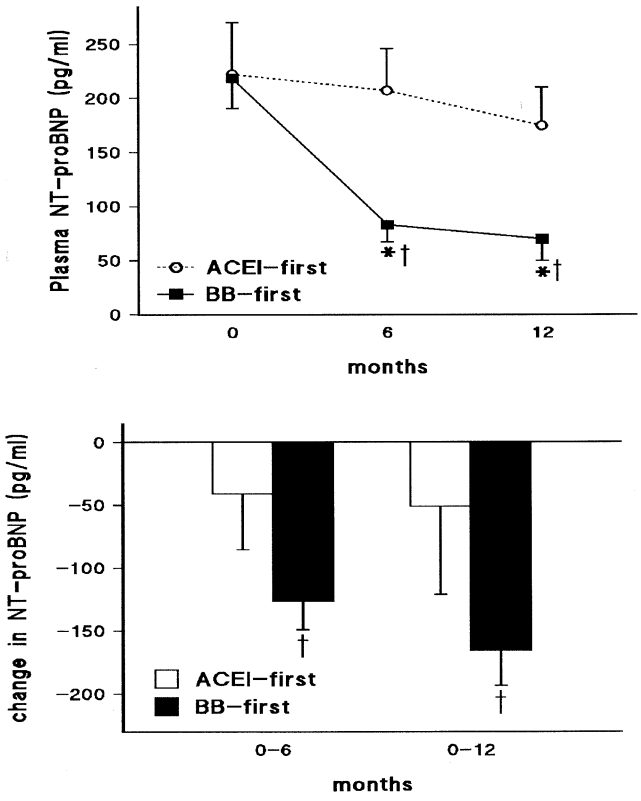

Figure 3. Impact of initiating carvedilol before perindopril therapy (beta-blocker [BB]-first group) compared with the effect of the commencement of perindopril first (angiotensin-converting enzyme inhibitor [ACEI]-first group) on plasma N-terminal-pro-brain natriuretic peptide (NT-pro-BNP) concentrations. *$p < 0.0005$ versus baseline data (0 months); †$p < 0.01$ versus absolute values and change from baseline in the ACEI-first group.

months with a trend for a decrease after 6 months (Table 1) in the BB-first group. In the ACEI-first group, a trend for a reduction in LVESD and LVEDD occurred at both 6 and at 12 months (Table 1), but these changes failed to reach significance.

In the BB-first group, there was a marked prolongation of the deceleration time at both 6 and at 12 months (Table 1) with no significant changes in the ACEI-first group.

Plasma NT-pro BNP concentrations. In both groups of patients, plasma NT-pro-BNP concentrations were markedly raised compared with normal values for healthy, age-matched volunteers from the same population (BB-first group: 219 ± 141 pg/ml; ACEI-first group: 222 ± 254 pg/ml; normal volunteers: 12 pg/ml, $p < 0.0001$). The BB-first group had a marked reduction in plasma NT-pro BNP concentrations at both 6 and 12 months (Fig. 3). In the ACEI-first group, a trend for a reduction in plasma NT-pro-BNP concentrations occurred at 12 months but not at 6 months of therapy (Fig. 3). The decrease in plasma NT-pro-BNP concentrations was, therefore, greater, and final plasma NT-pro-BNP concentrations at 12 months were lower in the BB-first group (166 ± 142 pg/ml vs. 51 ± 384 pg/ml) (Fig. 3).

Dose of medication and relationship with functional changes. All patients received digoxin at a dose of 0.25 mg daily throughout the study. The mean dose of furosemide was lower in the BB-first group (Table 2). Patients in the BB-first tolerated a higher dose of carvedilol at 12 months compared with patients in the ACEI-first group (Table 2). In the ACEI-first group, 13 patients only could tolerate 12.5 mg carvedilol daily, and 3 patients 25 mg carvedilol daily, whereas the rest could tolerate 50 mg daily. In contrast, in the BB-first group, all except two patients (who tolerated a 25-mg dose) could tolerate a 50-mg dose. Maximal tolerable doses of carvedilol were achieved within two months of initiating therapy in both groups. Lower doses of carvedilol were achieved in the ACEI-first group because of complaints of intolerable dizziness at higher doses. No differences in the dose of perindopril were achieved in the two groups (Table 2). An association between the final dose of carvedilol achieved and changes in

Table 2. Doses of Pharmacologic Agents Received After 12 Months of Therapy in Patients With Heart Failure in Whom Either Perindopril (ACEI-First) or Carvedilol (BB-First) Therapy Was Initiated First

	ACEI-First Group	BB-First Group
Furosemide (mg)	116 ± 44	80 ± 37*
Carvedilol (mg)	33 ± 18	43 ± 17*
Perindopril (mg)	7.3 ± 2.1	7.2 ± 1.6

*$p < 0.05$ versus the other group.
Abbreviations as in Table 1.

LVEF (radionuclide values, $p < 0.02$; echocardiographic values, $p < 0.01$), NYHA FC ($p < 0.0001$), and deceleration time ($p < 0.05$) from baseline to 12 months was noted.

DISCUSSION

In the present study, we have shown that, in patients with newly diagnosed congestive cardiac failure, initiation of treatment with carvedilol before, as compared with subsequent to, an ACEI results in greater improvements in LV function and symptoms. Patients receiving carvedilol at the outset tolerated a higher dose of carvedilol and required lower doses of diuretic agents at 12 months after initiating therapy. In the group receiving carvedilol first (BB-first group), better improvements in functional class, more marked changes in LV systolic (LVEF) and diastolic function, and a biochemical index of raised filling pressures (plasma NT-pro-BNP concentrations) were noted.

Although blockers of neurohumoral activation have proven benefits on hemodynamic function and symptoms in heart failure (14–16), the present study is the first to demonstrate that the order of initiation of these agents influences improvements in NYHA FC and both systolic and diastolic function in patients with heart failure and pump dysfunction. Patients who received carvedilol as initial therapy tolerated a higher dose of carvedilol after one year of therapy. The higher dose of the beta-adrenoreceptor blocker achieved in the group receiving carvedilol first could, in part, explain the differences in hemodynamic and symptomatic improvement between the two groups. Indeed, in the present study, the final dose of carvedilol achieved was associated with improvements in LVEF, diastolic function, and NYHA FC. This is consistent with data that demonstrates a better outcome after the use of higher doses of both ACEI and beta-adrenoreceptor blockers in heart failure (17,18).

An alternative explanation for the differences in hemodynamic and symptomatic outcomes between the groups in the present study is that beta-adrenoreceptor blocker therapy is more effective than ACEI therapy in newly diagnosed heart failure. Sympathetic activation occurs before that of the renin-angiotensin-aldosterone system in heart failure, as shown by measurements of plasma neurohormonal levels in the Studies Of Left Ventricular Dysfunction (SOLVD) trials (8). Thus, prevention of the deleterious effects of beta-adrenergic stimulation should be achieved as early as possible if LV dysfunction is present (19). Evidence to support this hypothesis is that marked differences in changes in measures of LV systolic function and functional class between the two groups were noted after six months of therapy.

In the treatment of heart failure, reverse remodeling is regarded as one of the more important determinants of long-term outcome. Although ACEI arrest the remodeling process, no reverse remodeling has been observed with this class of agents (14). In contrast, carvedilol administered to patients with heart failure due to ischemic heart disease reverses LV remodeling (20). In this regard, in the present study, LV diastolic cavity dimensions were reduced in the group of patients in whom carvedilol was initiated first, whereas in those patients receiving the ACEI as initial therapy only a trend for a reduction was noted.

Patients included in the present study had newly diagnosed heart failure due to idiopathic dilated cardiomyopathy. Although temporal changes in the cellular, molecular, biochemical, and interstitial changes that characterize heart failure have been poorly studied in idiopathic dilated cardiomyopathy, an agent with the capacity to modulate these alterations, such as carvedilol (21,22), might be the drug of choice to initiate in order to appropriately reverse the remodeling process.

In the present study, plasma concentrations of NT-pro-BNP were markedly reduced in patients receiving carvedilol compared with perindopril as initial therapy. B-type natriuretic peptide, a cardiac neurohormone synthesized predominantly in the LV of the heart, appears to be a powerful predictor of prognosis in heart failure (23) and has been used to monitor therapy (11). It is, therefore, of potential prognostic importance that patients in the present study receiving carvedilol as initial therapy achieved a more substantial decrease in plasma NT-pro-BNP concentrations compared with those receiving an ACEI first. As BNP has been suggested to be a marker for cardiac remodeling (24), potential mechanisms for its decline in our study could include reverse remodeling in addition to a reduction in ventricular filling and myocardial stretch.

The limitations of the present study include the lack of mortality data, an outcome that cannot be adequately assessed in a single-center study. In addition, this was an open-label rather than double-blind study. Nevertheless, in the present study, assessments of hemodynamic function were conducted by investigators and laboratory technicians unaware of medication received by patients. Lastly, with the design of this study, we were not able to determine whether the benefit seen in the group of patients receiving carvedilol as initial therapy was truly due to the timing of carvedilol administration or rather whether we achieved a carvedilol dose threshold beyond which reverse remodeling occurs.

In conclusion, the present study provides the first evidence to indicate that, in comparison with the conventional approach to treating heart failure, where BBs are added to

ACEI therapy, initiation of carvedilol therapy before an ACEI leads to higher tolerable doses of carvedilol, better improvements in NYHA FC, and more marked changes in LV systolic and diastolic function in patients with newly diagnosed heart failure. These results are encouraging and suggest an alternative therapeutic approach in patients with newly diagnosed heart failure, data that requires confirmation in larger trials with mortality as one of the outcome measures.

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