Tolerability and Efficacy of Carvedilol in Patients With New York Heart Association Class IV Heart Failure

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OBJECTIVES

The purpose of this study was to assess the tolerability and efficacy of carvedilol in patients with New York Heart Association (NYHA) functional class IV symptoms.

BACKGROUND

Carvedilol, a nonselective beta-adrenergic blocking drug with alpha-adrenergic blocking and antioxidant properties, has been shown to improve left ventricular function and clinical outcome in patients with mild to moderate chronic heart failure.

METHODS

We retrospectively analyzed the outcomes of 230 patients with heart failure treated with carvedilol who were stratified according to baseline functional class: 63 patients were NYHA class IV and 167 were NYHA class I, II or III. Carvedilol was commenced at 3.125 mg b.i.d. and titrated to 25 mg b.i.d. as tolerated. Patients with class IV symptoms were older (p<0.03), had lower left ventricular fractional shortening (p<0.001), had lower six-min walk distance (p<0.001) and were receiving more heart failure medications at baseline compared with less symptomatic patients.

RESULTS

Nonfatal adverse events while taking carvedilol occurred more frequently in class IV patients (43% vs. 24%, p<0.0001), and more often resulted in permanent withdrawal of the drug (25% vs. 13%, p<0.01). Thirty-seven (59%) patients who were NYHA class IV at baseline had improved by one or more functional class at 3 months, 8 (13%) were unchanged and 18 (29%) had deteriorated or died. Among the less symptomatic group, 62 (37%) patients had improved their NYHA status at 3 months, 73 (44%) were unchanged and 32 (19%) had deteriorated or died. The differences in symptomatic outcome at three months between the two groups were statistically significant (p<0.001, chi-square analysis). Both groups demonstrated similar significant improvements in left ventricular dimensions and systolic function.

CONCLUSIONS

Patients with chronic NYHA class IV heart failure are more likely to develop adverse events during initiation and dose titration when compared with less symptomatic patients but are more likely to show symptomatic improvement in the long term. We conclude that carvedilol is a useful adjunctive therapy for patients with NYHA class IV heart failure; however, they require close observation during initiation and titration of the drug. (J Am Coll Cardiol 1999; 33:924–31) © 1999 by the American College of Cardiology

Traditionally, beta-adrenergic blocking agents have been considered contraindicated in patients with heart failure due to short-term adverse effects; however, there is clinical evidence dating back to the 1970s that these drugs may be beneficial in selected patients (1,2). These and more recent studies have reported a range of benefits including improved systolic function (1,3–7), improved symptomatic status (3,8,9) and reduced hospitalization (10,11). Furthermore, meta-analyses of the randomized clinical trials of beta-blockers in heart failure suggest that this class of drugs reduces mortality in heart failure by about 35% when added to angiotensin-converting enzyme inhibitors (12,13).

The largest clinical trial experience reported for any beta-blocker in heart failure has been obtained with carvedilol, a nonselective beta-blocker with alpha-blocking and antioxidant properties. In addition to the clinical benefits described above, carvedilol has been shown to produce reverse remodeling of the dilated left ventricle (7) and to delay progression of mild heart failure (14). The randomized clinical trials of carvedilol in heart failure have been conducted predominantly in patients with mild to moderate symptomatic heart failure. As shown in Table 1, only 37 of 1,672 patients entered into randomized studies of carvedilol...
Abbreviations and Acronyms

ANOVA = analysis of variance
ANZ = Australia and New Zealand
LV = left ventricular
LVEDD = left ventricular end-diastolic dimension
LVEDV = left ventricular end-systolic dimension
NYHA = New York Heart Association

in heart failure were New York Heart Association (NYHA) class IV at baseline (5,8–11). Currently, there is very limited information regarding the safety and efficacy of carvedilol or other beta-blockers in patients with severe symptomatic heart failure, that is, those who are in NYHA functional class IV at the time the drug is commenced.

The primary goal of this study was to assess the tolerability and efficacy of carvedilol in chronic heart failure patients who were established in NYHA functional class IV at the time of its initiation. A secondary goal was to determine if there were any baseline characteristics that discriminated between those class IV patients who tolerated carvedilol from those who did not.

METHODS

Patient population. We retrospectively analyzed the outcomes of 230 patients who received carvedilol for the treatment of chronic heart failure. All patients included in this analysis were attending a Heart Failure and Heart Transplant Assessment Clinic at our institution and had been receiving heart failure therapy for at least three months before commencement of carvedilol. All patients had left ventricular systolic dysfunction at baseline as defined by a left ventricular fractional shortening of less than 28% on echocardiography. Patients were not considered for carvedilol if they had any of the following at baseline assessment: cardiogenic shock, intractable pulmonary or systemic edema, heart failure requiring intravenous inotropic or mechanical support, bradycardia with heart rate less than 50 beats/min, systemic hypotension with blood pressure less than 80/50 mm Hg or chronic airflow limitation with evidence of 20% or greater reversibility in airways obstruction in response to inhaled salbutamol. Apart from these exclusions, all class IV patients referred to our Heart Failure Clinic were challenged with carvedilol.

Carvedilol administration. Throughout the duration of this study, carvedilol was available as an investigational agent for the treatment of heart failure (Special Access Scheme of the Therapeutic and Goods Administration Division of the Australian Department of Health). Its use for this indication was approved by the St. Vincent’s Hospital Human Ethics and Research Committee. The decision to use carvedilol was at the discretion of the attending cardiologist (P.S.M. or A.M.K.). Carvedilol was commenced in a dose of 3.125 mg b.i.d. The dose of carvedilol was doubled at two weekly intervals as tolerated up to a target dose of 25 mg b.i.d.

Assessment and follow-up. All patients underwent clinical assessment at baseline, one month and then every three months after commencement of carvedilol. This included an evaluation of NYHA functional status and physical examination including measurement of supine resting heart rate and blood pressure. Patient symptomatic outcome was graded at each follow-up evaluation as “improved,” “unchanged” or “worse” according to changes in NYHA status. Patients who died, were transplanted or who were unable to tolerate carvedilol were considered “worse.” An echocardiogram and 6-min walk test were performed at baseline, and 3-month and 12-month follow-up. Left ventricular (LV) dimensions were made using two-dimensionally guided M-mode echocardiography according to the American Society of Echocardiography standards for LV dimensions (15). Left ventricular ejection fraction was calculated from echocardiographic M-mode dimensions using the formula of Teichholz (16). In addition, the following major clinical events were recorded: worsening heart failure resulting in hospitalization or prolongation of hospitalization, hospitalization for any other reason, heart transplantation and death.

Statistical analysis. Unless otherwise stated data are presented as mean ± standard error of the mean. Comparisons between classes were made using factorial analysis of variance (ANOVA) for continuous variables and chi-square analyses for categorical variables. For continuous variables in which the p value was <0.05 by ANOVA, post hoc analyses with unpaired t tests using Bonferroni correction were used to detect differences between individual classes. Comparisons between the less symptomatic group and the class IV patients were made using unpaired t tests for continuous variables and chi-square analyses for categorical variables. Kaplan–Meier cumulative survival curves were constructed for each group to compare mortality and the incidence of adverse events. Differences between Kaplan–Meier curves were tested for significance using the Mantel–Cox log-rank test. A p value <0.05 was considered significant.

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Patients</th>
<th>NYHA Class IV Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metra et al. (5)</td>
<td>40</td>
<td>0</td>
</tr>
<tr>
<td>Olsen et al. (8)</td>
<td>60</td>
<td>0</td>
</tr>
<tr>
<td>Krum et al. (9)</td>
<td>65</td>
<td>5</td>
</tr>
<tr>
<td>ANZ Study (11)</td>
<td>415</td>
<td>0</td>
</tr>
<tr>
<td>U.S. Carvedilol Heart Failure Program (10)</td>
<td>1,094</td>
<td>32</td>
</tr>
<tr>
<td>Total</td>
<td>1,674</td>
<td>37</td>
</tr>
</tbody>
</table>

ANZ = Australia and New Zealand; NYHA = New York Heart Association.
RESULTS

Patient population. The distribution of patients according to baseline NYHA functional class at the time of initiation of carvedilol and selected baseline characteristics for the study population are shown in Table 2. Compared with the less symptomatic patients, those with NYHA class IV heart failure at baseline were significantly older and were more likely to have ischemic heart disease. They had lower fractional shortening and ejection fraction as assessed by echocardiography. In addition, they had a significantly lower baseline 6-min walk distance. The use of digoxin and direct acting vasodilators was significantly higher in NYHA class IV patients. Overall, just one third of patients were receiving amiodarone therapy at baseline with no significant difference between the class IV and the less symptomatic patients. There were also nonsignificant trends toward a higher resting heart rate and larger LV end-systolic dimension in the class IV patients.

In subsequent analyses, the 167 patients who were NYHA functional class I, II or III (less symptomatic group) were compared with the remaining 63 patients in NYHA functional class IV heart failure. The mean duration of follow-up was 365 days (range: 96 to 749 days). The average maintenance dose of carvedilol was 32 ± 2 mg per day in the less symptomatic group versus 36 ± 2 mg per day in the class IV group (p = NS).

Actuarial survival. Actuarial survival for the two groups is shown in Figure 1. One-year actuarial survival for the less symptomatic group was 94 ± 2% compared with 84 ± 5% for the NYHA class IV patients (p < 0.01). Actuarial transplant-free survival for the less symptomatic group was 90 ± 3% at one year compared with 77 ± 6% for the NYHA class IV patients (p < 0.001).

Tolerability of carvedilol—adverse events. Serious adverse events excluding death or transplantation occurred in 24% of the less symptomatic group compared with 43% of class IV patients (p < 0.0001) and resulted in permanent withdrawal of carvedilol in 13% and 25%, respectively. Nonfatal adverse events are summarized in Table 3. The major difference between the two groups was in the higher rate of worsening heart failure in the class IV patients compared with the less symptomatic patients. Worsening heart failure occurred in 16 (10%) of the less symptomatic group and 14 (21%) of the class IV group (p < 0.05); however, carvedilol was able to be resumed or continued in

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### Table 2. Selected Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Class I (n = 10)</th>
<th>Class II (n = 45)</th>
<th>Class III (n = 112)</th>
<th>Class IV (n = 63)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>45 ± 1</td>
<td>52 ± 2</td>
<td>54 ± 1</td>
<td>57 ± 2*</td>
</tr>
<tr>
<td>Gender (% male)</td>
<td>90</td>
<td>84</td>
<td>84</td>
<td>89</td>
</tr>
<tr>
<td>Diagnosis (CM:IHD:other)</td>
<td>8:2:0</td>
<td>28:14:3</td>
<td>67:35:10</td>
<td>27:32:4*</td>
</tr>
<tr>
<td>Duration (months)</td>
<td>30 ± 12</td>
<td>30 ± 5</td>
<td>33 ± 6</td>
<td>28 ± 4</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>83 ± 5</td>
<td>79 ± 2</td>
<td>82 ± 2</td>
<td>86 ± 2</td>
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<tr>
<td>Echocardiographic measures</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEDD (mm)</td>
<td>77 ± 3</td>
<td>73 ± 2</td>
<td>72 ± 1</td>
<td>75 ± 1</td>
</tr>
<tr>
<td>LVESD (mm)</td>
<td>64 ± 5</td>
<td>62 ± 2</td>
<td>62 ± 1</td>
<td>67 ± 2</td>
</tr>
<tr>
<td>FS (%)</td>
<td>18 ± 3</td>
<td>15 ± 1</td>
<td>14 ± 1</td>
<td>11 ± 1†</td>
</tr>
<tr>
<td>EF (%)</td>
<td>29 ± 5</td>
<td>26 ± 1</td>
<td>24 ± 1</td>
<td>19 ± 1†</td>
</tr>
<tr>
<td>6-min walk (m)</td>
<td>580 ± 31</td>
<td>513 ± 13</td>
<td>417 ± 10‡</td>
<td>321 ± 16†</td>
</tr>
<tr>
<td>Treatment (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE inhibitors</td>
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<td>97</td>
<td>97</td>
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<td>Diuretics</td>
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<tr>
<td>Antithrombotic</td>
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<td>67</td>
<td>82</td>
<td>80</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>20</td>
<td>31</td>
<td>40</td>
<td>35</td>
</tr>
</tbody>
</table>

*p < 0.05 class IV vs. other classes. †p < 0.001 class IV vs. other classes. §p < 0.005 class III vs. classes I or II.

ACE = angiotensin-converting enzyme; CM = cardiomyopathy; EF = ejection fraction; FS = fractional shortening; IHD = ischemic heart disease; LVEDD = left ventricular end-diastolic dimension; LVESD = left ventricular end-systolic dimension.
11 of these patients (eight less symptomatic and three class IV patients) after adjustment of concomitant antifailure therapy.

Symptomatic bradyarrhythmias occurred in only 3% of patients with no difference between class IV and less symptomatic patients. Concurrent amiodarone therapy, which was used in approximately one third of all patients, did not increase the incidence of bradyarrhythmias.

Figure 2 shows the actuarial freedom from adverse events in the two patient groups. Most adverse events occurred within the first six weeks of commencement of carvedilol therapy with more than half occurring during the first two weeks, when patients were receiving the lowest dose of carvedilol.

**Predictors of adverse events in class IV heart failure patients.** Table 4 shows a comparison of selected baseline variables between NYHA class IV patients who experienced an adverse event during follow-up and those who did not. Two variables differed significantly between the two groups on univariate analysis. Class IV patients who experienced an adverse reaction attributable to carvedilol had a significantly lower systolic blood pressure and lower serum sodium at baseline compared with patients who did not (Table 4). Linear regression analysis revealed a highly significant relationship between serum Na⁺ and systolic blood pressure (p < 0.001). Serum Na⁺ was the most potent predictor of an adverse event. Fifteen of 24 (63%) patients who were hyponatremic (serum Na⁺ <137 mmol/liter) at baseline experienced an adverse event during follow-up compared with 8 of 39 (20%) class IV patients who had a normal serum Na⁺ level at baseline (p < 0.002).

**Efficacy of carvedilol—symptomatic outcome.** Symptomatic outcome data were available on all patients after 3 months; 37 (59%) of 63 patients who were NYHA class IV at baseline had improved by one or more functional class at 3 months, 8 (12%) were unchanged and 18 (29%) had deteriorated or died. Of the 37 NYHA class IV patients who improved at 3 months, 21 improved to NYHA class II and 3 improved to NYHA class I. Among the less symptomatic group, 63 (37%) of 167 patients had improved their NYHA status at 3 months, 73 (44%) were unchanged and 32 (19%) had deteriorated or died. The differences in symptomatic outcome at 3 months between the two groups were statistically significant (p = 0.001, chi-square analysis). The differences in symptomatic outcome between the two groups were unaffected by exclusion of seven patients (three class IV and four class III) who underwent heart transplantation within three months of commencing carvedilol.

Increases in concomitant heart failure therapy (predominantly diuretic dosage) during the first three months of carvedilol treatment were made in 15% of the less symptomatic group and 22% of the class IV group (p = NS compared with the less symptomatic group). Increases in concomitant therapy were made predominantly in those patients whose symptomatic status worsened during carve-
dilol treatment. Only 2 of 99 patients who improved during the first 3 months of carvedilol treatment (one in each group) were receiving increased concomitant heart failure therapy after 3 months.

**Efficacy of carvedilol—left ventricular dimensions and systolic function.** The effect of carvedilol on left ventricular dimensions at three months as assessed by echocardiography is shown in Figure 3. Paired baseline and 3-month echocardiograms suitable for comparative analysis were obtained in 163 (86%) of 190 patients who continued on carvedilol beyond 3 months. Left ventricular end-systolic dimension (LVESD) decreased significantly in both groups after 3 months of carvedilol treatment; mean LVESD fell by 4.0 \( \pm \) 1.0 mm in NYHA class IV patients \((n = 41, p < 0.0005\) compared with baseline) and by 3.3 \( \pm \) 0.6 mm in NYHA class I–III patients \((n = 122, p < 0.0001\) compared with baseline). Left ventricular end-diastolic dimension (LVEDD) also decreased, but the difference only achieved significance in the less symptomatic group; mean LVEDD fell by 1.3 \( \pm \) 0.9 mm in NYHA class I–III patients \((n = 122, p < 0.0001\) compared with baseline). Left ventricular end-diastolic dimension (LVEDD) decreased, and the difference only achieved significance in the less symptomatic group; mean LVEDD fell by 1.3 \( \pm \) 0.9 mm in NYHA class I–III patients \((n = 122, p < 0.0001\) compared with baseline). Left ventricular fractional shortening increased by 2.8 \( \pm \) 0.6% in the less symptomatic group \((n = 122, p < 0.0001\) compared with baseline) and 4.0 \( \pm \) 0.9% in the class IV patients \((n = 41, p < 0.0001\) compared with baseline). Corresponding increases in calculated LV ejection fraction were 4.7 \( \pm \) 0.9% and 6.9 \( \pm \) 1.5%, respectively.

**Efficacy of carvedilol—6-min walk distance.** The effect of carvedilol on 6-min walk distance is shown in Figure 5. The 6-min walk distance improved by 38 \( \pm \) 7 meters \((n = 121, p < 0.001\) compared with baseline) in the less symptomatic patients and by 76 \( \pm \) 18 meters \((n = 39, p = 0.0002\) compared with baseline) in the NYHA class IV patients.

**DISCUSSION**

**Tolerability of carvedilol.** The primary finding of this study was that carvedilol was tolerated by most heart failure patients who were NYHA class IV at the time of initiation of carvedilol. Overall, 71% of this group tolerated long-term carvedilol treatment, with 59% showing symptomatic im-

![Figure 3](image-url)  
**Figure 3.** Change in left ventricular (LV) end-diastolic dimension (solid bar) and end-systolic dimension (hatched bar) after three months of therapy with carvedilol. **p < 0.002, ****p < 0.0001** compared with baseline. Paired data were obtained in 122 New York Heart Association (NYHA) class I–III patients and 41 class IV patients.

![Figure 4](image-url)  
**Figure 4.** Change in left ventricular fractional shortening (solid bar) and ejection fraction (hatched bar) after 3 months of therapy with carvedilol. ****p < 0.0001 compared with baseline. Paired data were obtained in 122 New York Heart Association (NYHA) class I–III patients and 41 class IV patients.

![Figure 5](image-url)  
**Figure 5.** Change in 6-min walk distance after 3 months of therapy with carvedilol. Open circles = New York Heart Association classes I to III \((n = 121)\); solid circles = class IV \((n = 39)\).
provement by three months. This improvement in symp-
toms was associated with significant improvements in LV
dimensions and contraction as assessed by echocardiography
and in 6-min walk distance. It is important to emphasize
that not all class IV patients were commenced on carvedilol.
In particular, patients were not considered for carvedilol if
they were in cardiogenic shock, or had intractable pulmo-
nary or systemic edema or heart failure requiring intrave-
nous inotropic support or mechanical support. In addition,
patients were excluded if they had a resting bradycardia with
heart rate less than 50 beats per minute, systemic hypoten-
sion with blood pressure less than 80/50 mm Hg or asthma.
Apart from these exclusions, all class IV patients referred to
our heart failure clinic were challenged with carvedilol. We
believe that the class IV patients whom we enrolled were
broadly representative of class IV patients referred to our
center and were not a highly selected group. The mean
systolic blood pressure for the class IV patients at baseline
was 101 mm Hg, and 40% were hyponatremic or had a
systolic blood pressure less than 90 mm Hg at the time of
initiation of carvedilol.

As expected, carvedilol was better tolerated by the less
symptomatic group of heart failure patients. We found that
approximately 90% of heart failure patients who were
NYHA class I–III at baseline tolerated long-term carve-
dilol. This experience is consistent with that of the U.S.
Heart Failure Program (10) and the Australia and New
Zealand (ANZ) Study Group (11), both of whom studied
similar patient populations. Packer et al. (10) reported that
1.4% of patients did not tolerate open-label run-in, and a
further 5.7% were withdrawn after randomization due to
adverse events. In the ANZ Study (11), 3.6% of patients did
not tolerate open-label run-in, and 14% of patients were
withdrawn from carvedilol after randomization. In a study
of patients with more severe heart failure, most of whom
were class III at baseline, Krum et al. (9) reported that
12.5% of patients died or were withdrawn from carvedilol
during open-label run-in, and 37% developed worsening
heart failure after randomization. When compared in
relation to the present findings, these results indicate that
the likelihood of serious adverse events necessitating with-
drawal of carvedilol increases with increasing NYHA func-
tional class at baseline. Nonetheless, our findings suggest
that carvedilol is a useful adjunctive therapy in selected
NYHA class IV patients, some of whom show dramatic
symptomatic improvement.

**Adverse events.** The major difference in nonfatal adverse
events between the class IV and the less symptomatic
patients was the more than twofold increase in the incidence
of worsening heart failure in the former group. If patients
developed adverse symptoms during initiation and titration
of carvedilol therapy, we attempted to adjust concurrent
therapies to allow continuation of carvedilol. In general,
worsening heart failure was treated with either an increased
diuretic or nitrate therapy. Further up-titration of carvedilol
was only attempted after the symptoms and signs of
worsening heart failure resolved completely. Approximately
one third of patients who developed worsening heart failure
on carvedilol were able to be maintained on the drug
chronically. Sackner-Bernstein et al. (17) have reported that
such patients have a similar favorable long-term outcome to
patients who tolerate carvedilol at the first attempt.

Other recognized adverse reactions to carvedilol therapy,
namely symptomatic bradycardia, hypotension and fatigue,
were infrequent and occurred with similar frequency in the
two groups. Most adverse events occurred during initiation
and titration of carvedilol. This occurred despite commen-
tence of carvedilol at a dose of only 3.125 mg twice
daily. Indeed, more than half the adverse events occurred
during the first two weeks of carvedilol therapy. Clearly,
patients with NYHA class IV heart failure require close
observation during initiation of carvedilol. The class IV
patients who were at most risk of adverse events were those
who were hyponatremic at the time of commencement of
carvedilol. Sackner-Bernstein et al. (17) also found that
hyponatremia was the most powerful predictor of adverse
events after initiation of carvedilol in patients with moderate
to severe heart failure. This is not surprising. Hyponatremia
has been shown to correlate closely with neurohormonal
activation in heart failure, particularly of the renin–
angiotensin system (18), and is an independent predictor of
mortality in patients with severe heart failure (19,20).

Furthermore, as noted in the present study, hyponatremic
patients are more likely to be hypotensive (18,19). They are
also more likely to have evidence of impaired peripheral and
renal perfusion than class IV heart failure patients with
normal serum sodium (18,19). Our current policy is to
admit all class IV patients with hyponatremia or hypoten-
sion to hospital during initiation of carvedilol.

**Symptomatic outcome.** Our findings with regard to the
effect of carvedilol on symptomatic status in class I–III heart
failure at three months are consistent with those reported in
the ANZ Study at six months (21). In the ANZ Study, 23%
had improved, 65% were unchanged and 12% had deterio-
rated by six months. In comparison, 33% of patients
improved, 45% were unchanged and 23% deteriorated after
three months of carvedilol therapy in our study. In contrast,
class IV patients as a group tended to either improve or
deteriorate on carvedilol. Although the hazards of carvedilol
are clearly greatest in class IV patients, this group potentially
has the most to gain from this therapy, because more than
half improved their symptomatic status after three months
of therapy. The improvement in symptomatic status after
initiation of carvedilol cannot be attributed to changes in
concomitant heart failure therapy, because only 2 of 99
patients who had improved their symptomatic status after 3
months of carvedilol treatment were receiving increased
doses of concomitant heart failure medications.

**Left ventricular size and function.** Several studies have
demonstrated a favorable effect of carvedilol on left ventric-
ular dimensions (11,21) and LV systolic function (5,6,8,11) in patients with chronic heart failure. Our study demonstrates that these beneficial effects of carvedilol extend to class IV patients. Furthermore the magnitude of the improvement observed in class IV patients is comparable to that observed in the less symptomatic patients. This finding provides a further rationale for the use of carvedilol in these patients, as Packer et al. (22) have recently reported that the clinical benefits of carvedilol noted in the U.S. Carvedilol Heart Failure Program were closely correlated with the drug’s beneficial effects on LV systolic function.

**Six-minute walk distance.** Previous studies have reported conflicting results regarding the effects of carvedilol and other beta-blocking drugs on exercise performance in patients with heart failure (23). In view of the well recognized ability of beta-blockers to attenuate exercise-induced increases in heart rate (24), Krum et al. (9) have suggested that submaximal rather than maximal exercise performance may provide a more accurate assessment of the effect of beta-blockade on functional capacity in patients with heart failure; however, the effects of carvedilol on this parameter have also been conflicting (5,8,9,21). One possible explanation for this discrepancy is the difference in baseline symptomatic status between studies. Studies that recruited patients with milder symptoms (8,21) have generally failed to show a significant improvement in submaximal exercise performance, whereas studies with a greater proportion of more symptomatic patients (5,9) have shown a positive treatment effect. Overall, we found that heart failure patients significantly improved their 6-min walk distance after three months of carvedilol treatment. The average increase in walk distance seen in the less symptomatic group after three months was very similar to that reported by Krum et al. (9). The class IV patients showed an even greater improvement observed in class IV patients is comparable to the less symptomatic patients. This finding provides a further rationale for the use of carvedilol in these patients, as Packer et al. (22) have recently reported that the clinical benefits of carvedilol noted in the U.S. Carvedilol Heart Failure Program were closely correlated with the drug’s beneficial effects on LV systolic function.

**Actuarial survival.** The one-year mortality in the class I–III group was only 6 ± 3%. This is similar to the mortality rate reported for comparable patients receiving carvedilol reported in the U.S. Heart Failure program (10) and the ANZ Carvedilol Study (11). Not surprisingly, mortality was higher in the class IV patients than in the less symptomatic group. In the absence of a matched control group it is not possible to determine the impact of carvedilol on mortality in class IV patients; however, the one-year mortality of 16 ± 5% in this patient group treated with carvedilol compares favorably with the mortality reported for similar patient groups in other studies (19,25–27). The impact of carvedilol on mortality in patients with NYHA class IV heart failure is currently being addressed in the ongoing Copernicus Study.

**Study limitations.** The major limitations of this study were the lack of a control group and the open-label administration of carvedilol. We can only speculate regarding the extent to which placebo response and observer (patient and doctor) bias contributed to the observed benefits of carvedilol in our patients, particularly with respect to the improved 6-min walk distance that we observed; however, the other outcomes that we observed in the class I–III patients were highly consistent with what has been reported previously in placebo-controlled randomized studies.

The greater tendency for the class IV patients to improve their symptomatic status after the initiation of carvedilol compared with the less symptomatic patients may simply reflect an inherent bias in the analysis. Class IV patients could only feel better and not worse. At the other end of the spectrum, class I patients could only deteriorate, whereas class II and III patients could either improve or worsen their symptomatic status. We attempted to address this bias by categorizing all patients who died, underwent transplantation or failed to tolerate carvedilol as having a worse functional outcome; 29% of class IV patients fell into this category.

Another limitation is the relatively young age of our heart failure population compared with the average age of heart failure patients in the general community (28). We did not exclude any patients for carvedilol therapy because of age and believe that the relatively young age of the patients reported in this series simply reflects the referral bias toward younger patients to our transplant program. Forty-three patients in this series were over 65 years of age at the time of commencement of carvedilol. After adjusting for differences in baseline functional class, we did not observe any difference in their response to carvedilol compared with the younger patients (data not shown). Fisher et al. (29) have also reported that beta-blockers are well tolerated by elderly heart failure patients.

**Conclusions.** Most patients with chronic NYHA class IV heart failure tolerate carvedilol and show benefits in both symptomatic status and left ventricular size and function three months of therapy. As a group, they are more likely to develop adverse events during initiation and dose titration, when compared with less symptomatic patients, but are more likely to show symptomatic improvement in the long term. The risk of adverse events is particularly high in class IV patients who are hyponatremic at the initiation of carvedilol. We conclude that carvedilol is a useful adjunctive therapy for patients with NYHA class IV heart failure; however, they require close observation during initiation and titration of the drug.

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