Enalapril in Infants With Single Ventricle
Results of a Multicenter Randomized Trial

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Background—Angiotensin-converting enzyme inhibitor therapy improves clinical outcome and ventricular function in adults with heart failure. Infants with single-ventricle physiology have poor growth and are at risk for abnormalities in ventricular systolic and diastolic function. The ability of angiotensin-converting enzyme inhibitor therapy to preserve ventricular function and improve somatic growth and outcomes in these infants is unknown.

Methods and Results—The Pediatric Heart Network conducted a double-blind trial involving 230 infants with single-ventricle physiology randomized to receive enalapril (target dose 0.4 $mg \cdot kg^{-1} \cdot d^{-1}$) or placebo who were followed up until 14 months of age. The primary end point was weight-for-age z score at 14 months. The primary analysis was intention to treat. A total of 185 infants completed the study. There were 24 and 21 withdrawals or deaths in the enalapril and placebo groups, respectively ($P=0.74$). Weight-for-age z score was not different between the enalapril and placebo groups (mean±SE -0.62 ± 0.13 versus -0.42 ± 0.13, $P=0.28$). There were no significant group differences in height-for-age z score, Ross heart failure class, brain natriuretic peptide concentration, Bayley scores of infant development, or ventricular ejection fraction. The incidence of death or transplantation was 13% and did not differ between groups. Serious adverse events occurred in 88 patients in the enalapril group and 87 in the placebo group.

Conclusions—Administration of enalapril to infants with single-ventricle physiology in the first year of life did not improve somatic growth, ventricular function, or heart failure severity. The results of this randomized trial do not support the routine use of enalapril in this population.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00113087.

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Key Words: trials ■ angiotensin ■ heart defects, congenital ■ heart failure ■ pediatrics

Single-ventricle physiology results from underdevelopment of the left or right ventricle during fetal life. Although single-ventricle defects constitute just over 1% of all congenital cardiovascular defects,[1] they account for a disproportionate amount of the morbidity and mortality in infants and children with congenital heart disease. Mortality in the first year of life ranges from 15% to 30%,[2,3] and management of these infants is associated with high levels of resource utilization.[4] One of the most challenging problems in pediatric cardiology is to improve survival and decrease mortality in children with single-ventricle physiology.

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In early infancy, the single ventricle has a significant volume overload because of the need to support both the pulmonary and systemic circulations. The superior cavopul-

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monary connection (SCPC), performed at ≈6 months of age, decreases the volume load on the ventricle; nevertheless, maladaptive ventricular hypertrophy and dysfunction have been described in single-ventricle patients.[5–7] Growth impairment is commonly seen in infants with single-ventricle physiology, and persistent or progressive abnormalities in ventricular structure and function are likely mechanisms that lead to failure to thrive.[2,3,8–10] Previous small studies have shown that, similar to results reported in adults, angiotensin-converting enzyme (ACE) inhibitor therapy can reverse ventricular remodeling and preserve ventricular function in children with volume-overload conditions such as atrioventricular valve regurgitation.[11,12] ACE inhibitor therapy also improves growth in infants with volume overload secondary to large left-to-right shunts.[13–15] On the basis of these findings, the empirical use of ACE inhibitor therapy in infants with a single ventricle is common in many pediatric cardiac centers; however, few data are available on the safety and efficacy of this approach.[16,17] The present trial was designed to determine whether ACE inhibition improves ventricular function and hemodynamic status in infants with single-ventricle physiology, thereby improving a clinically important outcome, somatic growth.

Methods

Study Design

The study was a randomized, double-blind, placebo-controlled trial conducted by the Pediatric Heart Network comparing the effects of enalapril with those of placebo in infants with a single ventricle.[18,19] Patients were enrolled from August 2003 through May 2007 at 10 centers in the United States and Canada. A detailed description of the study design and quality assurance methods for anthropometric measurement has been published.[19] In brief, inclusion criteria consisted of age ≤45 days, age >1 week if born at 35 weeks' gestation, presence of single-ventricle physiology, stable systemic and pulmonary blood flow, and planned SCPC surgery. Exclusion criteria included anatomic diagnosis of pulmonary atresia with intact ventricular septum, <3 days after palliative cardiac surgical procedure (if performed), aortic oxygen saturation <65%, current mechanical ventilatory or intravenous inotropic support, creatinine >1.0 mg/dL, absolute neutrophil count <1000 cells/mL, chromosomal or recognizable phenotypic syndrome of noncardiac congenital abnormalities associated with growth failure, and prior ACE inhibitor use for >7 consecutive days. The protocol was approved by the institutional review boards at the participating institutions, and written informed consent was obtained from the parent or guardian of each patient.

The primary outcome was weight-for-age z score at 14 months of age. Patients were followed up until 14 months of age to allow assessment of the effects of ACE inhibitor therapy for at least 6 months after the volume unloading that occurred after the SCPC surgery. Secondary end points included other measures of somatic growth, Ross heart failure class,[20] brain natriuretic peptide concentration, ventricular geometry and function obtained by 2-dimensional echocardiography, and neurodevelopmental and functional status. Echocardiograms were analyzed centrally by a single core laboratory observer. The methods used for measuring ventricular volumes and assessment of intraobserver variability in single-ventricle patients have been detailed previously.[21] In brief, echocardiographic images were analyzed from the apical (ventricular long-axis) and parasternal short-axis views. The endocardial border of the single ventricle was traced at end diastole and end systole, and the epicardial border was traced at end diastole in both planes. End-diastolic volume, end-systolic volume, and mass were calculated with a biplane-modified Simpson rule. The ejection fraction was calculated as (end-diastolic volume−end-systolic volume)/end-diastolic volume. Ventricular mass was calculated as myocardial end-diastolic volume (epicardial volume−endocardial volume)×myocardial density (1.05 g/mL). Echocardiographic measurements and derived indexes were expressed as z scores relative to body surface area or age in normal children.[22] Brain natriuretic peptide concentration was analyzed centrally. End points were measured at the study visit performed immediately before the SCPC surgery (mean age 5.1±1.8 months) and at the final study visit (mean age 14.1±0.9 months).

Patients were randomly assigned in a 1:1 ratio to the enalapril and placebo treatment groups by use of randomly permuted blocks within strata defined by the presence or absence of hypoplastic left heart syndrome, with dynamic balancing within center. The initial enalapril dose was 0.1 $mg \cdot kg^{-1} \cdot d^{-1}$. Medication was uptitrated as tolerated over a period of 2 weeks to the target dose of 0.4 $mg \cdot kg^{-1} \cdot d^{-1}$, given in 2 divided doses. The dose of study drug was adjusted for weight gain.

Adverse events were classified as nonserious, moderately serious, and serious with the Common Terminology Criteria for Adverse Event version 3.0 categories[23] and compared between groups. All serious adverse events were adjudicated by an independent physician who was unaware of treatment group assignment.

Statistical Analysis

The trial design allowed 85% power to detect a 0.5 mean difference in weight-for-age z score at the final study visit, with 23% inflation for dropout and interim analysis. The primary analysis was performed according to the intention-to-treat principle. A mixed model with a piecewise linear fit for age at measurement for longitudinal analysis of growth z scores by treatment arm was used as the primary analysis to account for intrapatient correlation. This model included an interaction term for age by treatment assignment. A secondary analysis was performed to compare the raw mean growth z scores at the pre-SCPC surgery and final study visits by treatment group with the t test and Wilcoxon rank sum test. A secondary non–intention-to-treat analysis was also performed.

The continuous echocardiographic outcomes and neurodevelopmental scores were compared by treatment group with the Student t test for nonskewed variables and the Wilcoxon rank sum test for other measures. Categorical measures by treatment group were compared with a Fisher exact test. Adverse event rates were compared with Poisson regression.

Prespecified subgroup analyses were performed according to single left ventricle versus single nonleft ventricle; Norwood versus other neonatal palliation; and, among patients who underwent a Norwood procedure, systemic-to–pulmonary artery versus right ventricle–to–pulmonary artery shunt. The presence or absence of heterotaxia was a prespecified subgroup; however, the small number of patients with heterotaxia in the study sample (n=10) precluded analysis. Covariate-by-treatment interaction tests were performed to assess the treatment effect across subgroups. Subgroup analyses of growth outcomes were adjusted for baseline value and gestational age.

Results

Patient Population

A total of 1245 infants <45 days old with single-ventricle anatomy were screened; 533 (43%) were eligible, and 230 (115 in each group, 43% consent rate) were randomized (Figure 1). The eligible patients who were not enrolled were younger (11±8 versus 14±9 days, $P<0.001$), less likely to be male (61% versus 70%, $P=0.02$), and less likely to have hypoplastic left heart syndrome (54% versus 63%, $P=0.04$) than those who were enrolled. Race, gestational age, birth weight, and type of surgery did not differ between the eligible enrolled and nonenrolled patients.

Baseline characteristics were similar for the 2 groups (Table 1), except for gestational age, which was higher in the enalapril group (median 39 versus 38 weeks, $P=0.01$). Of the 230 patients in the study, 45 did not complete the final study

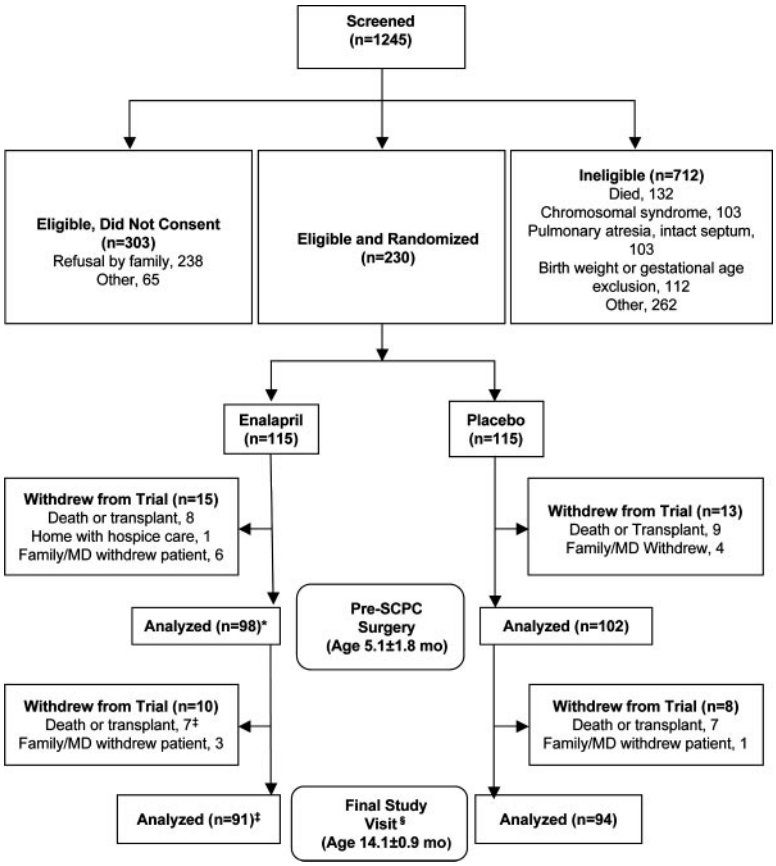

Figure 1. Trial flow diagram. *Two patients who did not undergo the pre-SCPC visit were excluded from analysis at this time point, but they remained in the trial and were included in the final analysis. ‡Includes 1 patient who had growth measurements obtained at the final study visit but died before the neurodevelopmental testing. §Among patients who completed the study, 20 in the enalapril group and 33 in the placebo group discontinued study drug before the final study visit.

visit (24 in the enalapril and 21 in the placebo group, $P=0.74$), which left 185 patients with data for primary end-point analysis (Figure 1). For patients who completed the study (and were randomized to enalapril), the mean enalapril dose administered was 0.31 ± 0.13 mg $\cdot$ kg^{-1} $\cdot$ d^{-1}. The percentage of patients who did not reach the target volume of study drug did not differ between groups (enalapril 43% and placebo 33%). The mean age at the time of SCPC surgery did not differ by treatment assignment (5.6 ± 1.8 versus 5.4 ± 1.8 months, $P=0.52$). Median hospital stay after SCPC surgery was 7 days for both treatment groups (interquartile range 6 to 10 days, $P=0.76$).

Primary Outcome

Intention-to-Treat Analysis

Weight-for-age, height-for-age, and weight-for-height z scores analyzed longitudinally did not differ between the enalapril and placebo groups at age 14 months (Table 2; weight-for-age estimated mean$\pm$SE -0.62 ± 0.13 versus -0.42 ± 0.13, respectively, $P=0.28$). Furthermore, there were no age-specific treatment group differences (weight-for-age z score interaction $P=0.29$; Figure 2). Mean head circumference–for-age z score at age 14 months was lower in the enalapril group than in the placebo group ($P=0.008$); the mean head circumference was 45.7 ± 1.8 cm in the enalapril group and 46.4 ± 2.2 cm in the placebo group. Secondary analysis of visit-specific raw mean growth z scores (see Methods) at the final study and pre-SCPC surgery time points also did not differ by treatment group with the exception of head circumference–for-age z score at the final study visit (Table 2). Inferences were unchanged after adjustment for gestational age.

Non–Intention-to-Treat Analysis

A non–intention-to-treat analysis was performed because of the high proportion (53/185, 29%) of patients who discontinued the study drug during the course of the study. Among those who remained in the study, 20 patients in the enalapril group and 33 in the placebo group permanently discontinued the study drug ($P=0.05$). Patients who received at least 10 consecutive months of study drug and/or open-label enalapril (n=81) were compared with patients who received at least 10 consecutive months of placebo or no ACE inhibitor therapy (n=73). The results confirmed those of the primary analysis, with no difference seen in any of the growth z scores at the pre-SCPC or final study visit except for a lower head circumference–for-age z score at the final study visit in the enalapril group ($P=0.04$). Similar results were also obtained for the subset of 132 patients who received the study drug throughout the course of the study.

Secondary Outcome Comparisons

Compared with normal values, the ventricular mass-to-volume ratio and mass-to-volume ratio z scores were higher in both groups at the pre-SCPC surgery and final study visits ($P<0.01$). The mean ventricular mass-to-volume ratio and mass-to-volume ratio z scores were significantly lower in patients in the enalapril group than in those in the placebo group at the pre-SCPC visit ($P=0.02$), although not at the

Table 1. Baseline Characteristics by Treatment Assignment

Characteristic	Enalapril (n=115)	Placebo (n=115)
Male sex, % (230 patients)	65	76
Mean age at enrollment, d (230 patients)	20.1±8.9	20.7±9.1
Male, d	19.3±9.0	19.6±8.3
Female, d	21.6±8.7	24.3±10.8
Race (229 patients), %		
White	83	77
Black	11	17
Asian	4	3
Other	3	3
Hispanic (225 patients)	14	16
Gestational age* (230 patients), wk		
Median	39	38
Interquartile range	38–40	37–39
Gestational age <37 weeks, %	6	11
Weight, kg (229 patients)	3.4±0.6	3.4±0.5
Weight-for-age *z* score (229 patients)	−1.18±1.29	−1.36±1.24
Weight-for-height *z* score (229 patients)	−0.76±1.28	−0.92±1.27
Height, cm (229 patients)	51.1±2.3	51.1±2.5
Height-for-age *z* score (229 patients)	−1.02±1.27	−1.08±1.28
Head circumference, cm (228 patients)	34.4±1.5	34.2±1.5
Head circumference *z* score (228 patients)	−1.58±1.39	−1.84±1.35
SV anatomic diagnosis (230 patients), %		
SV	30	28
Hypoplastic left heart syndrome	63	64
Other functional SV	7	8
Unclassified	1	0
Type of surgery (225 patients), %		
Norwood	69	79
Systemic-to-pulmonary shunt	20	15
PA band	8	4
Damus-Kaye-Stansel	4	3
Overall AV valve regurgitation (229 patients), %		
None	22	25
Mild	57	51
Moderate	22	24
Severe	0	1
Systemic ventricular dysfunction (229 patients), %		
None	83	77
Mild	12	17
Moderate	5	4
Severe	0	1

SV indicates single ventricle; PA, pulmonary artery; and AV, atrioventricular.

Plus-minus values are mean±SD. Percentages may not add to 100 because of rounding. All *z* scores were calculated with World Health Organization standards. No between-group comparisons were significant (all $P>0.10$) except for gestational age ($P=0.01$).

*Gestational age imputed as 40 weeks for 5 full-term patients.

final study visit ($P=0.34$). Moderate to severe atrioventricular valve regurgitation was present in 12% of the enalapril group and 24% of the placebo group at the final study visit ($P=0.06$). Mean *z* scores at the final study visit were higher in the enalapril group for 3 of the 4 domains of the MacArthur-Bates Communicative Development Words and Gestures Inventory, a measure of early language development. No other differences were found between the treatment groups (Table 3).

Subgroup Analyses

There was no difference in the effect of enalapril on the primary end point of weight-for-age *z* score at the final study visit across the predetermined subgroups defined by anatomy or type of palliation. Furthermore, no other end points had a treatment group interaction with a subgroup factor below the 0.05 level.

Adverse Events

No difference in the number of adverse events was observed between the treatment groups (423 in the enalapril group and 389 in the placebo group, $P=0.23$). Four or more events per patient occurred in 37% of the enalapril group and 30% of the placebo group. Serious adverse events occurred in 88 of the enalapril group patients (220 events) and 87 of the placebo group patients (208 events). The proportions of serious adverse events (in the categories of general cardiac [nonarrhythmia], gastrointestinal, infection, pulmonary, and vascular) were similar in the enalapril and placebo groups (86% and 81%, respectively). Serious cardiac events occurred in 29 patients in the enalapril group and 19 in the placebo group ($P=0.14$). Death occurred in 24 patients (12 in each group). Three patients in the enalapril group and 4 in the placebo group underwent transplantation. A serious renal adverse event occurred in 1 patient in the enalapril group (1 event) and 1 patient in the placebo group (2 events).

Discussion

This trial is the largest randomized, double-blind study performed to date to assess the impact of a medical intervention in infants with a single ventricle. Despite standard surgical palliation, there was a high incidence of death, heart transplantation, ventricular dysfunction, growth failure, neurodevelopmental delay, and other complications during the course of the present study, and these outcomes highlight the need for better evidence-based therapies in this population. This study, however, failed to demonstrate a beneficial effect of enalapril therapy on the primary end point of weight-for-age at 14 months of age or on the secondary end points of height-for-age, head circumference–for-age, ventricular structure and function, or clinical heart failure in this population of infants with single ventricle, the majority of whom had normal ventricular function and no significant atrioventricular valve regurgitation. Although the present study was not designed to analyze the effect of enalapril on the subset of infants with ventricular dysfunction, there was no difference in the proportion of patients who died or underwent cardiac transplantation between the 2 groups, which implies that enalapril was not protective against end-stage heart failure or

Table 2. World Health Organization Growth *z* Scores by Treatment Assignment

	Enalapril	Placebo	Difference* (95% CI)	*P*†
Predicted mean±SE at age 14 mo based on longitudinal modeling‡				
Weight-for-age *z* score	−0.62±0.13 (91)	−0.42±0.13 (94)	−0.20±0.18 (−0.56 to 0.16)	0.28
Weight-for-height *z* score	−0.18±0.13 (91)	−0.08±0.13 (94)	−0.11±0.18 (−0.47 to 0.25)	0.55
Height-for-age *z* score	−1.00±0.13 (91)	−0.86±0.13 (94)	−0.14±0.18 (−0.50 to 0.21)	0.42
Head circumference–for-age *z* score	−0.55±0.17 (91)	0.09±0.17 (94)	−0.64±0.24 (−1.11 to −0.17)	0.008
Raw mean±SD at pre-SCPC surgery and final study visits§				
Pre-SCPC surgery visit‖				
Weight-for-age *z* score	−1.60±1.16 (97)	−1.66±1.12 (100)	0.07±1.14 (−0.25 to 0.39)	0.69
Weight-for-height *z* score	−0.88±1.18 (97)	−1.03±1.28 (100)	0.14±1.23 (−0.20 to 0.49)	0.42
Height-for-age *z* score	−1.30±1.37 (97)	−1.28±1.17 (100)	−0.02±1.27 (−0.37 to 0.34)	0.93
Head circumference–for-age *z* score	−1.49±1.33 (97)	−1.32±1.05 (99)	−0.17±1.20 (−0.51 to 0.17)	0.32
Final study visit				
Weight-for-age *z* score	−0.54±1.09 (91)	−0.43±1.13 (94)	−0.11±1.11 (−0.44 to 0.21)	0.49
Weight-for-height *z* score	−0.16±1.04 (91)	−0.00±1.16 (94)	−0.16±1.10 (−0.48 to 0.16)	0.34
Height-for-age *z* score	−0.92±1.20 (91)	−0.94±1.13 (94)	0.02±1.16 (−0.32 to 0.35)	0.92
Head circumference–for-age *z* score	−0.40±1.28 (91)	0.09±1.59 (94)	−0.48±1.44 (−0.90 to −0.06)	0.02

*Difference was defined as the mean for the enalapril group minus the mean for the placebo group.

†*P* for predicted means was calculated using a contrast of the estimated group means at 14 months and their associated standard errors from longitudinal modeling. *P* for raw means was based on the 2-sample *t* test (inferences were similar with the use of a Wilcoxon rank sum test and after adjustment for gestational age). *P* values are unadjusted for the 1 interim look at the data.

‡Data from all 230 subjects were used in longitudinal analysis (see Methods).

§All mean *z* scores differ from zero (the normal population mean), $P<0.05$ by 1-sample *t* test with 3 exceptions, all at the final study visit: Weight-for-height *z* score for both treatment arms and head circumference–for-age *z* score for the placebo group were not significantly different from zero.

‖Weight measurements were not available for 1 patient in the enalapril group and 2 patients in the placebo group at the pre-SCPC visit.

death. There was no treatment effect identified within prespecified subgroups, which suggests that enalapril is not beneficial even for targeted subsets of patients.

The failure of enalapril to improve somatic growth is likely multifactorial. Enalapril failed to cause a sustained improvement in ventricular structure and function, which indicates that enalapril did not result in hemodynamic improvement and promotion of somatic growth. The lack of a remodeling effect of enalapril may be a result of differences in activation of the renin-angiotensin-aldosterone system in the single-ventricle population compared with adult patients with heart failure.[24] Coupled with the recent negative trial results of carvedilol in pediatric heart failure,[25] the present findings suggest that standard heart failure therapy may not be beneficial in patients with complex single-ventricle physiology. The SCPC surgery resulted in significant ventricular remodeling and catch-up growth, which suggests that surgical volume unloading is a more effective strategy than ACE inhibitor therapy for improving cardiac performance in these patients. In addition, growth failure in single-ventricle patients often results from noncardiac causes such as chronic feeding difficulties, gastrointestinal reflux, or unknown or

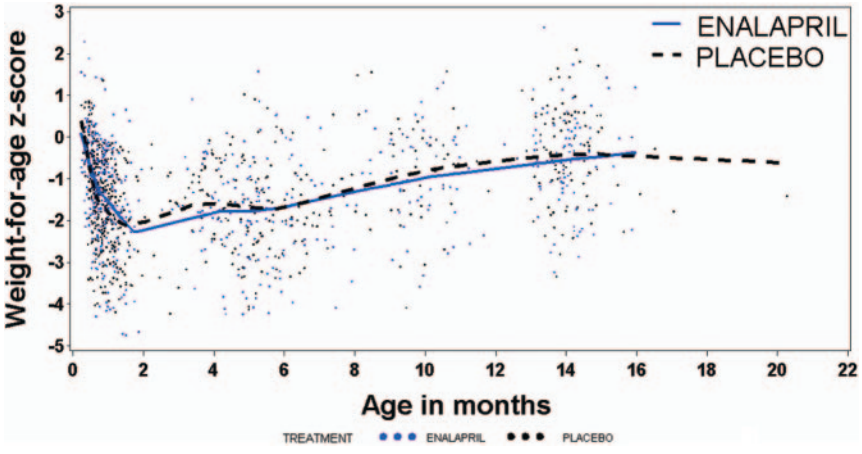

Figure 2. LOWESS (locally weighted scatterplot smoothing) curves of weight-for-age *z* score by treatment assignment vs age in months. The default smoothing parameter was 0.26. All data for final study visit (target age 14 months, actual mean age 14.1±0.9 months) were included. Blue points denote assignment to enalapril, and black points denote assignment to placebo.

Table 3. Secondary Outcomes by Treatment Assignment

	Pre-SCPC Surgery			Final Study Visit		
Variable	Enalapril	Placebo	*P**	Enalapril	Placebo	*P**
BNP, pg/mL						
Median (No. of patients)	79.0 (83)	84.0 (90)	0.74	25.0 (69)	39.0 (65)	0.22
Interquartile range	30–182	36–196		13–55	21–86	
Ejection fraction, %	57.9±9.8 (94)	56.6±10.2 (95)	0.36	59.3±9.6 (87)	57.9±10.4 (91)	0.37
Ventricular mass, g	25.5±9.2 (93)	28.1±10.6 (94)	0.08	31.4±10.3 (87)	34.4±11.4 (89)	0.07
Ventricular mass *z* score	4.0±2.9 (92)	4.9±3.3 (92)	0.05	2.5±2.3 (87)	3.1±2.5 (89)	0.11
End-diastolic volume, mL	24.1±10.1 (94)	23.2±9.0 (95)	0.49	29.2±10.0 (87)	30.7±11.3 (91)	0.35
End-diastolic volume *z* score	2.3±2.5 (93)	2.1±2.5 (93)	0.62	1.1±2.1 (87)	1.3±2.4 (91)	0.43
Mass-volume ratio	1.15±0.43 (93)	1.31±0.50 (94)	0.02	1.14±0.38 (87)	1.20±0.44 (89)	0.34
Mass-volume ratio *z* score†	1.6±2.8 (93)	2.6±3.2 (94)	0.02	1.5±2.5 (87)	1.9±2.9 (89)	0.34
Ventricular filling pressure, mm Hg	10.9±3.6 (58)	11.1±4.0 (63)	0.81			
Ross Heart Failure class I	53/96 (55)	56/102 (55)	1.00	72/91 (79)	77/94 (82)	0.71
Moderate to severe AV valve regurgitation	20/98 (20)	32/98 (33)	0.08	11/90 (12)	22/93 (24)	0.06
Bayley Scales of Infant Development, 2nd edition						
Mental Developmental Index *z* score	N/A	N/A	N/A	−0.26±0.91 (87)	−0.33±1.02 (83)	0.60
Psychomotor Developmental Index *z* score	N/A	N/A	N/A	−1.29±1.19 (86)	−1.32±1.22 (83)	0.88
Total behavior rating scale						
Median (No. of patients)	N/A	N/A	N/A	58.0 (87)	49.0 (82)	0.19
Interquartile range	N/A	N/A	N/A	29–83	23–71	
Functional status II (revised) total score						
Median	N/A	N/A	N/A	96.4 (89)	96.4 (89)	0.60
Interquartile range	N/A	N/A	N/A	89–100	86–100	
MacArthur-Bates Communicative Development Inventory (Words and Gestures)						
Phrases understood *z* score	N/A	N/A	N/A	−0.48±1.11 (90)	−0.92±1.17 (87)	0.01
Words understood *z* score	N/A	N/A	N/A	−0.46±0.91 (90)	−0.82±0.83 (87)	0.008
Total gestures *z* score	N/A	N/A	N/A	−0.86±1.07 (90)	−1.31±0.97 (87)	0.004
Words produced *z* score						0.31
Median (No. of patients)	N/A	N/A	N/A	−0.60 (90)	−0.63 (87)	
Interquartile range	N/A	N/A	N/A	−0.72 to 0.41	−0.75 to 0.42	

BNP indicates brain natriuretic peptide; AV, atrioventricular; and N/A, not applicable.

Values are mean±SD (No. of patients) or n/N (%) unless otherwise indicated.

**P* for categorical variables was calculated with the use of a Fisher exact test. *P* for variables presented as means and medians was calculated with a 2-sample *t* test and a Wilcoxon rank sum test, respectively. *P* for BNP was calculated with a 2-sample *t* test of the natural logarithm of BNP.

†Mass-volume ratio *z* score was slightly skewed. Medians for the enalapril and placebo groups were 1.00 vs 2.05 (Wilcoxon $P=0.03$), respectively, at pre-SCPC surgery. Mass-volume ratio *z* score medians for the enalapril and placebo groups were 0.96 vs 1.10 (Wilcoxon $P=0.57$), respectively, at the final study visit.

The 1-sample *t* test and Wilcoxon signed-rank test were used to compare the distribution of the Bayley Scales of Infant Development and MacArthur Communicative Development Inventory *z* scores from the trial (presented in Table 3) with the normal population. These *z* scores differ from zero ($P<0.02$). The Bayley Total Behavior Rating Scale percentile did not differ from the 50th percentile in either treatment arm. All echocardiographic *z* scores differed from zero ($P<0.01$).

uncharacterized genetic influences. These factors may not be modified by enalapril therapy and may be more important than any potential hemodynamic effect of enalapril.[26] The clinical implications of the findings of better catch-up growth in head circumference–for-age in the placebo group and higher MacArthur Bates Communicative Development Index scores (which indicate more advanced language and communication skills[27]) in the enalapril group are unclear. Further investigation is needed, because there is no known physiological basis for a primary effect of enalapril on either of these outcomes.

An important adverse effect of volume loading shown in the present study was an inappropriate degree of ventricular

hypertrophy, with a marked increase in ventricular mass that was disproportionate to the degree of ventricular dilation, as seen by the increased mass-to-volume ratio. This effect was present before the SCPC surgery in both treatment groups. Although volume-unloading surgery reduced ventricular mass and volume, it failed to normalize the ventricular mass-to-volume z score. The lower mass-to-volume z scores in the enalapril group than in the placebo group before the SCPC surgery suggest that enalapril may have an antihypertrophic effect on the volume-loaded single ventricle. By the final study visit, ventricular mass, volume, and mass-to-volume ratio did not differ between the groups.

There are several important limitations to the present study. The 20% loss-to-follow-up rate was high, although anticipated in the study design. The permanent discontinuation of the study drug in 29% of the patients who completed the trial is substantial. However, in the secondary non–intention-to-treat analysis, even patients who received enalapril for at least 10 months did not differ from those who received placebo. The high number of patients included in the intention-to-treat analysis who did not reach the target dose of enalapril raises the possibility that the lack of effect may reflect a subtherapeutic dose. Overall, the failure to achieve the target dose in many patients reflects the challenges of administering an afterload-reducing agent to fragile infants with single-ventricle physiology, even in those with normal single-ventricle function. Treatment guidelines do not recommend the use of ACE inhibitor therapy in adult patients with atrioventricular valve regurgitation and normal ventricular function.[28] The present study was not designed to determine the effect of enalapril on the subset of patients with significant atrioventricular valve regurgitation at baseline, and the small number of patients with this finding limited further analysis. Finally, the trial may have been inadequately powered to detect a treatment effect in patient subgroups.

In conclusion, this randomized trial did not show a favorable effect of enalapril on somatic growth, clinical outcomes, ventricular function, or overall neurodevelopmental outcomes in infants with single-ventricle physiology and does not support the routine use of enalapril in this population. These results highlight the need to develop newer and more specific therapies targeted to this complex and growing population of patients.

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Disclosures

None.

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CLINICAL PERSPECTIVE

Infants with complex heart lesions that lead to single-ventricle physiology are at risk for abnormalities in ventricular systolic and diastolic function and for poor growth. Extrapolation of data from the adult literature has led to the empiric use of angiotensin-converting enzyme inhibitor therapy in this population; however, its efficacy has never been studied. The Pediatric Heart Network conducted a multicenter, double-blind, placebo-controlled trial involving 230 infants with single-ventricle physiology randomized to receive enalapril (target dose 0.4 $mg \cdot kg^{-1} \cdot d^{-1}$) or placebo and followed up to 14 months of age. Overall, the majority of the study population had normal ventricular function and no clinical heart failure at 14 months of age, regardless of the treatment group. Growth was significantly impaired, and there were neurodevelopmental abnormalities noted. The incidence of death or transplantation was 13% and did not differ between treatment groups. Administration of enalapril did not improve somatic growth, ventricular function, or heart failure severity. The results of this randomized trial do not support the routine use of enalapril in this population.

Enalapril in Infants With Single Ventricle: Results of a Multicenter Randomized Trial

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