

Rationale and design of a trial of angiotensin-converting enzyme inhibition in infants with single ventricle

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Background Angiotensin converting enzyme (ACE) inhibitors are known to improve clinical outcome and ventricular function in adults with heart failure. Infants with single-ventricle physiology show abnormalities in ventricular function as well as poor growth. The ability of an ACE inhibitor to preserve ventricular function and improve growth in these infants is unknown.

Methods The Pediatric Heart Network designed a randomized, double-blind trial to compare outcomes in infants with single-ventricle physiology receiving enalapril or placebo. Neonates ≤ 45 days old were eligible. The primary outcome is weight-for-age Z-score at 14 months of age. Secondary outcomes include other measures of somatic growth, laboratory and functional measures of heart failure, developmental indices, measures of ventricular size and function, and the relationship of the renin-angiotensin-aldosterone system genotype to the response to enalapril. The incidence and spectrum of adverse events will also be compared between treatment groups.

Results A total of 1,245 neonates were screened and 533 (43%) were eligible. The consent rate was 43%; 230 subjects were enrolled. Parental reluctance to participate was the primary reason for non-consent in 79% of the eligible nonconsenting patients. Randomized patients were older, more likely to be male, and more likely to have hypoplastic left heart syndrome than the eligible patients who did not enroll.

Conclusions The results of this randomized trial will make an important contribution to the management of infants with single-ventricle physiology by determining whether initiation of ACE inhibition therapy in the neonatal period improves growth, clinical outcome, and ventricular function. (Am Heart J 2009;157:37-45.)

Background

Defining the optimal therapeutic approach to the child with single-ventricle physiology is one of the most

challenging problems in pediatric cardiology.¹⁻³ The benefits of angiotensin converting enzyme (ACE) inhibition in volume-loaded hearts were demonstrated in studies that reported both acute and long-term reduction in left ventricular volume and mass with ACE inhibitor use in children with chronic valvar regurgitant lesions and other congenital heart defects.^{4,5} In addition, studies have demonstrated a rapid beneficial effect of ACE inhibition on growth in infants with severe congestive heart failure,^{6,7} with a 2- to 3-fold increase in weight gain within a 1- to 3-month follow-up period.⁸ Although ACE inhibitors are commonly administered to infants and children for treatment of heart failure due to cardiomyopathy or volume overload lesions,⁹ there are few reports regarding administration of ACE inhibitors to infants with single-ventricle physiology^{10,11} and no randomized trials evaluating the efficacy of ACE inhibition in this population have been performed.

Growth impairment is common in infants and children with various forms of congenital heart disease,¹² most often in the presence of congestive heart failure and/or

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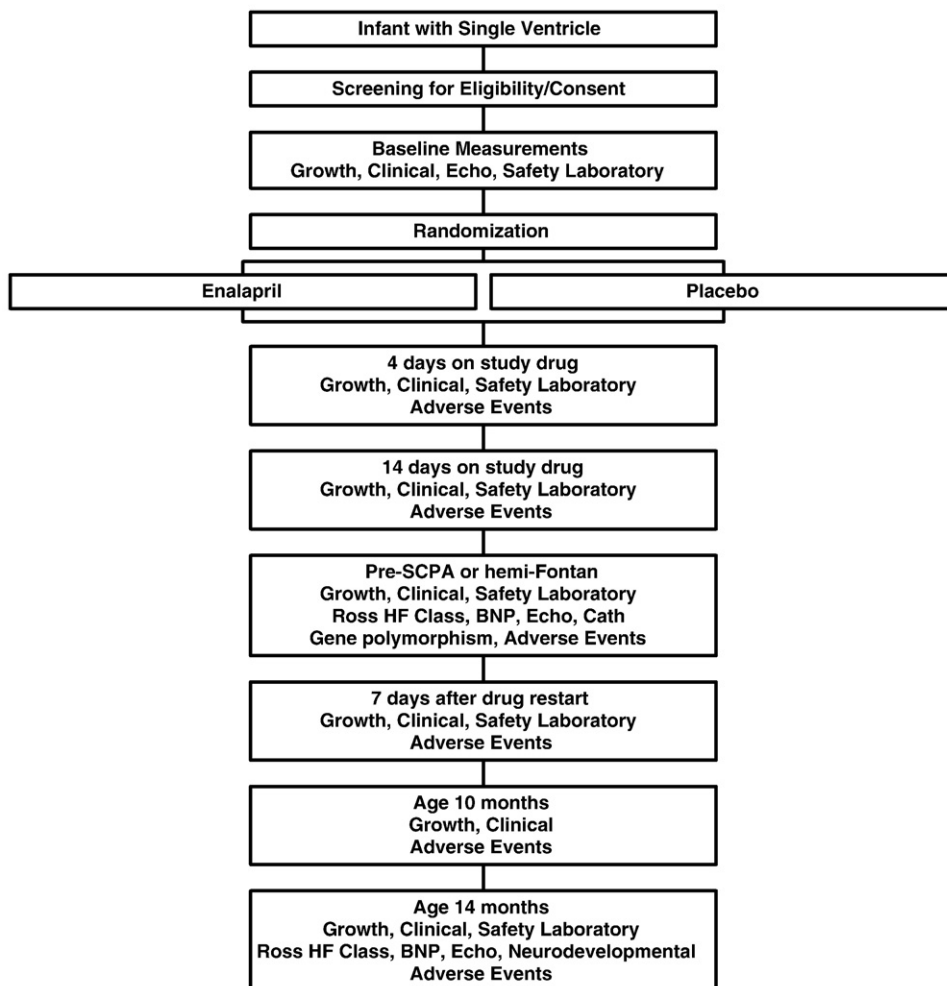
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Figure 1



Pediatric Heart Network Infant Single-Ventricle Trial Protocol. SCPA, Superior cavo-pulmonary anastomosis; HF, heart failure, BNP, B-type natriuretic peptide; Echo, echocardiogram.

cyanosis.¹³ In particular, growth failure is noted in many infants with single ventricle who manifest both cyanosis and heart failure.¹⁴⁻¹⁶ In infancy and early childhood, the single ventricle is exposed to chronic hypoxemia and volume overload, which can result in an inappropriate increase in myocardial mass and abnormalities in ventricular systolic and diastolic function. The growth impairment seen in infants with single-ventricle physiology may be the result of persistent or progressive abnormalities in cardiac structure and function that lead to the development of clinical heart failure.

Study overview

This randomized, double-blind, placebo-controlled trial was designed to determine whether ACE inhibition improves ventricular function and cardiac output in

infants with single-ventricle physiology, thereby decreasing the severity of heart failure in this population. The primary hypothesis is that somatic growth will be greater in infants receiving ACE inhibition therapy compared to those receiving placebo. The primary outcome of weight-for-age Z-score at age 14 ± 1 months was chosen because it is a clinical measure of heart failure that is readily obtained and easily interpretable. Secondary outcomes include comparison of other measures of somatic growth, indicators of congestive heart failure, neurodevelopmental indices, echocardiographic measures of ventricular size, and function and the relationship of the renin-angiotensin-aldosterone system (RAAS) genotype to response to ACE inhibition. The incidence of adverse events will also be compared between groups.

This trial was designed by the National Heart, Lung, and Blood Institute-funded Pediatric Heart Network (PHN).¹⁷

Table 1. Inclusion and exclusion criteria

Inclusion criteria

1. Age ≤ 45 days
2. Age > 1 week if born at 35 weeks gestation
3. Single ventricle physiology
4. Stable systemic and pulmonary blood flow
5. Planned superior cavopulmonary anastomosis (either the bidirectional Glenn shunt or hemi-Fontan surgery)

Exclusion Criteria

1. Birth weight ≤ 2.5 kg if gestational age is ≥ 38 weeks; birth weight $<$ the 5th percentile for gestational age if gestational age is 35-37 weeks
2. < 35 weeks gestation
3. Anatomic diagnosis of pulmonary atresia with intact ventricular septum
4. < 3 days after palliative cardiac surgical procedure, if performed
5. Systemic oxygen saturation $< 65\%$
6. Current mechanical ventilatory support
7. Current intravenous inotropic support
8. Creatinine > 1.0 mg/dL
9. Absolute neutrophil count < 1000 cells/mL
10. Chromosomal or recognizable phenotypic syndrome of non-cardiac congenital abnormalities associated with growth failure (e.g. trisomy 21, Noonan syndrome, Turner syndrome)
11. Prior ACE inhibitor use for > 7 consecutive days
12. Unable to return for follow-up because of distance from clinical site.

The study is being conducted at ten clinical centers, three of which were added 17 months after study initiation to augment the enrollment rate (Appendix A). A flow chart of the study design is shown in Figure 1.

Subject selection

The inclusion and exclusion criteria were chosen to include neonates with stable pulmonary and systemic blood flow to minimize the potential negative hemodynamic effects of ACE inhibition. Patients were excluded based on cardiac anatomy if there was a possibility of a 2-ventricle repair, e.g., pulmonary atresia with intact ventricular septum. Low birth weight and noncardiac conditions associated with poor growth in the first year of life were exclusions because of the potential confounding effect on the primary outcome of growth. Patients < 35 weeks of gestation were excluded because of the possible increased risk of renal dysfunction with administration of enalapril in this subgroup. The inclusion and exclusion criteria are listed in Table 1. If the patient met all inclusion and no exclusion criteria, the family was approached to provide informed consent.

Randomization and masking

Subjects were randomly assigned in a 1:1 ratio to the enalapril or placebo treatment groups using randomly permuted blocks within strata defined by the presence or

absence of hypoplastic left heart syndrome. This stratification was chosen because of the association of growth impairment with the diagnosis of hypoplastic left heart syndrome. Dynamic balancing by center was used to ensure that treatment arm totals were balanced within center. All study personnel, other than the research pharmacist, were masked to the treatment assignment. The central reader for study echocardiograms was masked to both treatment assignment and study visit.

Trial organization

The PHN Infant Single Ventricle Trial Committee and PHN Steering Committee, together with the National Heart, Lung, and Blood Institute, are responsible for all aspects of this study. The protocol has been approved by an independent protocol review committee, a data and safety monitoring board, and by the institutional review board at each clinical center and at the data coordinating center. The trial is registered at <http://www.clinicaltrials.gov/ct2/show/NCT00113087>.

Study drug

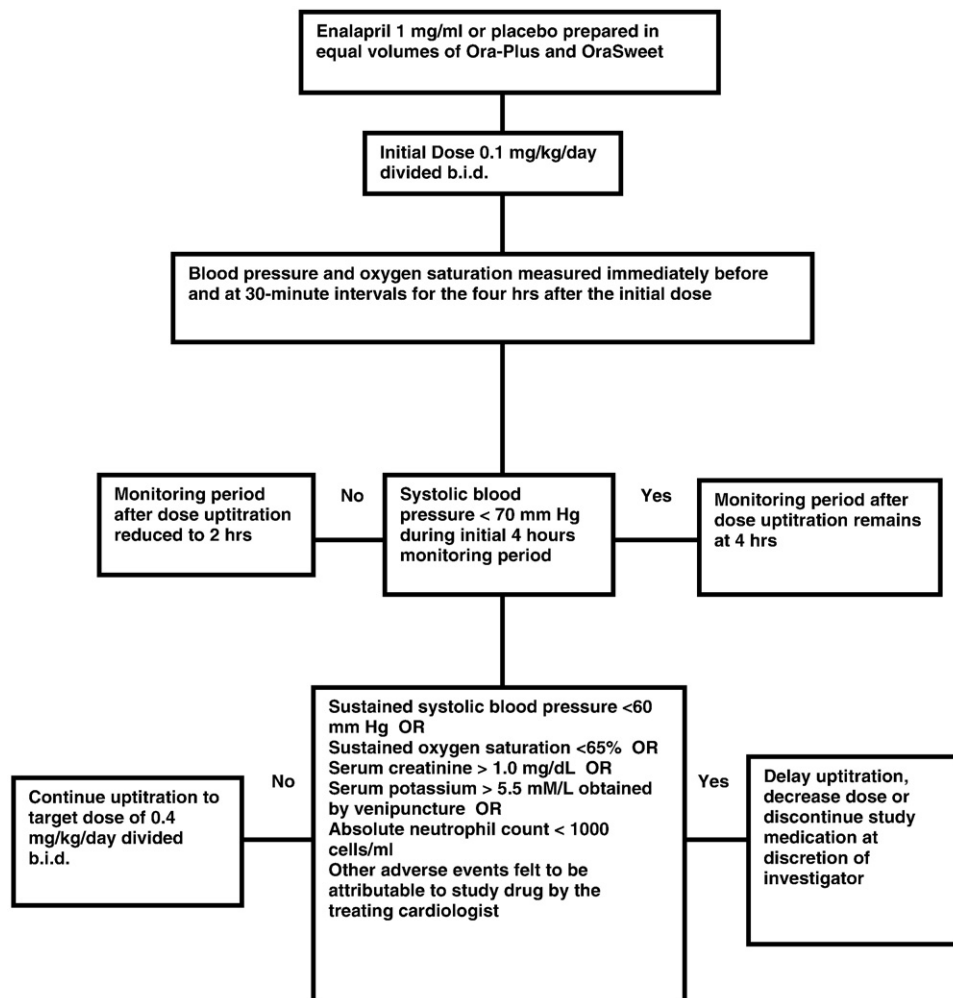
Enalapril was selected as the ACE inhibitor because it is labeled for use in pediatric patients with systemic hypertension and is administered twice a day. Pharmacokinetics and dosing data are available for children as young as 1 month of age. The initial dose was 0.1 mg/kg per day and was uptitrated as tolerated to the target dose of 0.4 mg/kg per day (Figure 2). At each study visit, the dose of study drug was adjusted for weight gain. Study drug compliance was assessed by comparing the expected to the measured residual volume of study drug returned to the pharmacy during the maintenance phase. Study drug was permanently discontinued in the case of an anaphylactoid reaction, serum creatinine > 1.0 mg/dL, neutropenia (absolute neutrophil count $< 1,000$ cells/mL) or if open label use of an ACE inhibitor was planned. If study drug was permanently discontinued the subject was followed until 14 ± 1 months of age. A research investigational new drug application, required due to use of enalapril in neonates without a previously approved indication, was filed with the United States Food and Drug Administration prior to initiating the trial.

Outcome measures

Study measures were collected at prespecified time points summarized in Figure 1.

The superior cavopulmonary anastomosis was electively planned in patients with single-ventricle physiology between 4 and 8 months of age in an attempt to decrease the volume load of the single ventricle. Patient follow-up until 14 months of age provided at least 6 months of observation beyond the surgery to assess the effects of ACE inhibition independent of the acute effects of the

Figure 2



Preparation and up-titration of study drug. *b.i.d.*, Twice daily.

superior cavopulmonary anastomosis. To determine whether ACE inhibition therapy improves growth before the superior cavopulmonary anastomosis, outcome measures before this procedure were also collected.

Somatic growth

The primary outcome of weight-for-age Z-score at age 14 ± 1 months of age will be compared between treatment groups. Height and head circumference-for-age and weight-for-height will be compared as secondary outcomes. Training in the accurate and reliable measurement of weight, height, and head circumference of infants was performed using the training modules from the Health Resources and Service Administration Maternal and Child Health Bureau (<http://depts.washington.edu/growth/>). Quality assurance for the primary outcome included a third

measurement at the examination if the first two measurements were not within 0.1 kg of each other. Absolute weight, height, and head circumference values will be translated into the corresponding Z-scores for age as determined by the National Health and Nutrition Examination Survey (<http://www.cdc.gov/nccdphp/dnpa/growthcharts/resources/sas.htm>).

Severity of heart failure

Angiotensin-converting enzyme inhibitor therapy may improve ventricular function and thereby reduce signs and symptoms of heart failure. Therefore, the Ross Heart Failure Score will be used to assess the effect of ACE inhibition on clinical heart failure,^{18,19} and serum B-type natriuretic peptide (BNP) levels will be used to assess the effect of ACE inhibition on neurohormonal activation. Ross Heart Failure class and BNP levels will be assessed

prior to the superior cavopulmonary anastomosis and at 14 months of age. Resting BNP levels at these two time points were measured at a core laboratory using the Shionogi BNP-32 human assay.²⁰

Neurodevelopmental status

The Bayley Scales of Infant Development-Second Edition²¹ (BSID-II), MacArthur Communicative Development Inventory/Words and Gestures (CDI),²² and the Functional Status II-Revised (FSII-R)²³ provide a profile of the motor and cognitive capabilities of the study subjects that will allow assessment of whether ACE inhibition results in improved functional and neurodevelopmental status relative to placebo at 14 months of age. The BSID-II provides scores designated as the Psychomotor and Mental Development Index scores. Although mild-to-moderate cognitive impairment may be missed by the BSID-II, the BSID-II has been demonstrated in preliminary studies of infants with single ventricle to be sensitive in detecting significant neurodevelopment delay.²⁴ The MacArthur CDI is a parent-report instrument for assessing early language skills. The FSII-R is a parent report questionnaire that measures normal, daily, and age-appropriate functions and has been used to assess the health status of children with chronic disorders. The instrument correlates well with other markers of disease.²⁵ The MacArthur CDI and FSII-R were self-administered in either English or Spanish.

Ventricular geometry and function

Each subject underwent a complete two-dimensional and Doppler echocardiographic examination at baseline, prior to the superior cavopulmonary anastomosis procedure and at 14 months of age to evaluate ventricular and atrioventricular valve function. Image acquisition was performed at centers according to a standard technical protocol. Echocardiograms were interpreted at the core echocardiography laboratory by a single reader to minimize bias and interobserver error. Measurements to be compared between treatment groups include ventricular volume, mass, and ejection fraction using a modified biplane Simpson's algorithm, vena contracta of regurgitant jets, atrioventricular valve inflow Doppler analysis (peak early velocity, peak atrial velocity, early deceleration velocity, and a-wave duration), duration of pulmonary vein flow reversal, tissue Doppler parameters (peak systolic velocity, peak early and late diastolic velocities), valve gradients, and ventricular flow propagation velocity.²⁶

Hemodynamic indices of cardiac function

To gain further insight into ventricular function, locally obtained hemodynamic measurements including the ventricular end diastolic pressure and the pulmonary-to-systemic flow ratio will be compared between treatment

groups in those subjects undergoing cardiac catheterization as part of routine care before the superior cavopulmonary anastomosis.

Relationship between RAAS genotype and response to ACE inhibition

RAAS genotype modifies the response of the ventricle to loading conditions²⁷ and may also influence the response to therapy.²⁸ The impact of RAAS polymorphisms on the response to ACE inhibition will be evaluated by comparing differences in ventricular mass between treatment groups in subjects with and without RAAS polymorphisms. DNA was extracted from whole blood in a core laboratory. The following genes will be evaluated: ACE gene, angiotensinogen gene, angiotensin II receptor type 1 gene, aldosterone synthase gene, and cardiac chymase A gene.^{28,29}

Adverse events with ACE inhibition

The incidence and spectrum of adverse events related to ACE inhibition were collected, including but not limited to hypotension, cyanosis, renal dysfunction, neutropenia, angiodema, allergic reactions, and rash and will be compared between treatment groups. The impact of ACE inhibition therapy on the age of the subject at the time of the superior cavopulmonary anastomosis and length of hospital stay will also be evaluated.

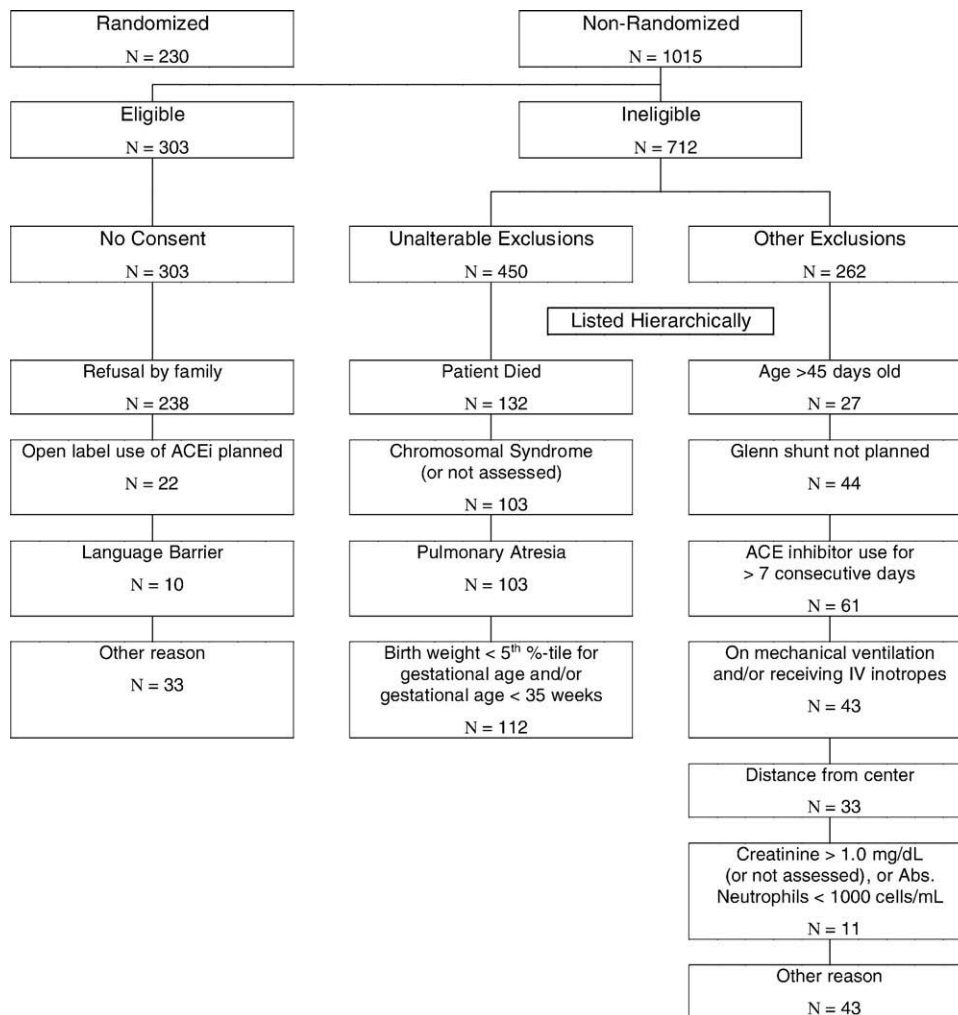
Statistical considerations

The primary end point of the trial is the weight-for-age *Z*-score determined at age 14 ± 1 months. Existing data from the literature^{14,15} and Columbia University indicated that the SD of weight-for-age *Z*-scores in this patient population is approximately 1.1. A mean difference between treatment groups of half a standard deviation (mean *Z*-score difference of 0.5) was considered clinically meaningful. At age 14 months, this is equivalent to a 0.52 kg mean difference between treatment groups. The mean weight-for-age *Z*-score of subjects in the placebo group at age 14 months is expected to be about the 10th percentile for age. A mean group difference in *Z*-scores of 0.5 results in a mean *Z*-score equivalent to the 22.5th weight percentile for age in the ACE inhibition group. A total of 176 subjects (88 per arm) is required to detect this difference with 85% power using a 2-sided .05-level test. Using a conservative inflation rate (20% for loss to follow-up and 3% for group sequential interim analysis), a total target of 230 subjects were randomized (115 per arm).

Interim analysis

One formal interim analysis was planned and executed when approximately half the subjects reached the 14 ± 1 month visit. Lan-DeMets methodology was used to

Figure 3



Pediatric Heart Network infant single-ventricle trial screening results. ACEi, Angiotensin converting enzyme inhibitor; IV, intravenous; abs, absolute.

adjust the boundary appropriately for the precise timing of the interim analysis.³⁰

Analysis plan

The primary analysis will be according to the intention-to-treat principle. All subjects will be analyzed according to their treatment group assignment regardless of actual treatment received. The mean weight-for-age Z-score at age 14 ± 1 months of the 2 groups will be compared using the *t* test. If there is a severe departure from normality, the Wilcoxon rank sum test will be conducted because the presence of negative Z-scores prevents simple transformation of the data. The mean of the two closest measurements made at the exam is used as the final value for analysis. If a subject is withdrawn from the trial, imputation of weight at 14 months will

not be conducted because it is not known what effect the superior cavopulmonary anastomosis may have on weight. Longitudinal weight measurements will be analyzed using mixed model analysis of variance to determine the association over time between ACE inhibitor use and growth.

If there are imbalances on covariates that are prognostic for study outcomes, then covariate-adjusted comparisons will be made as a secondary analysis. A secondary non-intent-to-treat analysis will also be performed using a categorical measure of compliance to account for treatment crossover.

Subgroup analyses

Covariate by treatment group interaction tests will be performed to test whether the treatment effect is

Table II. Infant single ventricle trial baseline characteristics by screening status

Characteristic	Eligible			P*
	Ineligible	Not enrolled	Enrolled	
N	712	303	230	
Mean age at screening (d)	11.9 ± 11.1	11.3 ± 8.4	13.8 ± 9.2	<.001
Male	11.8 ± 11.3	11.3 ± 7.5	13.2 ± 8.0	.028
Female	12.0 ± 10.9	11.2 ± 9.7	15.4 ± 11.4	.008
Median (Q1,Q3) age at screening (d)	8.0 (4.0, 15.5)	10.0 (5.0, 14.0)	13.0 (8.0, 17.0)	<.001
Male	8.0 (4.0, 15.0)	10.0 (6.0, 14.5)	13.0 (8.0, 16.0)	.008
Female	9.0 (4.0, 16.0)	9.0 (4.0, 14.0)	12.5 (6.5, 22.0)	.010
Male	58%	61%	70%	.022
Race				.096
White	74%	72%	80%	
Black or African American	18%	18%	14%	
Asian	4%	4%	3%	
Other	4%	6%	3%	
Hispanic	18%	14%	15%	.703
Gestational age <37 wk	22%	9%	9%	.879
Median (Q1,Q3) gestational age (wk)†	38.0 (37.0, 39.0)	39.0 (38.0, 40.0)	38.0 (37.0, 39.0)	.212
Mean birth weight (kg)	2.9 ± 0.7	3.2 ± 0.5	3.3 ± 0.5	.283
Male	3.0 ± 0.7	3.3 ± 0.5	3.3 ± 0.5	.383
Female	2.8 ± 0.7	3.2 ± 0.4	3.2 ± 0.5	.948
Single ventricle anatomic diagnosis				.168
Single ventricle	33%	36%	29%	
Hypoplastic left heart	42%	54%	63%	
Other functional SV	23%	9%	8%	
Unclassified	2%	0.3%	0.4%	
At least 1 associated anatomic diagnosis	53%	50%	46%	.370
Type of surgery				.138
Norwood	48%	66%	72%	
Systemic-to-pulmonary shunt	25%	21%	17%	
Pulmonary artery band	6%	7%	6%	
Damus-Kaye-Stansel	1%	1%	3%	
Others	20%	5%	2%	
Median number of concurrent surgeries	0.0 (0.0, 1.0)	0.0 (0.0, 1.0)	0.0 (0.0, 1.0)	.317
Median number of interventional cardiac catheterizations: birth to screening	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	.116
Median number of other cardiac surgeries: post-palliation to screening	0.0 (0.0, 1.0)	0.0 (0.0, 1.0)	1.0 (0.0, 1.0)	.061

Q, Quartile.

*Test of significance for differences between enrolled patients and eligible but not enrolled patients. Exact test for categorical variables and t-test or Wilcoxon rank sum test for continuous variables.

†Gestational age imputed as 40 weeks for 72 full-term patients.

homogenous across subgroups. Statistical testing within subgroups will not be conducted unless the interaction test *P* value is <.10. Prespecified subgroups are the following:

- Genotype: the presence or absence of RAAS gene polymorphisms
- Heterotaxy versus no heterotaxy
- Type of systemic single ventricle: left ventricle versus non-left ventricle
- Type of initial surgical palliation: Norwood versus other palliation
- Type of surgery performed to control pulmonary blood flow in the Norwood procedure: right ventricular to pulmonary artery conduit vs. aorto-pulmonary shunt

Time-line and trial enrollment

The enrollment period was from August 2003 through July 2007, and the last subject completed the end-of-study visit in September 2008. Of the 1,245 patients screened during the enrollment period, 712 (57%) did not meet eligibility criteria. Figure 3 summarizes the reasons for exclusion. Inalterable exclusions were present in 450 (63%) of 712 patients. Treatment with open label ACE inhibition during the screening period was the reason for exclusion in 9% (61/712) of ineligible patients. Other reasons for noneligibility included distance from center and the presence of hemodynamic instability requiring mechanical ventilation or inotropic support. Consent was not obtained in 303 (57%) of the 533 eligible patients. Parental or guardian reluctance to participate

in the study was the primary reason for non-consent in 79%. Consent was not sought in 7% because of planned open label use of ACE inhibition.

Table II summarizes the characteristics of the screened population and compares demographics of the eligible patients who did and did not provide consent for randomization. There were several significant differences among the enrolled and not enrolled eligible patients. Patients who were enrolled were more likely to be older at screening completion, to be male and to have hypoplastic left heart syndrome by univariate analysis. The enrolled and not enrolled eligible patients were similar in regard to gestational age, birth weight, race, and type and number of surgeries prior to enrollment.

Conclusions

This trial is designed to assess the safety and efficacy of ACE inhibition in infants with single-ventricle physiology during the first year of life and represents the first double-blind, randomized, placebo-controlled trial of medical therapy to be performed in this population. The primary outcome of weight-for-age Z-score was chosen because growth impairment is common in these infants and ventricular performance is an important factor influencing growth. Secondary outcomes were chosen to assess the impact of ACE inhibition on ventricular remodeling and clinical outcomes, such as heart failure symptoms and neurodevelopment. This study will provide data to determine if RAAS polymorphisms have an important role in modulating the effect of ACE inhibition in this population. By standardizing the drug administration protocol and collecting adverse events prospectively, the data will allow informed risk/benefit assessment of the use of ACE inhibition in this medically fragile population.

Patients who underwent surgical intervention were not eligible for trial enrollment for the first three postoperative days and until such time that stable systemic and pulmonary blood flow was established. Several discussions with the family were often needed to explain the study procedures and obtain consent. Hospital stay and, thus, access to the parents or guardian for study recruitment were shorter for patients not having surgery and for those undergoing simpler procedures, such as aortopulmonary shunt or pulmonary artery banding, than for patients undergoing the Norwood procedure. Differences between the nonrandomized and randomized trial-eligible population are explained in part by the fact that patients with hypoplastic left heart syndrome were in the hospital for a longer period of time, allowing the study investigators and nurse coordinators greater access to the family during the recruitment process.

The 1,245 neonates screened and 230 subjects enrolled in this study are by far the largest number of subjects screened and enrolled in a medical treatment trial in infants with single-ventricle physiology. The results of this double-blind, randomized, placebo-controlled trial will allow the formulation of evidence-based recommendations regarding the use of ACE inhibition in the first year of life in infants with single-ventricle physiology.

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Appendix A

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