Safety of Enalapril in Infants: Data from the Pediatric Heart Network Infant Single Ventricle Trial

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Objective To assess the safety profile of angiotensin-converting enzyme inhibitor therapy in infants with single ventricle.

Study design The Pediatric Heart Network conducted a double-blind trial involving infants with single ventricle physiology randomized to receive enalapril or placebo and followed to 14 months of age. Data including demographics, drug administration, hemodynamic monitoring, laboratory measurements, adverse events, and survival were extracted from the public use data set and compared between the placebo and enalapril-treated groups.

Results The Infant Single Ventricle trial randomized 230 patients, with 115 patients in each group. Initial enalapril dose was 0.10 mg/kg/d and median maximal dose was 0.38 mg/kg/d. There was no significant difference in change in blood pressure at study drug initiation or when resuming study drug after Glenn surgery. The incidence of hyperkalemia and neutropenia did not differ between groups. Renal dysfunction occurred in 3% of the enalapril group and none of the placebo patients, which was not statistically significant. There was a high frequency of serious adverse events in both groups. There was no difference in the frequency of heart transplant or death between groups.

Conclusions Enalapril did not have sustained hemodynamic effects at initiation or up-titration of drug. Creatinine and potassium were not different between groups, although renal dysfunction occurred more often in the patients on enalapril. Although efficacy of enalapril in neonates with single ventricle has not been demonstrated, the safety profile of angiotensin-converting enzyme inhibitors appears to be low risk in infants and children with significant heart disease. *(J Pediatr 2020;227:218-23)*.

Angiotensin-converting enzyme (ACE) inhibitors are used frequently in infants and children for a variety of medical conditions. They are recommended as first-line therapy in children with heart failure and left ventricular systolic dysfunction[1] as well as in children and adolescents with hypertension.[2] There is a paucity of data regarding the efficacy and safety of ACE inhibitors in pediatric patients, which can cause hypotension, hyperkalemia, renal dysfunction, and neutropenia. Several retrospective analyses and reviews have described adverse events associated with ACE inhibitor therapy.[3] These studies have identified patients who are particularly vulnerable to the side effects of ACE inhibitors, including preterm and term neonates[4] and infants or children with congenital heart disease.[5-8] There are a few, small randomized controlled trials assessing the efficacy and safety of ACE inhibitor use in pediatric patients with hypertension. These trials found that ACE inhibitors are well tolerated in these older populations, although there was limited laboratory data in these studies.[9-11]

The Pediatric Heart Network (PHN) Infant Single Ventricle (Infant Single Ventricle) trial provides an opportunity to examine the use and safety of an ACE inhibitor in a large population of infants. The Infant Single Ventricle trial was a multicenter, double-blind trial of infants with a single ventricle randomized to receive enalapril or placebo. The aim of the PHN Infant Single Ventricle trial was to determine whether ACE inhibition would improve ventricular function and the hemodynamic status in infants with a single ventricle, with a primary outcome of improved weight-for-age z score. Although the study did not demonstrate a beneficial effect of enalapril on somatic growth, heart failure classification, neurodevelopmental outcomes, or ventricular function, it did provide the opportunity to assess the safety profile of enalapril in this population of infants.

Methods

The PHN Infant Single Ventricle trial enrolled infants with single ventricle anatomy anatomy who had undergone surgical palliation at 10 centers in the US and Canada between 2003 and 2007. A total of 230 infants were randomized to receive enalapril or placebo and followed until 14 months of age. Detailed description of the original study design, methods, and results have been

ACE	Angiotensin-converting enzyme
ANC	Absolute neutrophil count
PHN	Pediatric Heart Network

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The analysis of the public-use trial dataset was performed independently of the National Heart, Lung, and Blood Institute–funded Pediatric Heart Network. The authors declare no conflicts of interest.

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published.[12,13] Comprehensive vital signs and laboratory monitoring were collected at regular intervals (drug initiation, 4 days after drug initiation, 2 weeks after drug initiation, before Glenn surgery, 7 days after drug re-initiation, 10 months of age, and 14 months of age). Adverse events were classified by category of severity using the Common Terminology Criteria for Adverse Events v3.0.[14] Serious adverse events were reviewed and adjudicated by an independent monitor.

Study drug was started at 0.1 mg/kg/d divided every 12 hours and up-titrated to a target dose of 0.4 mg/kg/d divided every 12 hours. Up-titration was determined by individual cardiologist discretion, with a goal of reaching the target dose 2 weeks after initiation. Up-titration was delayed or the dose decreased if subjects had sustained blood pressure <60 mm Hg, sustained oxygen saturation <65%, serum creatinine >1.0 mg/dL, serum potassium >5.5 mM/L, absolute neutrophil count (ANC) <1000 cells/mm^3, or other adverse events felt to be attributable to study drug.

At the time of initial drug administration, blood pressure was monitored at 30-minute intervals until 240 minutes following drug administration. Study drug was discontinued after Glenn surgery per protocol and restarted at the discretion of the patient's cardiologist. At the time that study drug was restarted, blood pressure was measured 120 minutes after drug administration. Patients who had a systolic blood pressure <70 mm Hg at 120 minutes after study drug was restarted had their blood pressure rechecked at 240 minutes.

The National Institutes of Health/National Heart, Lung, and Blood Institute PHN Infant Single Ventricle trial dataset was used in preparation of this work. Data were downloaded from https://www.pediatricheartnetwork.org//pud_login.asp?study_id=ISV on 3/01/2016. Data including patient demographic information, hemodynamic monitoring, serum laboratory values, adverse events, and survival data were extracted for all patients enrolled and randomized in the trial. Hemodynamic measures and laboratory data were analyzed at drug initiation, scheduled monitoring visits, and at drug re-initiation. The primary aim of this analysis was to compare the safety profile of enalapril compared with placebo in patients with single-ventricle physiology, specifically focused on changes in blood pressure, serum potassium, serum creatinine, and absolute neutrophil count. The secondary aim was to compare and describe adverse events in the placebo and enalapril-treated groups.

Hyperkalemia was defined as serum potassium ≥5.5 mEq/L (5.5 mmol/L). Renal dysfunction was defined as serum creatinine ≥1.0 mg/dL (88.4 μmol/L). Neutropenia was defined as ANC ≤1500 cells/mm^3 (1500 cells/μL), rather than ≤1000 cells/mm^3 (1500 cells/μL) as used in the trial.

Intention-to-treat analysis was performed. Descriptive statistics were performed for all variables of interest. Categorical variables were expressed as counts and percentages. Continuous variables were expressed as means with SD for normally distributed variables and medians with IQR for non-normally distributed variables. The Student t test was used for normally distributed continuous variables, The Mann–Whitney U test was performed for non-normally distributed continuous variables, and the χ^2 test or Fisher exact (used for cell counts <5) analysis were performed on all categorical variables. Statistical significance was defined as a P value ≤.05.

Results

The trial randomized 230 patients with single ventricle with 115 patients in each group. Baseline characteristics were similar for the 2 groups, except for the mean gestational age, which was 38.2 weeks in the placebo group and 38.6 weeks in the enalapril group. The enalapril cohort had a mean age of 22 ± 15 days and a mean weight of 3.4 ± 0.6 kg at the time of drug initiation (**Table I**). The initial enalapril dose was 0.10 mg/kg/d divided every 12 hours, and median maximal dose was 0.38 mg/kg/d divided every 12 hours (IQR 0.21-0.4 mg/kg/d). Median time for up-titration to maximal dose was 3 days (IQR 2-11 days).

A total of 45 patients withdrew from the study (21 in the placebo group, 24 in the enalapril group, P = .74). Among the 185 patients who completed the study, 53 patients permanently discontinued study drug before the last study

Table I. Baseline characteristics by treatment assignment

Characteristics	Placebo (N = 115)	Enalapril (N = 115)	P value
Mean gestational age, wk (SD)	38.2 ± 1.4	38.6 ± 1.4	**.04***
Mean birth weight, kg	3.2 ± 0.5	3.3 ± 0.5	.3*
Mean age at initiation, d	22 ± 9	22 ± 15	.89*
Mean weight at initiation, kg	3.3 ± 0.5	3.4 ± 0.6	.49*
Race			
White, %	77	83	.74†
Black, %	17	10	.15†
Asian, %	3	4	1‡
Other, %	3	2	1‡
Hispanic, %	16	14	.7†
Single-ventricle diagnosis			
Hypoplastic left heart syndrome, %	64	63	.9†
Single ventricle, %	28	30	.76†
Other functional single ventricle, %	8	8	1†
Type of surgery			
Norwood, %	79	69	.17†
Systemic-to-pulmonary shunt, %	15	20	.36†
PA band, %	4	8	.38‡
DKS, %	3	4	1‡
AV valve regurgitation			
None, %	25	22	.62†
Mild, %	51	57	.43†
Moderate, %	24	22	.74†
Severe, %	1	0	1‡
Systemic ventricular dysfunction			
None, %	77	88	.11†
Mild, %	17	12	.32†
Moderate, %	4	5	1‡
Severe, %	1	0	1‡

AV, atrioventricular; *DKS*, Damus–Kaye–Stansel; *PA*, pulmonary artery.
Bold values denote statistically significant P values.
*Indicates P value calculated by Student t test.
†Indicates P value calculated by χ^2 analysis.
‡Indicates P value calculated by Fisher exact test.

visit (33 in the placebo group, 20 in the enalapril group, $P = .05$). The median age at discontinuation of study drug was 73 days (IQR 38-164 days) in the placebo group vs 56 days (IQR 30-142 days) in the enalapril group, $P = .32$. Among the patients who withdrew or discontinued study drug, 33 started an open-label ACE inhibitor (19 in the placebo group, 14 in the enalapril group, $P = .62$).

There was no significant difference in systolic blood pressure between the placebo and enalapril-treated groups at any time point during the 240-minute monitoring period after drug initiation (**Figure**, A). The mean decrease in systolic blood pressure was 11 ± 12% in the placebo group and 11 ± 11% in the enalapril-treated group during the monitoring period, $P = .51$.

Blood pressure was significantly lower in the enalapril group at a median of 3 days (IQR 3-5 days) following drug initiation (79 ± 11 mm Hg) compared with the placebo group (83 ± 12 mm Hg), $P = .01$. There was no significant difference in blood pressure between treatment groups 2 weeks following drug initiation, or before Glenn surgery (**Figure**, C).

After Glenn surgery, the enalapril cohort restarted study drug at a median age of 167 days (IQR 144-193 days). Enalapril was restarted at a median dose of 0.29 mg/kg/d divided every 12 hours (IQR 0.2-0.39 mg/kg/d). There was a range of practice variation at the time study drug was restarted, with some patients starting at a lower dose, some at the same dose, and some at a higher dose than previously prescribed. There was no significant difference in the systolic blood pressure between the placebo and enalapril-treated groups at 120 minutes (**Figure**, B). In patients who had a systolic blood pressure less than 70 mm Hg 120 minutes after restarting study drug, blood pressure was checked again at 240 minutes. In the subgroup of patients who required further monitoring at 240 minutes, systolic blood pressure was significantly lower in the enalapril group at 92 ± 12 mm Hg (n = 23) vs 100 ± 14 mm Hg in the placebo group (n = 30), $P = .02$.

Blood pressure was significantly lower in the enalapril group at a median of 5 days (IQR 4-8 days) after drug re-initiation following Glenn surgery (93 ± 13 mm Hg) compared with the placebo group (99 ± 12 mm Hg), $P = .01$ (**Figure**, C). Blood pressures at the 10- and 14-month visits were not significantly different between groups.

The mean creatinine was significantly greater in the treatment cohort at 37 days, which was 2 weeks after starting study drug (0.44 ± 0.16 mg/dL in the enalapril group vs 0.40 ± 0.1 mg/dL in the placebo group, $P = .05$). There was no significant difference between creatinine at any other time point (**Table II**). The mean maximal creatinine was not significantly different between placebo (0.48 ± 0.13 mg/dL) or enalapril groups (0.55 ± 0.38 mg/dL), $P = .06$. There was no significant difference in the number of patients in each group with a maximal creatinine between 0.5 and 1 mg/dL (54 in the placebo group vs 61 in the enalapril group, $P = .36$). Renal dysfunction as defined by creatinine ≥1.0 mg/dL occurred in 3 of the patients treated with enalapril and none of the placebo patients, which was not statistically significant (**Table III**).

There was no significant difference in the mean serum potassium at different time points throughout the study (**Table II**), or in the incidence of hyperkalemia between groups (**Table III**). The placebo group had a significantly lower median ANC at 173 days (4792 cells/mm^3, IQR 3149-6478 cells/mm^3) compared with the enalapril group at the same monitoring visit (5630 cells/mm^3, IQR 4075-8107 cells/mm^3), $P = .007$ (**Table II**). However, there was no significant difference in the incidence of neutropenia between groups (**Table III**).

There was a high rate of adverse events in both groups, including events categorized as serious adverse events (**Table III**). The most common types of serious adverse events were infectious and respiratory. Both groups also experienced a similar frequency of serious vascular events, including shunt occlusion. There was no difference between the 2 groups in the number of patients who experienced hypotension as an adverse event (8 in the placebo group vs 17 in the enalapril group, $P = .06$). There was no difference in the number of adverse events possibly attributed to study drug between groups (33 of 389 in the placebo group vs 41 of 423 in the enalapril group, $P = .35$). There was no difference in the frequency of transplant or death between groups, or in the number of deaths possibly attributed to study drug (1 of 12 in the placebo group vs 2 of 12 in enalapril group, $P = 1$).

Discussion

In this subanalysis of infants with single ventricle randomized to placebo or enalapril, we showed no sustained hemodynamic effects at the time that enalapril was initiated or re-initiated after Glenn surgery. Blood pressures were significantly lower in the enalapril-treated group compared with placebo the first week of both drug initiation and after resuming study drug. These differences resolved at subsequent monitoring visits. There was no significant difference in the incidence of hypotension, hyperkalemia, renal dysfunction, or neutropenia between groups. Both the placebo group and enalapril-treated group experienced a high incidence of adverse events. The most common types of serious adverse events were infectious and respiratory events, with a similar distribution between groups. There was no difference in the rate of heart transplant or death between groups.

Current data regarding the safety of ACE inhibitor use in infants with heart disease is primarily based on single center, retrospective studies. The few randomized controlled trials that have been conducted have been in older children with hypertension. Although ACE inhibition was found to be clinically well tolerated in these studies, laboratory safety data were limited.[9-11] A small, prospective trial was recently conducted to assess safety when rapidly up-titrating ACE

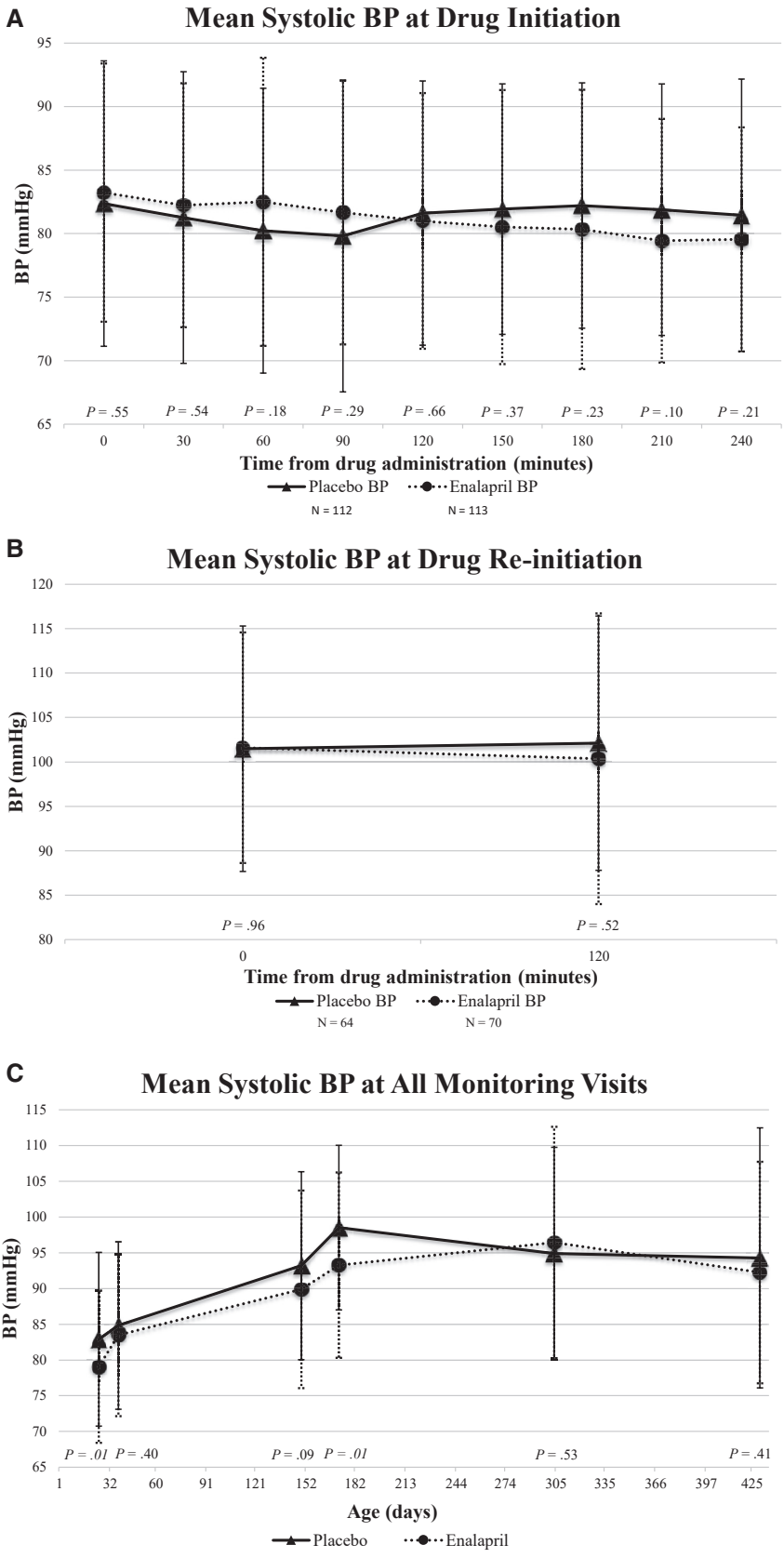

Figure. Mean systolic blood pressure at **A,** study drug initiation; **B,** when restarting study drug after Glenn surgery; and **C,** at all study monitoring visits. *BP*, blood pressure.

Table II. Laboratory safety monitoring by treatment assignment

	Mean creatinine, mg/dL			Mean potassium, mM/L			Median ANC, cells/mm^3		
Mean age, d	Placebo	Enalapril	*P* value	Placebo	Enalapril	*P* value	Placebo	Enalapril	*P* value
22	0.46 ± 0.15	0.46 ± 0.13	.89*	4.61 ± 0.91	4.54 ± 0.85	.54*	7056	6721	.22†
25	0.44 ± 0.12	0.46 ± 0.13	.26*	4.99 ± 0.72	5.11 ± 0.76	.23*	5449	5892	.68†
37	0.40 ± 0.11	0.44 ± 0.16	**.05***	5.07 ± 0.79	5.11 ± 0.69	.66*	4295	4470	.46†
149	0.33 ± 0.10	0.35 ± 0.09	.14*	4.63 ± 0.71	4.63 ± 0.75	1*	2746	3105	.07†
173	0.32 ± 0.09	0.34 ± 0.10	.15*	4.63 ± 0.64	4.80 ± 0.72	.16*	4792	5630	**.007†**
430	0.35 ± 0.11	0.39 ± 0.47	.53*	4.63 ± 0.45	4.55 ± 0.57	.37*	3285	3854	.33†

Bold values denote statistically significant *P* values.
*Indicates *P* value calculated by the Student *t* test.
†Indicates *P* value calculated by the Mann–Whitney *U* test.

inhibitors in children with congenital heart disease or dilated cardiomyopathy.[15] The indications to start ACE inhibitor therapy included ventricular dysfunction, pulmonary overcirculation, atrioventricular valve regurgitation, hypertension, and protein-losing enteropathy. A subset of these patients had single ventricle physiology. In this study, captopril was initiated in 46 patients, with the optimal dose defined as 3 mg/kg/d divided every 8 hours. A large percentage of the rapid titration group achieved optimal dosing of captopril by day 3. A few patients in the rapid titration group were later transitioned to enalapril, with the optimal dose defined as 0.6 mg/kg/d divided every 12 hours. The patients in the rapid titration group did not have increased frequency of hyperkalemia, renal dysfunction, or hypotension during up-titration compared with those whose dose was slowly increased by day 9. These findings are similar to our larger analysis, although all of the patients in the Infant Single Ventricle trial were significantly younger with more complex physiology.

Even though the index study concluded against the routine use of ACE inhibitors in this population due to the lack of efficacy on growth, cardiac function, neurodevelopmental outcomes, and heart failure symptoms, there is still a substantial use of ACE inhibitor therapy in patients with single ventricle physiology. A recent survey conducted by the PHN demonstrated a significant change in clinical practice within the pediatric cardiology community since the publication of the PHN Infant Single Ventricle trial, but showed that a subset of practitioners consistently uses ACE inhibitors in infants with single ventricle.[16] In addition, a cross-sectional study conducted by the PHN showed that 57% of patients with Fontan circulation were on ACE inhibitor therapy.[17] A review of Fontan literature demonstrated ACE inhibitor use in multiple study populations, including in 36% of patients within the Australia and New Zealand Fontan Registry.[18] As ACE inhibitors continue to be a mainstay of therapy in pediatric patients with congenital heart disease, left ventricular dysfunction, and hypertension, the PHN Infant Single Ventricle trial provided the opportunity to describe the safety and adverse effects associated with ACE inhibitor use over an extended period of time in a vulnerable pediatric population.

There are several limitations to this analysis. Only 57% of the enalapril-treated group achieved the target dose of 0.4 mg/kg/d, which may account for the safety findings. Renal dysfunction was defined as creatinine ≥1.0 mg/dL, which may have underestimated the incidence of nephrotoxicity in this neonatal population. In addition, concomitant use of medications associated with nephrotoxicity or other laboratory abnormalities were not accounted for in this analysis. The high discontinuation and loss-to-follow-up rates are also important limitations to this study.

ACE inhibitors have an acceptable safety profile in infants with complex congenital heart disease, who represent a particularly fragile patient population. In addition, rapid up-titration appears feasible and safe with appropriate hemodynamic and biochemical monitoring in place. ■

Table III. Adverse events by treatment assignment

Characteristics	Placebo (N = 115)	Enalapril (N = 115)	*P* value
Adverse events	87%	88%	.84*
Number of adverse events	389	423	
Serious adverse events	77%	76%	.88*
Number of serious adverse events	208	220	
Cardiac, nonarrhythmia	23 (11%)	37 (17%)	.09*
Cardiac, arrhythmia	6 (3%)	6 (3%)	.92*
Respiratory	51 (25%)	43 (20%)	.21*
Infectious	44 (21%)	55 (25%)	.35*
Vascular	27 (13%)	30 (14%)	.84*
Gastrointestinal	26 (13%)	25 (11%)	.72*
Neurologic	5 (2%)	4 (2%)	.67*
Other	26 (13%)	20 (9%)	.26*
Hypotension	8 (7%)	17 (15%)	.06*
Hyperkalemia	57 (50%)	65 (57%)	.29*
Renal dysfunction	0 (0%)	3 (3%)	.25†
Neutropenia	18 (16%)	14 (12%)	.58*
Death	12 (10%)	12 (10%)	1*
Transplant	4 (3%)	3 (3%)	1†

*Indicates *P* value calculated by χ^2 analysis.
†Indicates *P* value calculated by the Fisher exact test.

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