PRELIMINARY COMMUNICATION

Carvedilol for Children and Adolescents With Heart Failure

A Randomized Controlled Trial

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Context Although β-blockers improve symptoms and survival in adults with heart failure, little is known about these medications in children and adolescents.

Objective To prospectively evaluate the effects of carvedilol in children and adolescents with symptomatic systemic ventricular systolic dysfunction.

Design, Setting, and Participants A multicenter, randomized, double-blind, placebo-controlled study of 161 children and adolescents with symptomatic systolic heart failure from 26 US centers. In addition to treatment with conventional heart failure medications, patients were assigned to receive placebo or carvedilol. Enrollment began in June 2000 and the last dose was given in May 2005 (each patient received medication for 8 months).

Interventions Patients were randomized in a 1:1:1 ratio to twice-daily dosing with placebo, low-dose carvedilol (0.2 mg/kg per dose if weight <62.5 kg or 12.5 mg per dose if weight ≥62.5 kg), or high-dose carvedilol (0.4 mg/kg per dose if weight <62.5 kg or 25 mg per dose if weight ≥62.5 kg) and were stratified according to whether each patient's systemic ventricle was a left ventricle or not.

Main Outcome Measures The primary outcome was a composite measure of heart failure outcomes in patients receiving carvedilol (low- and high-dose combined) vs placebo. Secondary efficacy variables included individual components of this composite, echocardiographic measures, and plasma b-type natriuretic peptide levels.

Results There was no statistically significant difference between groups for the composite end point based on the percentage of patients who improved, worsened, or were unchanged. Among 54 patients assigned to placebo, 30 improved (56%), 16 worsened (30%), and 8 were unchanged (15%); among 103 patients assigned to carvedilol, 58 improved (56%), 25 worsened (24%), and 20 were unchanged (19%). The rates of worsening were lower than expected. The odds ratio for worsened outcome for patients in the combined carvedilol group vs the placebo group was 0.79 (95% CI, 0.36-1.59; $P = .47$). A prespecified subgroup analysis noted significant interaction between treatment and ventricular morphology ($P = .02$), indicating a possible differential effect of treatment between patients with a systemic left ventricle (beneficial trend) and those whose systemic ventricle was not a left ventricle (nonbeneficial trend).

Conclusions These preliminary results suggest that carvedilol does not significantly improve clinical heart failure outcomes in children and adolescents with symptomatic systolic heart failure. However, given the lower than expected event rates, the trial may have been underpowered. There may be a differential effect of carvedilol in children and adolescents based on ventricular morphology.

Trial Registration clinicaltrials.gov Identifier: NCT00052026

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HEART FAILURE DUE TO SYSTEMIC ventricular dysfunction is a significant medical problem for children and represents the reason for at least 50% of pediatric referrals for heart transplantation.[1] To date, there have been no large randomized controlled trials of any medication in children and adolescents with chronic heart failure. Treatment recommendations in children and adolescents with heart failure are extrapolated from the results of clinical trials conducted in adults, which may be problematic.[2]

For editorial comment see p 1214.

Although multiple studies in adults have demonstrated beneficial effects of β-blockers on left ventricular function, symptoms, and survival,[3-7] little is

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known about their effects in children and adolescents with heart failure resulting from systemic ventricular dysfunction. Small, nonrandomized studies have suggested a possible beneficial effect of β-blockers in children with heart failure[8-13]; however, these are limited by sample size and lack of contemporaneous control populations. Although several β-blockers have been shown to be efficacious in heart failure in adults, carvedilol may be superior.[14] This may be due to its dual mechanism of action: nonselective β-blockade and vasodilation due primarily to α_1-blockade.[15] We sought to prospectively evaluate the effects of carvedilol in children and adolescents with symptomatic systemic ventricular systolic dysfunction.

METHODS

A detailed description of this study has been published.[16] This study was designed, executed, and analyzed by a steering committee (which also functioned as an end point committee), a data coordinating center, and a data and safety monitoring board, all of whom operated independently of the study's sponsor. The data and safety monitoring board reviewed safety data only; there was no interim analysis of the efficacy outcomes. The protocol was approved by the institutional review boards of all participating institutions. Written, dated informed consent was obtained from all parents or guardians of all patients, and informed assent was obtained from all children and adolescents older than 9 years.

Study Patients

Patients were enrolled at 26 centers in the United States. Patients had to be younger than 18 years with chronic symptomatic heart failure due to systemic ventricular systolic dysfunction. On echocardiography, patients with systemic left ventricular dysfunction were required to have an ejection fraction of less than 40%, while qualitative evidence of ventricular dilation with at least moderate systemic ventricular systolic dysfunction was required for enrollment in patients with a systemic right ventricle or single ventricle.

Heart failure etiology included dilated cardiomyopathy and congenital heart disease. All patients were receiving standard heart failure therapy for at least 1 month at the time of randomization, including angiotensin-converting enzyme inhibitors unless contraindicated or if patients could not tolerate it. Patients were to be in optimal fluid status prior to enrollment.

Study Design

The primary objective was to compare the efficacy of carvedilol administered twice daily for 8 months with placebo on a composite measure of clinical heart failure outcomes in children and adolescents with symptomatic systemic ventricular systolic dysfunction.

The secondary objectives were to evaluate (1) the effect of carvedilol on selected individual components of the composite measure; (2) the effect of carvedilol on echocardiographic indices of ventricular function and remodeling; (3) drug levels of carvedilol in pediatric heart failure patients; (4) effects of carvedilol on b-type natriuretic peptide (BNP); and (5) to establish the safety and tolerability of carvedilol in patients with pediatric heart failure.

This was a multicenter, randomized, double-blind, placebo-controlled, intent-to-treat, parallel-design study. Patients fulfilling all entry criteria were randomized to twice-daily dosing with placebo, low-dose carvedilol (target dose of 0.2 mg/kg per dose if weight $<$62.5 kg or 12.5 mg per dose if weight $\geq$62.5 kg) or high-dose carvedilol (target dose of 0.4 mg/kg per dose if weight $<$62.5 kg or 25 mg per dose if weight $\geq$62.5 kg) in a double-blind manner following a ratio of 1:1:1. Patients also were stratified according to the investigators' determination of whether the anatomic substrate of each patient's systemic ventricular dysfunction was a left ventricle or not a left ventricle. Randomization was stratified by both site and systemic ventricular substrate using permuted blocks of 3 within each stratum. Doses were titrated every 2 weeks as tolerated through 4 levels. The maximum tolerated or target dose was then maintained for 6 additional months of follow-up.

Primary Efficacy End Point

Patients were determined to have a response of worsened, improved, or unchanged. Worsened was defined as death; hospitalization for more than 24 hours for worsening heart failure requiring intravenous heart failure medication; permanent discontinuation of double-blind treatment due to worsening heart failure, treatment failure, lack of or insufficient therapeutic response, withdrawal of consent, or other administrative reason with worsening heart failure at the time of discontinuation; demonstrated worsening in heart failure class (New York Heart Association/Ross heart failure classification) at last observation carried forward; or moderate-marked worsening of global assessment score at last observation carried forward.

Improved was defined as a condition not worsening (as defined above), and demonstrated improvement in heart failure class at last observation carried forward, and/or moderate-marked improvement in global assessment score at last observation carried forward.

Unchanged was defined as neither improvement nor worsening.

The last observation carried forward was defined as the last value during the study period, in which the study period was defined for completers as the period from the first dose to 1 day after the last dose of randomized medication. For patients who were prematurely withdrawn from study medication, the study period was defined as the period from the first dose to 1 day after the planned last maximum dose of randomized medication (ie, 8 months after the first dose of randomized medication).

Secondary Efficacy End Points

Individual components of the heart failure composite response variables analyzed included all-cause mortality, hospitalization for worsening heart failure,

cardiovascular hospitalization, New York Heart Association/Ross heart failure classification, and global assessment scores.

The physician responded to the question "Specifically in reference to the patient's heart failure signs and symptoms, how does the patient's clinical status today compare to his/her status prior to taking the study medication?" The patient/parent responded to this question "Specifically in reference to you/your child's heart failure symptoms, how do/does you/your child feel today as compared to how you/your child felt before taking this medication?"

Parameters for patients with left ventricular systolic dysfunction were ejection fraction (Simpson method), shortening fraction (M mode), left ventricular end systolic and diastolic dimensions (M mode), left ventricular end systolic and diastolic volumes, left ventricular mass (area-length method), and degree of mitral regurgitation (none, mild, moderate, severe).[17] For patients with systemic right or single ventricular systolic dysfunction, the parameters were: (1) a qualitative assessment of systemic ventricular systolic function (normal, mildly depressed, moderately depressed, or severely depressed); and (2) a semiqualitative assessment of the degree of systemic atrioventricular valve regurgitation using the ratio of the maximal regurgitant jet area and the left (or pulmonary venous) atrial area.

Plasma BNP levels were measured at baseline and at the end point. Samples were assayed by enzyme immunoassay.

Safety was assessed by adverse events, clinical chemistry parameters (serum creatinine, aspartate aminotransferase, alanine aminotransferase), hematology (hemoglobin, hematocrit, white blood cell count, and platelet count), serum digoxin levels, urine pregnancy test, blood pressure, heart rate, cardiopulmonary examinations, height, weight, and electrocardiograms.

Plasma samples to assess steady-state trough concentrations were analyzed for both R(+)–carvedilol and S(–)–carvedilol by high-performance liquid chromatography fluorescence. The S(–)–enantiomer has β-blocking activity, while both enantiomers possess α_1-blocking activity. A total of 100 samples from 74 patients in the carvedilol groups were available for descriptive analysis.

Statistical Analysis

The prespecified primary analysis compared the combined carvedilol group (low dose and high dose) with the placebo group. Sample size determinations were based on the assumption that 19% would improve in the placebo group, 35% would be unchanged, and 46% would worsen; in the combined carvedilol group, 39% would improve, 37.5% would be unchanged, and 23.5% would worsen. The target sample size of 150 patients (2:1 randomization) would provide 88% power to detect a difference in responses between placebo and the combined carvedilol group with an α level of .05.

The prespecified primary analysis compared the combined carvedilol group with the placebo group using a Wilcoxon rank sum test for the 3 (ordered) categories of composite outcome. A prespecified secondary analysis examined the categories improved vs not improved and worsened vs not worsened as outcomes in logistic regression models using ventricular strata, age, and sex as covariates along with treatment group. Because there was evidence of an interaction between treatment and ventricular morphology for the improved outcome in these models, odds ratios (ORs) and 95% confidence intervals (CIs) adjusted for age and sex within each ventricular stratum were generated per the prespecified analysis plan.

Two prespecified groupings based on age at study entry were used (1) birth to 24 months, older than 24 months to younger than 60 months, older than 60 months to Tanner stage 3, Tanner stage 4 through aged 17 years; (2) birth to Tanner stage 2; Tanner stage 3 through aged 17 years. Because of the unexpectedly large number of patients younger than 2 years enrolled (45%), a post hoc analysis of those younger than 24 months and those older than 24 months was performed.

Hazard ratios for mortality and hospitalization were determined using time-to-event Cox proportional hazard regression analyses. Valve regurgitation was graded as 0 (none), 1 (mild), 2 (moderate), or 3 (severe). Qualitative assessment of depressed systolic function for patients with non–left ventricle dysfunction was graded as mild (0), moderate (1), or severe (2). Within-treatment comparisons of continuous echocardiographic values between baseline and month 6 maintenance were made using a paired *t* test, while BNP levels and categorical assessments were compared using a Wilcoxon signed rank test. Comparisons of changes over the study period in echocardiographic indices between the 3 ordered treatment groups (placebo, low dose, high dose) were made using an ordered trend test (Jonckeheere-Terpstra). Comparisons between groups of noncontinuous variables and changes in heart rate and blood pressure were performed using a Wilcoxon 2-sample test. All reported *P* values are 2-sided and are not adjusted for multiple testing. Data are expressed as mean (SD) or median (interquartile range). SAS statistical software version 9.1 (SAS Institute Inc, Cary, North Carolina) was used for all analyses.

RESULTS

A total of 161 patients were enrolled over 4 years (the first patient was enrolled in June 2000 and the last patient received the last dose in May 2005; FIGURE 1). Four patients were withdrawn from the trial before month 1 without reaching a study end point; per the study protocol, 4 additional patients were enrolled and randomized so that the total study sample size would remain unchanged. Demographic and baseline characteristics were similar between the treatment groups (TABLE 1).

There were no significant differences in study outcome with regard to completion, withdrawal, death, and transplantation. Death occurred in 11 patients (7%) during the intent-to-treat period (5 in the placebo group [9%] and 6 in the combined carve-

dilol group [6%]; 3 in both the low- and high-dose groups [6%]). No death was considered related to study medication. Five deaths occurred while patients were receiving study medication, of whom 1 had discontinued the study and was undergoing downtitration. Overall, 18 patients (11%) underwent nonelective heart transplantation during the study period.

Figure 1. Flow of Individuals Through the Trial

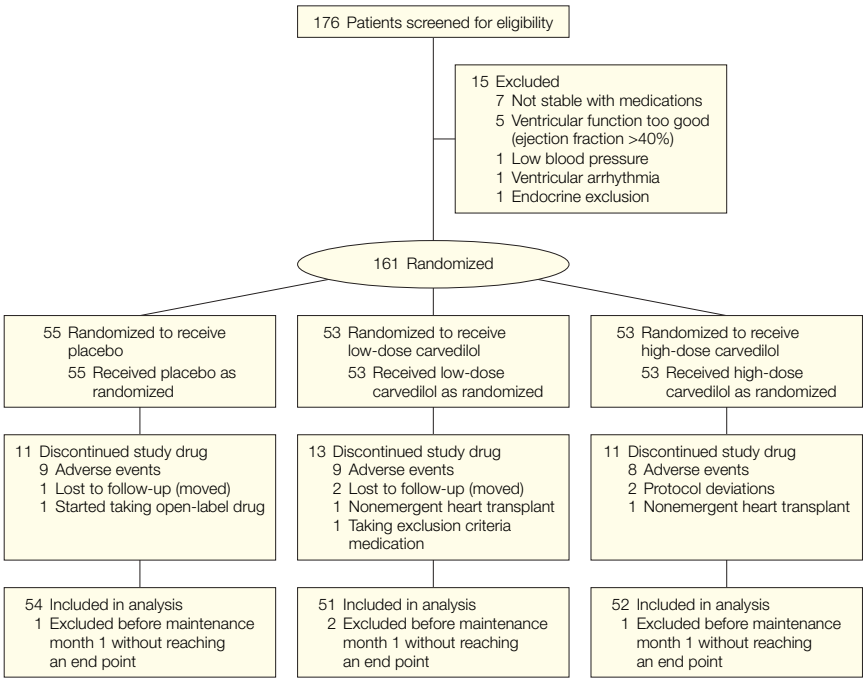


Table 1. Pretreatment Characteristics of the Patients[a]

	Placebo (n = 55)	Low-Dose Carvedilol (n = 53)	High-Dose Carvedilol (n = 53)
Age, median (IQR), mo	22 (9-73)	43 (14-154)	33 (13-122)
Male sex	30 (54.5)	28 (52.8)	25 (47.2)
Patients with systemic left ventricle	39 (70.9)	40 (75.5)	39 (73.6)
Congenital heart disease	6 (10.9)	10 (18.9)	7 (13.2)
Dilated cardiomyopathy	33 (60.0)	30 (56.6)	32 (60.4)
Patients with congenital heart disease and systemic non–left ventricle dysfunction	16 (29.1)	13 (24.5)	14 (26.4)
Concomitant medications			
Digitalis	46 (83.6)	47 (88.7)	48 (90.6)
Diuretics	46 (83.6)	45 (84.9)	45 (84.9)
ACE inhibitors	55 (100)	52 (98.1)	53 (100)
Spironolactone	22 (40.0)	20 (37.7)	18 (34)
New York Heart Association/Ross heart failure classification			
Class II	38 (69.1)	36 (67.9)	41 (77.4)
Class III	17 (30.9)	16 (30.2)	11 (20.8)
Class IV	0	1 (1.9)	1 (1.9)
Left ventricular ejection fraction, mean (SD), %	25.1 (9.0)	28.1 (7.0)	27.5 (6.7)
BNP level, median (IQR), pg/mL	116 (45-294)	91 (19-270)	123 (20-497)

Abbreviations: ACE, angiotensin-converting enzyme; BNP, b-type natriuretic peptide; IQR, interquartile range.
[a]Values are expressed as number (percentage) unless otherwise indicated.

Effect of Carvedilol on the Primary Efficacy Variable

No difference between the treatment groups was observed with regard to the percentage of patients who improved, worsened, or were unchanged during the course of the study (TABLE 2). The rates of worsening were lower than expected. The OR for worsened outcome for patients in the combined carvedilol group vs the placebo group was 0.79 (95% confidence interval [CI], 0.36-1.59; $P=.47$). For analysis of the improved vs not improved outcome, there was a significant interaction between study drug and ventricular morphology ($P=.02$; Table 2), suggesting a possible differential effect of treatment between patients with a systemic left ventricle (beneficial trend) and those whose systemic ventricle was not a left ventricle (nonbeneficial trend). Analyses of improved vs not improved were therefore performed.

No effect of age or sex (the other prespecified analysis subgroups in addition to ventricular morphology) on primary or secondary end points was found. However, when comparing patients according to a post hoc age categorization, a significantly higher proportion of younger patients improved compared with those older than 24 months (55 aged <24 months [70.5%] vs 33 aged >24 months [41.8%]; OR, 3.25 [95% CI, 1.64-6.45]; $P<.001$). While there was a higher proportion of patients with a systemic left ventricle in the younger group, ventricular morphology alone was not a significant predictor of improved outcome ($P=.09$). The interaction described above between dichotomized treatment groups (placebo vs the combined carvedilol group) and ventricular morphology remained statistically significant when adjusted for age effect ($P=.04$).

The hazard ratios for the mortality and hospitalization end points for placebo compared with carvedilol are shown in FIGURE 2. The hazard ratio for mortality was 0.68 (95% CI, 0.21-2.25; $P=.55$), with similar findings for the other end points. Although each estimate favors carvedilol, none are statistically significant.

Effect of Carvedilol on Ventricular Remodeling and Neurohormonal Parameters

In patients with a systemic left ventricle, ejection fraction increased significantly between screening and study completion in each of the 3 treatment groups although change in ejection fraction was not significantly different among the 3 groups ($P=.19$; TABLE 3). The remainder of the echocardiographic ventricular remodeling data are presented in Table 3. In patients with a systemic left ventricle, left ventricular shortening fraction increased between screening and study completion in all 3 groups. This increase was significantly different between groups ($P=.03$), with the high-dose carvedilol group having the greatest increase. Using an ordered trend test of 3 treatment groups (Jonckheere-Terpstra) for the change between screening and 6-month maintenance values, no other echocardiographic variable showed statistically significant differences. Among patients with non–left ventricle dysfunction, no significant changes in qualitative systemic ventricular function or atrioventricular valve regurgitation were noted during the study period.

Although plasma BNP concentrations decreased in all groups, this decrease was significant only in the placebo group (Table 3). Systolic blood pressure did not change during the study period in any group. Heart rates were similar at screening between the placebo group (mean [SD], 113/min [18.6/min]) and the combined carvedilol group (108.4/min [25.5/min]) ($P=.19$). However, heart rates at study completion were significantly lower in the carvedilol group (mean [SD], 98.2/min [20.3/min]) than in the placebo group (106.6/min [21.8/min]) ($P=.04$).

Safety

The majority of patients (54 while taking placebo [98%] and 103 while taking carvedilol [97%]) reported at least 1 adverse event. The most common adverse events were upper respiratory tract infections, vomiting, and cough. The frequency of cardiovascular adverse events was not significantly different between treatment groups; the most common of these was worsening heart failure, occurring in 12 patients in the placebo group (22%) and 21 patients in the carvedilol group (20%). Withdrawals for adverse events occurred in 7 patients taking placebo (13%) and 15 patients taking carvedilol (14%). Worsening heart failure was the most common event leading to withdrawal (6 patients in the placebo group [11%] and 12 patients in the carvedilol group [11%]).

Plasma Drug Concentrations

In general, median trough concentrations of R(+)-carvedilol and S(-)-carvedilol increased with dose but typically not in a dose-proportional manner. Steady state trough concentrations of R(+)-carvedilol and S(-)-carvedilol appeared to be lower in this group of patients with pediatric heart failure compared with historical data obtained in

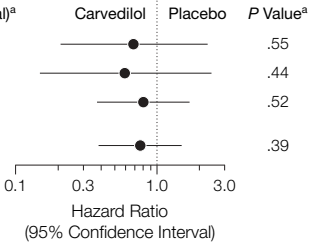
Table 2. Primary End Point and Prespecified Subgroup Analyses

	No. (%) of Participants		
	Placebo (n = 54)	Combined Carvedilol (n = 103)	*P* Value
All patients			
Improved	30 (56)	58 (56)	.74
Unchanged	8 (15)	20 (19)	
Worsened	16 (30)	25 (24)	
Dilated cardiomyopathy	**(n = 33)**	**(n = 60)**	
Improved	18 (55)	41 (68)	.24
Unchanged	6 (18)	6 (10)	
Worsened	9 (27)	13 (22)	
Congenital heart disease with systemic left ventricle	**(n = 6)**	**(n = 17)**	
Improved	2 (33)	8 (47)	.29
Unchanged	1 (17)	6 (35)	
Worsened	3 (50)	3 (18)	
Congenital heart disease without systemic left ventricle	**(n = 15)**	**(n = 26)**	
Improved	10 (67)	9 (35)	.14
Unchanged	1 (7)	8 (31)	
Worsened	4 (27)	9 (35)	
Systemic left ventricle[a]	**(n = 39)**	**(n = 77)**	
Improved	20 (51)	49 (64)	b
Not improved	19 (49)	28 (36)	
Without systemic left ventricle[c]	**(n = 15)**	**(n = 26)**	
Improved	10 (67)	9 (35)	b
Not improved	5 (33)	17 (65)	

[a] Prespecified analysis of improved vs not improved had an odds ratio of 1.71 (95% confidence interval, 0.78-3.76).
[b] The prespecified analyses were adjusted for age stratum and sex, thus a *P* value for the tabular data for these analyses would not include these adjustments and would misrepresent the data.
[c] Prespecified analysis of improved vs not improved had an odds ratio of 0.28 (95% confidence interval, 0.07-1.12).

Figure 2. Number of Events and Hazard Ratios for Mortality and Hospitalization End Points

End Point	No. of Events: Carvedilol (n = 106)	No. of Events: Placebo (n = 55)	Hazard Ratio (95% Confidence Interval)[a]	*P* Value[a]
All-cause mortality	6	5	0.68 (0.21-2.25)	.55
Cardiovascular mortality	4	4	0.59 (0.15-2.4)	.44
All-cause mortality or heart failure hospitalization	17	12	0.8 (0.38-1.68)	.52
All-cause mortality or cardiovascular hospitalization	23	15	0.76 (0.39-1.48)	.39



[a] From Cox proportional hazard regression model.

adult patients given tablets who had mild to severe heart failure or left ventricular dysfunction after myocardial infarction (FIGURE 3).[18]

COMMENT

This study did not detect a treatment effect of carvedilol on the primary composite end point of clinical heart failure outcomes. It is possible that children and adolescents with heart failure do not receive benefit from carvedilol; this would represent the first heart failure population not to show benefit with β-blockade and is inconsistent with the many small studies supporting the benefit of β-blockade in this patient population to date.[8-13] It is unclear why carvedilol would be beneficial in adults with heart failure but not in children and adolescents. It is possible that the differences in the etiologies of heart failure in children and adolescents (dilated cardiomyopathy and congenital heart disease) compared with adults (primarily ischemic heart disease) could influence its efficacy. Several factors in the study design and enrolled population also may have influenced the final result, including the choice of a composite clinical out-

Table 3. Ventricular Remodeling and Neurohormonal Parameters

	No. of Patients	Screening	6-Month Maintenance	*P* Value for Within-Group Change	*P* Value for Ordered Trend Test[a]
		Mean (SD)			
Left Ventricular Group Analyses					
Ejection fraction, %					
Placebo	31	25.1 (9.0)	34.9 (13.3)	<.001	
Low-dose carvedilol	30	28.1 (7.0)	39.4 (11.8)	<.001	.19
High-dose carvedilol	31	27.5 (6.7)	41.7 (11.5)	<.001	
Shortening fraction, %					
Placebo	30	13.9 (6.0)	19.0 (10.3)	.004	
Low-dose carvedilol	24	16.1 (6.9)	21.9 (8.6)	.006	.03
High-dose carvedilol	27	16.1 (5.3)	25.8 (8.3)	<.001	
End-systolic dimension, cm					
Placebo	29	4.1 (1.4)	3.8 (1.5)	.01	
Low-dose carvedilol	25	4.0 (1.1)	3.6 (1.4)	.07	.06
High-dose carvedilol	27	3.9 (1.1)	3.1 (1.1)	<.001	
End-diastolic dimension, cm					
Placebo	30	4.7 (1.5)	4.5 (1.5)	.07	
Low-dose carvedilol	27	4.8 (1.3)	4.6 (1.4)	.14	.31
High-dose carvedilol	29	4.6 (1.2)	4.2 (1.1)	.002	
Mass, g/m^2					
Placebo	31	102.0 (30.4)	100.9 (68.9)	.93	
Low-dose carvedilol	27	107.3 (45.9)	89.1 (37.4)	.04	.12
High-dose carvedilol	28	95.5 (23.5)	76.1 (19.0)	<.001	
		Median (IQR)			
Mitral regurgitation					
Placebo	30	1 (0-1)	1 (0-1)	.18	
Low-dose carvedilol	28	0 (0-1)	0 (0-1)	.51	.09
High-dose carvedilol	29	1 (0-1)	0 (0-1)	.002	
Non–Left Ventricular Group Analyses					
Non–left ventricular function					
Placebo	10	1 (1-1)	1 (1-1)	[b]	
Low-dose carvedilol	7	1 (1-1)	1 (0-1)	.50	.26
High-dose carvedilol	11	1 (1-2)	1 (1-2)	.50	
Atrioventricular valve regurgitation					
Placebo	12	0.5 (0-1.5)	0.5 (0-1.5)	.63	
Low-dose carvedilol	10	1 (0-1)	1 (0-1)	>.99	.32
High-dose carvedilol	11	1 (0-1)	1 (0-1)	[b]	
All Participants					
B-type natriuretic peptide plasma level, pg/mL					
Placebo	44	116 (45-294)	49 (5-222)	.01	
Low-dose carvedilol	39	91 (19-270)	43 (21-178)	.29	.55
High-dose carvedilol	39	123 (20-497)	35 (15-138)	.10	

Abbreviation: IQR, interquartile range.
[a] Indicates test of 3 treatment groups (Jonckeheere-Terpstra) for the change between screening and 6-month maintenance values.
[b] Indicates no difference between the values at screening and 6-month maintenance.

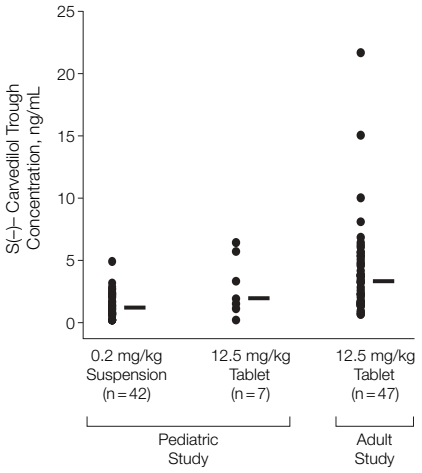
come as the primary end point, the assumptions made regarding the potential for clinical improvement over the study period, the inclusion of patients with differing ventricular morphologies, the distribution of heart failure severity present in the study population, and the doses used in the trial. The use of mortality as an end point was not feasible due to the anticipated difficulty in enrolling a sufficiently large number of patients. Surrogate end points such as echocardiographic or neurohormonal parameters are generally considered unacceptable when designing heart failure studies.[19] Thus, a composite of clinical, functional, structural, and laboratory outcomes may provide information as to whether a treatment positively influences morbidity and mortality.[20-22]

No composite end points, including the one used in this study, have been validated for heart failure studies in children and adolescents. With a median age of 3 years, this group of patients was in a period of rapid physical, mental, and emotional development. The perception of improvement by parents and/or physicians may have been affected by the observation of developmental progress (eg, starting to walk) during the study period, independent of the patients' cardiovascular status. However, the observed high incidence of improvement in the placebo and carvedilol groups is consistent with the improvement seen in the echocardiographically derived systolic function indices (ejection fraction and shortening fraction) observed in all 3 treatment groups.

No study has previously characterized the natural history of pediatric patients with heart failure in a randomized, blinded trial. Our power calculations, based on adult data, greatly underestimated the number of placebo-treated patients that would improve during the 8 months of the study. This study suggests that more than 50% of children and adolescents with heart failure will demonstrate improvement in symptoms if treated with angiotensin-converting enzyme inhibitors, digoxin, and diuretics alone. This is a higher placebo improvement rate than is seen in adult heart failure trials. Although most adult heart failure trials focus on end points that are "negative" (ie, lack of improvement or worsening), this pediatric heart failure trial has a greater focus on improvement in heart failure symptoms. Some retrospective reports suggest that younger children with dilated cardiomyopathy have a higher incidence of improvement than older children.[23-25] The large percentage of younger children in our study may partially explain the high percentage of improvement in the placebo group. Future heart failure trials in children and adolescents may benefit from focusing on a more homogeneous group of patients, such as patients with dilated cardiomyopathy. Using our preliminary data from this study, we estimate that 520 patients (260 in each group) would be required to achieve 90% power to detect a difference in a composite end point of improved vs not improved, comparing placebo with a single dose of carvedilol in children and adolescents with heart failure due to dilated cardiomyopathy. More would be required if one used a 3-level outcome (improved, worsened, unchanged).

The significant interaction between treatment and ventricular morphology raises important questions. Because there were no adjustments made for multiple comparisons in this study, these statistically significant differences need to be viewed cautiously. Evidence is increasing that systemic ventricles that are not of left ventricle morphology respond differently to medical interventions.[26-29] No significant benefit could be detected in young adults with systemic right ventricles who were treated with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers,[30,31] leading to speculation that vasodilators might be poorly tolerated in a circulation with intrinsically limited ventricular filling.[32] The high level of placebo response we observed, as well as the interaction between systemic ventricular anatomy and the primary outcome, are important considerations for the design of future clinical trials.

Figure 3. Representative S(−)–Carvedilol Steady-State Trough Concentrations



Pediatric patients in the carvedilol low-dose group (current pediatric study) and adult patients after administration of 12.5 mg of carvedilol.[18] Horizontal bars indicate median values.

Plasma BNP levels were relatively low in these patients compared with adult heart failure trials. This is consistent with the finding that 71% of these patients had class II heart failure symptoms. This is a higher percentage of patients with mild heart failure than in previous β-blocker trials in adults.[3-6] It is thus somewhat surprising that there was such a high incidence of death or transplantation (18%) in this group of children and adolescents who as a group symptomatically and neurohormonally would not normally be considered at high risk for either of these outcomes.

The trough concentrations we observed in this group of pediatric patients tended to be lower than those observed in adult patients. This is consistent with previous evidence that the elimination half-life of carvedilol is about 50% shorter in pediatric heart failure patients than in adult volunteers, indicating a more rapid clearance of carvedilol in children and adolescents.[33]

In conclusion, this study characterizes the clinical course of a pediatric heart failure population enrolled in a

randomized, double-blind, placebo-controlled trial. Carvedilol did not have a significant effect on a primary end point of composite clinical outcomes in children and adolescents with symptomatic heart failure due to systemic ventricular dysfunction. There may be a differential effect of carvedilol in children and adolescents with a systemic ventricle of left ventricle morphology compared with those with a systemic ventricle that is not of left ventricle morphology but further study is needed to prove this. Furthermore, the high proportion of infants and toddlers enrolled and the higher placebo improvement rate than anticipated are factors that may have influenced the results. The effect of carvedilol on echocardiographically derived indices of ventricular remodeling in children and adolescents with a systemic left ventricle suggests potential benefit. Using similar dosage per unit weight, twice daily dosing of carvedilol resulted in lower trough carvedilol plasma levels in children and adolescents than in adults.

This study provides an important framework for future studies of chronic heart failure in children and adolescents. The inherent heterogeneity of pediatric patients with heart failure and their high rate of spontaneous improvement make the definition of suitable clinical end points with a feasible sample size and sufficient statistical power a challenge for future treatment trials in this population.

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