The pediatric randomized carvedilol trial in children with chronic heart failure: Rationale and design

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Background Carvedilol is a medication with both β-receptor and α-receptor blocking properties that has been approved for the treatment of heart failure in adults. Little is known about its safety, efficacy, pharmacokinetics, and dosing profile in children.

Methods The primary objective of this study is to evaluate the efficacy of carvedilol administered twice daily for 8 months in terms of its effect compared with placebo on a composite measure of clinical outcomes in children with symptomatic systemic ventricular systolic dysfunction and heart failure. The secondary objectives are to determine the effect of carvedilol on individual components of a composite of clinical outcomes (hospitalizations for worsening heart failure, all-cause mortality and cardiovascular hospitalizations, all cause mortality, heart failure symptoms, and patient and physician global assessment); determine the effect of carvedilol on echocardiographic indices of ventricular function and remodeling; characterize the pharmacokinetics of carvedilol in pediatric patients with heart failure; characterize the effects carvedilol on neurohormonal systems; and provide data for the selection of an optimal titration schedule and daily dose of carvedilol in children with heart failure. This study will enroll 150 children between birth and 17 years of age with chronic symptomatic heart failure caused by systemic ventricular systolic dysfunction.

Conclusion This study will determine whether carvedilol improves symptoms in children with heart failure as a result of systemic ventricular systolic dysfunction. The study also will provide information on echocardiographic changes of ventricular performance and neurohormonal levels in children with heart failure before and after treatment with carvedilol, in addition to pharmacokinetics of carvedilol in children. (Am Heart J 2002;144:383-9.)

Congestive heart failure (CHF) as a result of systemic ventricular dysfunction is a significant medical problem for children and represents the reason for referral in at least 50% of all children referred for heart transplantation.[1] Although multiple studies have shown that β-blocking agents improve left ventricular function, symptoms, and survival rates in adults,[1-3] little is known about the effects of these medications in children with CHF. Small nonrandomized retrospective analyses of the use of metoprolol and carvedilol in children with heart failure as a result of systemic ventricular systolic dysfunction have shown potential beneficial effects of β-blockers in children.[4-7] Some investigators have suggested that carvedilol may have superior benefits to other β-blockers in terms of improved cardiac performance indices,[8] possibly because of its dual mechanism of action: nonselective β-blockade and vasodilation primarily caused by its α_1-receptor blockade.[9] Little published information is available about the safety, efficacy, or pharmacokinetics of carvedilol in children with CHF.[7] In addition, although increasing evidence is found that the plasma concentration of the neurohormone brain natriuretic peptide (BNP) is a useful indicator for screening, diagnosis, clinical management, and prognostic assessment in adults with CHF,[10,11] no data exist regarding the utility of BNP levels in children with CHF. The primary objective of this prospective, randomized, blinded, and placebo-controlled protocol is to compare the efficacy of carvedilol administered twice daily for 8 months, compared with placebo, on a composite measure of clinical CHF outcomes in children with symptomatic systemic ventricular systolic dysfunction and CHF. Pa-

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tients in this study also will have plasma BNP concentrations measured to collect baseline data in children with CHF and to evaluate the effects of pharmacologic intervention on BNP concentrations.

Methods

This study will enroll approximately 150 male and female children between birth and 17 years of age with chronic symptomatic CHF caused by systemic ventricular systolic dysfunction without a contraindication to administration of a β-blocking or α-blocking agent.

Inclusion criteria

1. Male or female children between the ages of birth and 17 years with chronic symptomatic CHF resulting from systemic ventricular systolic dysfunction undergoing standard heart failure therapy. Because adolescents with left ventricular dysfunction are similar to adults with this disease, this study will focus recruitment in the prepubertal age group of children. The number of adolescents enrolled will be limited to approximately 10% of study enrollment.
2. A diagnosis of CHF with New York Heart Association (NYHA) classification II to IV (older children) or Ross' CHF classification II to IV (infants and younger children)[12] for at least 1 month (at least 2 weeks for neonates) before screening will be necessary.
3. An estimated ejection fraction <40% in patients with systemic left ventricular dysfunction or qualitative evidence of a dilated ventricle with moderate systemic ventricular systolic dysfunction in patients with right ventricular or single ventricular physiology, documented within 4 weeks of randomization, will be required.
4. The etiology of the cardiomyopathy will include idiopathic dilated cardiomyopathy, postviral myocarditis cardiomyopathy, anthracycline-induced cardiomyopathy, ischemic cardiomyopathies (eg, Kawasaki disease, repaired anomalous left coronary artery arising from the pulmonary artery, dextro-transposition of the great arteries status post arterial switch), cardiomyopathies associated with functional single ventricle with ventricular systolic dysfunction, and levo-transposition of the great arteries. Excluded from enrollment will be dilated cardiomyopathies caused by muscular dystrophies, hemoglobinopathies, HIV, carnitine deficiency, and systemic ventricular dysfunction as the result of ventricular outflow tract obstruction.
5. Patients undergoing treatment for CHF with standard CHF therapy, such as diuretic, digoxin, and angiotensin-converting enzyme inhibitors. All patients should be receiving angiotensin-converting enzyme inhibitors before enrollment in this study unless contraindicated or intolerant. If intolerance has been established, the patient must have been withdrawn from these drugs for at least 1 month before randomization. Other medications, such as hydralazine, nitrates, or amiodarone, also may be used. Therapy with amiodarone should not have started or stopped within 2 months of randomization.
6. All patients should be receiving diuretics before enrollment in this study unless contraindicated or intolerant. Patients must be in optimal fluid status before enrollment.
7. Patients must be receiving a stable regimen of standard CHF medications for a period of at least 1 month (2 weeks in neonates) at the time of randomization into the study.

Exclusion criteria

1. NYHA or Ross' CHF classification I (asymptomatic) will be cause for exclusion.
2. Patients actively listed for transplantation at time of entry into the study or anticipated to undergo heart transplantation or corrective heart surgery during the 8 months after entry into the study will be excluded.
3. Sustained or symptomatic ventricular dysrhythmias uncontrolled with drug therapy or the use of an implantable defibrillator or significant cardiac conduction defects (eg, second-degree or third-degree atrioventricular block or sick sinus syndrome), unless a functioning pacemaker is in place, will be cause for exclusion.
4. Patients with uncorrected primary obstructive or severe regurgitative valvular disease, nondilated (restrictive) or hypertrophic cardiomyopathy, or significant systemic ventricular outflow obstruction will be excluded.
5. Dilated cardiomyopathies caused by muscular dystrophies, hemoglobinopathies, HIV, carnitine deficiency, and systemic ventricular dysfunction because of ventricular outflow obstruction will be cause for exclusion.
6. Active myocarditis will be cause for exclusion.
7. Unacceptable blood pressures and heart rates will be cause for exclusion. Sitting (supine in infants) systolic blood pressure must be >85 mm Hg in teens, >75 mm Hg in school-aged children, and >65 mm Hg in infants. Resting heart rate must be greater than the second percentile for age.
8. Renovascular hypertension or evidence of pulmonary hypertension (pulmonary vascular resistance index, >6 Wood units-m^2) unresponsive to vasodilator agents, such as oxygen, nitroprusside, or nitric oxide, will be cause for exclusion.
9. History or current clinical evidence of moderate-to-severe obstructive pulmonary disease or reactive airway diseases (eg, asthma) necessitating therapy will be cause for exclusion.
10. Patients with significant renal (serum creatinine level, >2.0), hepatic (serum aspartate aminotransferase or alanine aminotransferase >3 times upper limit of normal), gastrointestinal, or biliary disorders that could impair absorption, metabolism, or excretion of orally administered medications will be excluded.
11. Concurrent terminal illness or other severe disease (eg, active neoplasm) or other significant laboratory values that, in the opinion of the investigator, could preclude participation or survival will be cause for exclusion.
12. Endocrine disorders, such as primary aldosteronism, pheochromocytoma, hyperthyroidism or hypothyroidism, or insulin-dependent diabetes mellitus will be cause for exclusion.

13. Patients who are unwilling or unable to cooperate, or who have parents or guardians who do not give consent or allow the child to give assent, or who have any condition of sufficient severity to impair cooperation in the study will be excluded.
14. Girls of child-bearing potential who are pregnant, lactating, or sexually active and not taking adequate contraceptive precautions (eg, intrauterine device or oral contraceptives for 3 months before entry into the study) will be excluded.
15. Use of an investigational drug within 30 days of randomization or within 5 half-lives of the investigational drug (the longer period will apply), investigational vaccines, or biologic agents (eg, the monoclonal antibody palivizumab) may be granted exceptions through consultation with the principal investigator and SmithKline Beecham.
16. Patients with a history of drug sensitivity or allergic reaction to α-blockers or β-blockers will be excluded.
17. Use of any of the following medications within 2 weeks of randomization will be cause for exclusion: monoamine oxidase inhibitors; calcium entry blockers; α-blockers or labetalol; disopyramide, flecainide acetate, encainide hydrochloride, moricizine hydrochloride, propafenone hydrochloride; β-adrenergic agonists (including intravenous inotropes, such as dobutamine) or intravenous vasodilator agents, such as amrinone or milrinone; or intravenous CHF medications (eg, diuretics, digoxin).
18. Treatment with β-adrenergic blockers, including sotalol hydrochloride or carvedilol, within 2 months of randomization will be cause for exclusion.

Randomization

The randomization procedure is designed to populate 3 study arms with approximately equal numbers of subjects. In addition to the 3 study arms, subjects also will be stratified into 1 of 2 categories: those with a systemic left ventricle (LV) and those with a systemic ventricle that is a not an LV (NLV).

Each participating center will receive 2 enrollment lists labeled LV and NLV, corresponding to the 2 population groups described previously. Each list will contain 30 assignments, which should exceed each center's anticipated enrollment. Each participating center will designate a pharmacist who will be responsible for randomizing subjects and distributing study drug/placebo. Because this individual will know which agent each patient is receiving, it is necessary that they agree not to share this information with anyone connected to the study (participants, parents, investigators, nurses, coordinators, etc) unless directed to do so by the principle investigator. After a successful screening visit, subjects will each have a form completed by the investigator and issued to the pharmacist. This form will verify the subject's willingness to participate and will indicate either LV or NLV. The pharmacist will use the appropriate randomization list (LV or NLV) to determine the subject's randomization code and corresponding drug assignment (study arm). Other information will be recorded on the randomization list, including the enrollment date, subject's initials, and pharmacist's initials.

Study design

Patients who fulfill all entry criteria will be randomized in a 1:1:1 ratio to receive 1 of the following double-blind study medications: placebo, low-dose carvedilol (target dose, 0.2 mg/kg/dose), or high-dose carvedilol (target dose, 0.4 mg/kg/dose). Previous studies of carvedilol in adults with chronic heart failure required patients to complete a 2-week open-label period of low-dose carvedilol therapy before randomly assigning patients to double-blind therapy.[1,13] In these studies, only 5% to 8% of adults with heart failure did not tolerate low-dose carvedilol and therefore were not randomized. Because of this low incidence rate of adverse effects to open-label carvedilol in adults and previous anecdotal experience of the investigators with β-blockers in children with heart failure, neither the Food and Drug Administration (FDA) nor the investigators in this study believed that an open-label run-in period was warranted.

After randomization, patients will be followed during uptitration and for 6 months of maintenance therapy. The goal of the uptitration period is to reach the highest dose level that will be continued throughout the maintenance phase. After baseline clinical evaluation, all patients will be entered into the uptitration period, during which they will receive carvedilol or placebo in addition to their usual medications for heart failure. The first dose of double-blind medication will be administered with food at the clinic on the day of randomization. At 1 and 2 hours after administration of the dose, heart rate and blood pressure will be assessed. Doses of carvedilol (or matched placebo) are to be uptitrated biweekly with 1 of the 2 dosing schedules described subsequently. Appropriate doses of carvedilol in children are unknown, and this study was designed to help determine that. The higher dose of carvedilol for this study was extrapolated from adult doses with assumption of a weight of approximately 70 kg (eg, a 25-mg dose in a 70-kg adult is 0.36 mg/kg). The lower dose was then arbitrarily chosen to be half the higher dose. The maximum initial daily dose will be 3.125 mg twice daily. The maximum daily dose (target titration dose) will be 25 mg twice daily. Patients are to take their medications with food. The titration dose levels of carvedilol or matched placebo are shown in Table I.

At each dose level change, the first dose of double-blind medication will be administered in the clinic, with heart rate and blood pressure assessed 1 and 2 hours after administration of study drug. After completion of the uptitration period, patients will enter the 6-month maintenance phase of the study and take the highest dose of study medication that was tolerated during the uptitration phase, which may be dose level 1, 2, 3, or 4. During the maintenance period, if the patient was unable to reach the maximal dose level of study medication during the uptitration phase, the investigator may and should intermittently continue to increase the dosage level, as tolerated, in the hope of achieving level 4 in most patients. Study visits will be scheduled at 1, 2, 3, 4½, and 6 months during maintenance treatment. Additional visits may be scheduled by the investigator, as appropriate, on the basis of the clinical condition of the patient.

Table I. Four-visit, 6-week schedule of patient up titration

	Week of follow-up			
	0	**2**	**4**	**6**
Dose of carvedilol (subject <62.5 kg)	0.05 mg/kg	0.1 mg/kg	0.2 mg/kg	0.4 mg/kg
Dose of carvedilol (subject >62.5 kg)	3.125 mg	6.25 mg	12.5 mg	25 mg

Outcome measures

The primary objective of this protocol is to evaluate the efficacy of carvedilol administered twice daily for 8 months in terms of its effect compared with placebo on a composite measure of clinical CHF outcomes in children with symptomatic systemic ventricular systolic dysfunction and CHF.[14] Because no primary outcome measure has been validated in children with heart failure, the investigators chose to use a composite measure that includes some attempted measure of functional assessment, patient/parent global assessment, and major clinical events.

Patients are determined to have a CHF composite response of worsened, improved, or unchanged. The definitions of worsened, improved, and unchanged are as follows.

Worsened— Patient dies; is hospitalized for at least 24 hours for worsening heart failure necessitating intravenous heart failure medication; permanently discontinues double-blind treatment because of worsening heart failure, treatment failure, or lack of/insufficient therapeutic response; permanently discontinues double-blind treatment because withdrawal of consent or other administrative reason and has worsening heart failure at the time of study discontinuation; or shows worsening in NYHA or Ross' classification for CHF in children at last observation carried forward (LOCF) or moderate to marked worsening of patient/parent global assessment score at LOCF.

Improved— Patient has not worsened (as defined previously) and shows improvement in NYHA or Ross' classification for CHF in children at LOCF or moderate to marked improvement in patient/parent global assessment score at LOCF.

Unchanged— Patient is neither improved nor worsened.

The secondary objectives of this study are

1. To determine the effect of carvedilol on selected individual components of the CHF composite of clinical outcomes (hospitalizations for worsening heart failure, all-cause mortality and cardiovascular hospitalizations, all-cause mortality, NYHA or Ross' classification of CHF, patient/physician global assessment), compared with placebo.
2. To determine the effect of carvedilol on echocardiographic indices of ventricular function and remodeling, compared with placebo (all echocardiograms are sent to a core laboratory at Primary Children's Medical Center, Salt Lake City, Utah).
3. To characterize the pharmacokinetics of carvedilol exposure in pediatric patients with heart failure.
4. To characterize the effects of chronic therapy with carvedilol on neurohormonal systems, compared with placebo.
5. To provide data for the selection of an optimal titration schedule and daily dose of carvedilol in pediatric patients with heart failure.

The study design is such that a patient may reach a study end point (eg, hospitalization for worsening heart failure) at any time after randomization, including during uptitration. Although it is known that patients can have adverse effects during uptitration with carvedilol, most of these adverse effects either are self-limiting or can be managed with outpatient adjustments in carvedilol or concomitant medications.

Sample size and statistical analyses

Sample size calculations are made on the basis of the primary end point of a composite CHF assessment of worsened, improved, or unchanged. On the basis of review of the studies of β-blockers in adults with CHF and previous anecdotal experience with the use of other β-blockers in children, power analysis can estimate the sample size needed to determine the efficacy of carvedilol in improving symptoms of CHF. For the purpose of sample size calculations, we made the assumption that approximately 44% of children receiving carvedilol would improve compared with only 19% of children receiving placebo. At the time of randomization, patients will be stratified into study treatment arms according to the anatomic substrate of their ventricular dysfunction (ie, patients with systemic left ventricular dysfunction or patients with right ventricular or single ventricular physiology). Approximately 147 patients will be randomized in a 1:1:1 fashion (49 patients in each of 2 carvedilol arms, 49 patients in the placebo arm). One hundred forty-seven patients are estimated to provide 90% power to detect differences in CHF composite response between those patients who received either of the 2 carvedilol arms (n = 98) and those who received placebo (n = 49), with 2-sided testing and a type I error of 0.05.

Comparisons between groups for the primary end point of improved, worsened, or unchanged will be made with a Mantel-Haenszel ϑ^2 test. Comparisons of echocardiographic indices, BNP levels, and measurements of interest will be made with analysis of variance. Comparisons of CHF classification and global and symptom assessments will be made with a Wilcoxon signed rank test. Demographic and other baseline characteristics will be examined for differences between study regimens, and where differences of clinical interest are indicated, appropriate subgroup or covariance analyses will be done to characterize observed differences in efficacy indices. Summary descriptive statistics and graphic displays of the observed relationships between the indices will be presented to facilitate further evaluation of differences between the study regimens. Compliance, protocol

Table II. Titration dose levels of carvedilol or matched placebo

	Low dose (mg/kg)	High dose (mg/kg)	Frequency
Patients <62.5 kg			
Titration level			
1	0.025	0.05	q 12 hours (liquid suspension)
2	0.05	0.1	q 12 hours (liquid suspension)
3	0.1	0.2	q 12 hours (liquid suspension)
4	0.2	0.4	q 12 hours (liquid suspension)
Patients ≥62.5 kg			
Titration level			
1	1.563 mg	3.125 mg	q 12 hours (liquid suspension)
2	3.125 mg	6.25 mg	q 12 hours (pill)
3	6.25 mg	12.5 mg	q 12 hours (pill)
4	12.5 mg	25 mg	q 12 hours (pill)

q, Every.

violations, and reasons for dropout will be examined for possible introduction of bias in the comparisons.

Provisions for management of side effects of study medication

During uptitration and throughout the maintenance period, adverse effects will be monitored closely. Patients and families will be made aware of these effects and will report to the primary investigator or study coordinator at each institution if side effects occur. The risks of carvedilol include the potential of bradycardia or hypotension or both, potentially severe enough to necessitate inotropic support. Adverse effects are avoided by administering the first dose and subsequent increasing doses with close medical supervision. A worsening of CHF is also a potential risk for which patients will be monitored closely. Other reported side effects include fatigue, dizziness, headache, nausea, and diarrhea. A low risk (estimated, <1%) of asthma, postural hypotension, or syncope also exists. Patients who show any significant adverse effects to study medication will be treated accordingly as described subsequently, with medications if necessary, to reverse the adverse effect. Study medication may be decreased or temporarily discontinued if in the judgment of the investigator this may facilitate treatment of the adverse event. However, in adults, adjustment of concomitant CHF medications has been found to be efficacious in ameliorating most presentations of side effects associated with study medication during uptitration or maintenance therapy with carvedilol. A serious adverse event is any event that is fatal, life threatening, or disabling/incapacitating or results in hospitalization, prolongs a hospital stay, or is associated with congenital abnormality, cancer, or overdose (either accidental or intentional). In addition, any experience that the investigator regards as serious or that would suggest any significant hazard, contraindication, side effect, or precaution that may be associated with the use of the drug will be documented as a serious event.

Open-label carvedilol extension phase (optional)

On completion of the 8-month period from the time of randomization, subjects will enter the follow-up phase and will be provided the opportunity to receive open-label carvedilol treatment within an optional long-term extension phase of the study. Patients who prematurely withdraw from the study will not be allowed to start open-label β-blocker treatment until they have completed the 8-month time period. Safety and efficacy information on the long-term use of carvedilol in pediatric patients with heart failure will be collected in this extension study and will continue until completion of the double-blind portion of the study and thereafter until each patient who elects to participate in the extension phase has been provided the opportunity to receive a minimum of 6 months of open-label carvedilol treatment. During the follow-up phase, simultaneous downtitration of study drug and uptitration of carvedilol will be proposed for those who want to continue on into the open-label extension. Downtitration will occur in a blinded manner according to the subject's dose level at the end of the maintenance phase. All patients (low dose, high dose, placebo) will undergo uptitration in exactly the same manner with the 4-visit, 6-week schedule shown in Table II.

Just as with the uptitration of study drug, some patients may not easily titrate up from each level, and thus the guidelines for up titration as described previously will be followed. Therefore, some patients may take much longer than 6 weeks to uptitrate, and others may not be able to reach the highest dose level. However, all patients will downtitrate over a 2-week to 4-week period, depending on which level they were on at the end of maintenance. Thus, all patients will be off the study drug within 4 weeks (some within 2 weeks, some within 4 weeks), regardless of how the open-label uptitration of carvedilol is progressing.

Discussion

Heart failure in children that results from systemic ventricular dysfunction is an important problem. However, the evidence base for treatment of this condition in children is small. Most treatment strategies are extrapolated from studies in adults. Unfortunately, the etiologies, pathophysiology, and physiologic consequences of CHF in children are often different than in

adults. In adults, the primary abnormality that leads to the heart failure syndrome is usually left ventricular dysfunction. In contrast, the underlying abnormality in children is often an intracardiac left-to-right shunt with normal left ventricular function or a ventricular obstructive lesion. With improved treatments for structural congenital heart disease, chronic CHF from these etiologies is becoming less common. Even in the setting of systemic ventricular dysfunction as a cause of CHF, children differ from most adults in that the systemic ventricle in children is often not an LV but a right or single ventricle. Even in those clinical settings with treatment of LV dysfunction, age-related and developmental differences in responses to medications may complicate the application of adult pharmacologic strategies to children. During the last 20 years, the treatment of heart failure in adults has focused more on the treatment of the neurohormonal abnormalities associated with heart failure than on an attempt to solely augment systemic ventricular function. Most recommendations for treatment strategies in adults with heart failure have been developed from large multicenter trials of new drug therapies, yet there have been no multicenter pediatric drug trials examining the safety and efficacy of medications in children with chronic heart failure. Until recently, little motivation has been found for pediatricians or industry to carefully study medications in children. However, 2 recent major rulings from the FDA have provided new and important motivation for physicians and industry to form partnerships that can perform prospective, randomized, double-blind, placebo-controlled drug trials in children. These are the FDA Modernization Act of 1997 and the Pediatric Rule of 1998.[15,16] One provision of the FDA Modernization Act allows a drug's original sponsor an additional 6-month period of market exclusivity for new or already marketed drugs in exchange for the performance of pediatric studies. The Pediatric Rule mandates pediatric studies adequate to assess safety and effectiveness and support label directions for pediatric use of new or already marketed drugs.[17] This study hopes to provide important information on the safety and efficacy of carvedilol in children.

The prospective randomized pediatric carvedilol trial in children with heart failure is designed to answer a specific question. Does carvedilol improve symptoms in children with heart failure as the result of systemic ventricular systolic dysfunction? Patients with normal LV anatomy and those with functional single ventricle (right ventricle or LV) and a systemic ventricle that is not a LV will be included. This trial is designed to determine both the safety and efficacy of carvedilol in the treatment of chronic heart failure in children resulting from systemic ventricular systolic dysfunction. Additional information will be gained regarding the effect of carvedilol on echocardiographic indices of ventricular performance, BNP levels in heart failure in children before and after treatment with carvedilol, and pharmacokinetics of carvedilol in children. By examining 2 dose levels of carvedilol compared with placebo, we also hope to determine the optimal dose of carvedilol in children that maximizes benefit and minimizes adverse effects. Because of the great variability in age (birth through adolescence) and systemic ventricular anatomy (LV, right ventricle, and single ventricle), it was difficult to decide how best to study all these different groups. Because of the age proximity of young adults and adolescents, neither the investigators nor the FDA were interested on focusing the study on adolescents. However, exclusion of adolescents from the study did not seem justified either. Thus, we elected to limit the number of adolescents enrolled. We chose to stratify patients at the time of randomization to either LV (patients with systemic LV) or non-LV (patients with a systemic ventricle that is not a morphologic LV) to have equal numbers in each group randomized to each study arm (placebo, low-dose carvedilol, or high-dose carvedilol). We are confident that the study is adequately powered to detect a difference in outcomes between those who receive carvedilol and those who receive placebo.

Significant obstacles exist in performance of these types of studies in children. As with any research protocol in children, the highest ethical standards must be adhered to in order to ensure safe and appropriate treatment of children as research subjects. Because of the small number of patients who meet inclusion criteria, a multicenter trial is necessary to have adequate statistical power to answer the question. Informed consent and, when applicable, assent must be obtained, and any perception of coercion must be removed. Patient selection is difficult because of the inadequate and unvalidated outcome measures currently available for the definition of symptoms in children with heart failure. Also, enormous complexities are present in properly preparing and administering study drug (placebo and active drug) to children who will range in size from 2 kg to >100 kg. In this study, 3 arms (placebo, low-dose carvedilol, and high-dose carvedilol) and 2 stratifications (LV and non-LV), with 4 uptitration schedules, were required for both liquid preparation (patients <62.5 kg) and pills (patients ≥62.5 kg). Finally, significant complexities exist in the open-label extension phase because of the desire to simultaneously downtitrate patients off of the study drug while uptitrating patients onto open-label carvedilol. This requires complex pharmacy formulations for both liquid preparations and pills and strict adherence to protocols with the need for oversight by the coordinating center to eliminate errors in formulations and drug preparations. We also hope that this study will

stimulate the development of other studies in the area of pediatric cardiovascular diseases because these types of studies are critical for the determination of the optimal treatment of children.

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Appendix

End point/Steering Committee

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