Received: 28 September 2017 | Revised: 6 April 2018 | Accepted: 26 April 2018

DOI: 10.1111/chd.12622

ORIGINAL ARTICLE

WILEY Congenital Heart Disease

Angiotensin converting enzyme inhibitors and interstage failure in infants with hypoplastic left heart syndrome

Doris P. Yimgang MPH[1] | John D. Sorkin MD, PhD[2] | Charles F. Evans MD[3] | Danielle S. Abraham PhD, MPH[1] | Geoffrey L. Rosenthal MD, PhD[1,4]

[1]Department of Epidemiology and Public Health, University of Maryland School of Medicine, Baltimore, Maryland, USA

[2]Division of Gerontology and Geriatric Medicine, Department of Medicine, University of Maryland School of Medicine and Baltimore VA Medical Center Geriatric Research, Education, and Clinical Center, Baltimore, Maryland, USA

[3]Division of Cardiac Surgery, Department of Surgery, University of Maryland School of Medicine, Baltimore, Maryland, USA

[4]Division of Pediatric Cardiology, Department of Pediatrics, University of Maryland School of Medicine, Baltimore, Maryland, USA

Correspondence
Doris P. Yimgang, Department of Epidemiology and Public Health, University of Maryland School of Medicine, 737 W Lombard Street, Room 169 B, Baltimore, MD 21201.
Email: Doris_yimgang@umaryland.edu

Funding information
The National Institute on Aging, Grant/Award number: P30 AG028747 (Sorkin's work); The National Institute on Aging, Grant/Award number: T32 AG000262 (Abraham's work)

Abstract

Introduction: Angiotensin converting enzyme inhibitors are commonly prescribed medications after the Norwood procedure. There are little data that can be used to determine if angiotensin converting enzyme inhibitors improve interstage outcomes in children with single ventricle defects. The objective of this study was to investigate the relationship between angiotensin converting enzyme inhibitors and interstage failure among infants born with hypoplastic left heart syndrome.

Methods: We conducted a retrospective cohort study using data from the National Pediatric Cardiology Quality Improvement Collaborative database (collected between 2008 and 2015). We used logistic regression models to assess the exposure-outcome associations and propensity score matching to account for differences in baseline patient characteristics associated with use of angiotensin converting enzyme inhibitors.

Results: A total of 1 487 neonates participated in the study. Thirty-nine percent of patients were prescribed angiotensin converting enzyme inhibitors after the Norwood procedure; 11% experienced interstage failure (death, heart transplantation, and not being a candidate for the second-stage surgery). Before propensity score matching, patients receiving angiotensin converting enzyme inhibitors were significantly more likely to experience interstage failure, compared to patients not on angiotensin converting enzyme inhibitors (OR = 1.44; 95% CI: 1.04, 1.99; $P = 0.03$). Although there was an increased odds of interstage failure among patients receiving angiotensin converting enzyme inhibitors compared to patients not receiving angiotensin converting enzyme inhibitors in the propensity score-matched cohort, this association was not significantly different (adjusted OR = 1.29; 95% CI: 0.88, 1.95; $P = 0.18$).

Conclusion: Angiotensin converting enzyme inhibitor therapy did not demonstrate a beneficial effect on interstage failure among infants with hypoplastic left heart syndrome, even when patient characteristics associated with the use of angiotensin converting enzyme inhibitors were considered.

KEYWORDS
angiotensin converting enzyme inhibitors, hypoplastic left heart syndrome, interstage failure, pediatrics, single ventricle defects

1 | INTRODUCTION

Hypoplastic left heart syndrome (HLHS) describes a set of congenital heart defects that adversely affects systemic blood flow.[1] HLHS and its variants have a prevalence of 1.3 to 3.2 per 10 000 live births.[2–5] In the absence of anatomical intervention, HLHS is almost uniformly lethal in the neonatal period. Survival for most affected neonates is contingent on receiving a series of surgical or combined surgical and interventional catheterization procedures in the first months of life. A variation of the Norwood procedure is the first definitive palliative procedure in the series. The Norwood procedure, and its variations, create a reliable source of blood flow to the body, eliminate any blockage to

flow due to an abnormal atrial septum, and create a reliable source of pulmonary blood flow. Irrespective of which variation of the first-stage procedure is used to achieve these goals, balance between blood flow to the body (including coronary blood flow) and to the lungs is tenuous.

Establishing a connection between the superior vena cava and the pulmonary artery, and removing the path for pulmonary blood flow that was created during the first-stage, is the most common second-stage procedure (Glenn procedure). [6] While infants following the second-stage palliation usually remain somewhat medically fragile, many of the risks inherent in first-stage physiology are mitigated.

Although the thirty-day survival after the Norwood procedure has increased over the past three decades,[6,7] the interstage period, the time between the Norwood and the Glenn procedures, remains one of the most critical times in the management of infants with single ventricle defects, with mortality ranging from 4 to 15% depending on the surgical center.[6] Risk factors for interstage death include poor somatic growth, comorbid conditions (e.g., gastroenteritis, infection, fever), arrhythmias, and residual or recurrent anatomic lesions of the heart.[6–8]

Angiotensin converting enzyme inhibitors (ACE-I) are one of the most common outpatient medications used after the Norwood procedure, with 38% to 73% of neonates receiving these medications.[9,10] The reason for use of ACE-I therapy is to reduce cardiac afterload and by doing so increasing cardiac output to the systemic circulation. ACE-I have FDA approved indications for treatment of high blood pressure, heart failure, left ventricular dysfunction, and diabetic nephropathy.[11,12] The safety and efficacy of ACE-I therapy in neonates, who are more prone to hemodynamic and renal side effects of ACE-I therapy than older children and adults, have not been established.[13,14]

There is considerable variability in the use of ACE-I therapy in neonates and young infants with HLHS. ACE-I therapy is primarily based on empirical data[10] and evidence of beneficial effects of ACE-I therapy in children with heart failure.[15] Despite the paucity of evidence supporting ACE-I therapy in neonates and infants with HLHS,[10,16] ACE-I have been prescribed routinely in children with HLHS who have atrioventricular valve insufficiency, semilunar valve insufficiency, an imbalance between pulmonary and systemic circulation (with excessive blood going to the lungs, and not enough to the rest of the body), and right ventricular dysfunction. Prior observational studies[9,10] that investigated the effects of ACE-I on interstage outcomes in children with single ventricle defects have not accounted for baseline differences between treatment groups that may result in confounding by indication. Confounding by indication is a form of bias in observational trials (i.e. nonrandomized trials), in which the decision to use a treatment is a function the severity of disease.[17] If, for example, more severely-ill patients are more likely to receive a treatment, patients who by dint of the severity of their disease are thus less likely to have a salutary outcome; a comparison of outcome in patients who did and did not receive the treatment will be biased by the severity of the disease at the time treatment is begun.

The purpose of this study was to evaluate, in infants with HLHS, the relationship between use of ACE-I immediately after the Norwood procedure and interstage failure using a technique, propensity score matched cohorts, which addresses confounding by indication.[18] We defined interstage failure as death during the interstage period, heart transplantation, or not a being candidate for the second-stage procedure.

We tested the hypothesis that infants who were prescribed ACE-I at discharge from the Norwood procedure had decreased incidence of interstage failure compared to infants who were not discharged on ACE-I therapy.

2 | METHODS

2.1 | Data source

We used data from the National Pediatric Cardiology Quality Improvement Collaborative (NPC-QIC) as the basis for our retrospective cohort study. This NPC-QIC was created with the goal of improving care and outcome in children with HLHS and related single ventricle defects after the Norwood procedure. The NPC-QIC aims to reduce interstage mortality, growth failure, and to decrease hospital readmissions.[19] Data were extracted from medical records through a secure electronic database (REDCAP). Designated study team members at each center entered data using standard instructions and guidelines. A detailed description of the NPC-QIC protocol was described elsewhere.[20] NPC-QIC data, collected between 2008 and 2015, included demographic information, cardiac diagnoses, comorbidities, surgery information, discharge information, and reasons for early withdrawal from study including death, loss to follow-up, heart transplantation, not being a candidate for the Glenn, and other. As of April 2015, 55 surgical sites from across the US (located in 31 states and Washington DC) that provided care for this high-risk population contributed data to the NPC-QIC.[19,20] The study was approved by the Institutional Review Board of the University of Maryland, Baltimore (Protocol number: BP-00064137).

2.2 | Study population

Infants who had qualifying single ventricle defects, received the Norwood procedure, and were discharged from the hospital with tentative plans to have the second-stage surgery were included in the NPC-QIC. Children were enrolled in the registry with the consent of their parents or guardians who signed an informed consent. Children were not eligible to participate in the registry if they died before discharge from the Norwood procedure or if they were hospitalized during the entire interstage period.

2.3 | Primary outcome variable

The primary outcome of interest, interstage failure, was defined as death during the interstage period, heart transplantation, or not a being candidate for the second-stage procedure. Interstage failure was modeled as a dichotomous variable (failure or success).

2.4 | Primary exposure variable

The primary exposure variable was ACE-I use at discharge from the Norwood, defined as either prescribed or not prescribed. ACE-I medications included in this study were captopril, enalapril, and lisinopril.

2.5 | Statistical analyses

Student's *t*-tests and Pearson chi-square tests were used to compare characteristics of subjects receiving and not receiving ACE-I therapy. We used logistic regression to evaluate the relationship between ACE-I therapy and interstage failure. We ran three models. The first model was not adjusted for any covariates nor were propensity scores used in the analyses. All subjects (n = 1 487) for whom outcome and ACE-I usage (or nonusage) was known were included. The second model (Model 2, n = 1 446) included all subjects for whom a propensity score could be computed (i.e. the subjects had complete data for all the variables included in the propensity score), but the propensity scores were not considered in the analysis. Model 2, like Model 1 was not adjusted for any covariates. The third model (Model 3, n = 1 104), included subjects who received ACE-I therapy and were matched (1:1 matching, as described below) to a subject who did not receive ACE-I therapy based on the subject's propensity (ie, probability) of receiving ACE-I therapy. Model 3, run as a conditional logistic regression, assessed the relationship between ACE-I therapy and interstage failure in the propensity-score matched cohort adjusted for those covariates which, despite the matching, remained unbalanced between subjects who did and did not receive ACE-I therapy. A covariate was considered unbalanced when the absolute value of the between group standardized difference was $\geq$0.1.[18] Independent variables included in the model based on imbalance were primary cardiac diagnosis and type of operative procedure.

Based on a review of the literature[21] and consideration of clinical relevance we identified nine variables that we included in the computation of our propensity scores, the conditional probability of receiving ACE-I given the neonates' baseline health status. Variables used to compute the propensity scores included the subject's sex, race, primary cardiac diagnosis, preoperative and postoperative risk factors that were associated with either receiving ACE-I therapy or having an interstage failure, presence of renal dysfunction, major organ system abnormalities, type of operative procedure, and need for cardiac reoperation. Race was characterized as white, African American and other. Primary cardiac diagnosis included aortic atresia with mitral atresia, aortic atresia with mitral stenosis, aortic stenosis with mitral stenosis, and other. Factors associated with interstage failure or being prescribed ACE-I were divided into preoperative and postoperative risk factors. Preoperative risk factors included the presence of moderate-to-severe atrioventricular valve regurgitation, moderate-to-severe ventricular dysfunction, arrhythmia, or aortic coarctation. Postoperative risk factors included the presence of hypertension, the need for a ventricular assist device, and the need for extracorporeal membrane oxygenation (ECMO). Renal problems included the presence of renal insufficiency, acute renal failure or the need for dialysis. Major organ system abnormalities were dichotomized as the presence or absence of anomalies of the central nervous, musculoskeletal, endocrine, pulmonary, gastrointestinal, or otolaryngology systems. Type of operative procedure was either Norwood with Blalock-Taussig shunt, Norwood with a right ventricle to pulmonary artery (RV-PA) conduit, hybrid Norwood, or other. The need for reoperation was a dichotomous variable indicating whether the patient needed to undergo an additional surgery between the Norwood and discharge.

Patients discharged on ACE-I were matched (1:1) without replacement on propensity scores to patients who were not discharged on ACE-I. Matching was conducted using a caliper of width equal to 0.1 standard deviation of the estimated propensity scores.[22]

A two-tailed $P < 0.05$ was considered statistically significant. Data were analyzed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

3 | RESULTS

One thousand five hundred one patients were eligible to participate in this study (Figure 1). We excluded 14 participants because they were lost to follow-up or had biventricular repairs. Patients with missing covariates (n = 41) were not considered for propensity score matching. There were no differences in sex, race, primary cardiac diagnosis, the presence of pre- and postoperative risk factors, renal problems, and major organ system abnormalities between participants with complete data and those with missing covariates (data not shown). Ninety-seven percent (552/569) of patients discharged on ACE-I were matched to patients who were not discharged on ACE-I achieving a total of 1 104 participants for the matched analysis.

3.1 | Sample characteristics

The mean age of the neonates at the time of the Norwood procedure was 10.9 ± 71.1 days (mean ± SD) and 46.0 ± 75.4 days at discharge. The majority of our subjects were male (61%), White (75%), did not have preoperative risk factors (87%), postoperative risk factors (92%), renal problems (88%) or major organ system abnormalities (92%), and did not need a reoperation (80%).

3.2 | Comparison of patients who did and did not received ACE-I

Among the 1 446 subjects who had complete information on ACE-I usage, outcome, and covariates (Model 2), those discharged on ACE-I were more likely to have pre- and postoperative risk factors, renal problems, major organ system abnormalities, and Norwood with Blalock-Taussig shunt compared to patients not discharged on ACE-I (Table 1). After propensity score matching (Model 3, n = 1 104), treatment groups were comparable on almost all covariates except the presence of primary cardiac diagnosis ($|d|$=0.12) and type of operative procedure ($|d|$= 0.13) (Table 2). In the matched cohort, patients discharged on ACE-I were slightly more likely to receive the diagnosis of aortic stenosis with mitral stenosis and less likely to have undergone hybrid Norwood. Primary cardiac diagnosis and type of operative procedure were therefore included in the conditional logistic regression model.

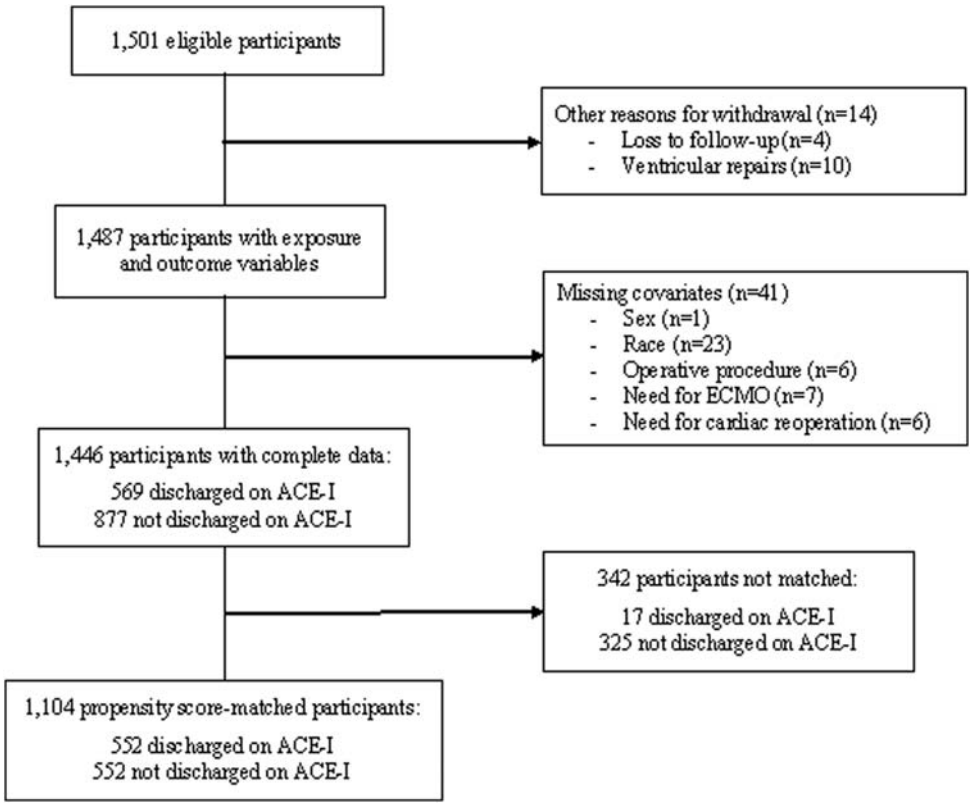

FIGURE 1 Study flowchart

3.3 | Relationship between ACE-I and interstage failure

In our original sample (Model 1), 39% of the patients were prescribed ACE-I at discharge from the Norwood, and 11% failed during the interstage period. Patients discharged on ACE-I were significantly more likely to fail during the interstage period compared to patients not discharged on ACE-I (odds ratio = 1.44; 95%CI: 1.04, 1.99; $P = 0.03$) (Table 3). After excluding patients for whom a propensity score could not be computed (Model 2), the odds of interstage failure was 1.37 times higher among patients discharged on ACE-I compared to those not discharged on ACE-I (95%CI: 0.98, 1.91; $P = 0.07$). After adjusting for primary cardiac diagnosis and the type of operative procedure in the propensity score-matched cohort (Model 3), the odds of interstage failure was higher among patients on ACE-I compared to those not on ACE-I in the matched sample (adjusted odds ratio = 1.29; 95%CI: 0.88, 1.95; $P = 0.18$).

4 | DISCUSSION

This study does not support our primary hypothesis that infants discharged on ACE-I would have decreased incidence of interstage failure compared to infants not discharged on ACE-I therapy. Our initial model (Model 1), run using data from all subjects with exposure and outcome variables found a statistically significant association between treatment with ACE-I and interstage failure (OR 1.44, $P = 0.03$). It is possible that that association was due to confounding by indication; sicker neonates who were more likely to suffer from interstage failure received ACE-I therapy specifically because they were sicker. Our propensity-score matched analysis (Model 3), which addresses the potential bias caused by confounding by indication, suggests that the etiology of the poor outcome was not due to confounding by indication, but rather due to some detrimental effect of ACE-I therapy in neonates with HLHS. Although the results of the propensity-score matched analysis (Model 3, OR = 1.29, $P = 0.18$) were not statistically significant, the 29% increase in the likelihood of interstage failure in children discharged on ACE-I compared to those not on ACE-I therapy brings into question the use of ACE-I in neonates with HLHS.

4.1 | ACE-I in children with single ventricle defects

Although use of ACE-I therapy has been associated with improved health in older children and adults with heart failure,[15] the use of enalapril has not shown beneficial effects in treating ventricular dysfunction in single ventricle defects. [23] In a randomized trial of children aged 45 days or younger with single ventricle defects, there was no difference in somatic growth, ventricular function, or heart failure severity among children who received enalapril during the first year of life and those who did not.[23] In a study of the use of any single ACE-I drug (enalapril, lisinopril or captopril) in children with single ventricle defects, ACE-I therapy did not improve interstage survival or weight gain.[9] These findings, like ours, do not support standard use of enalapril in children with single ventricle defects.

The reason for the apparent failure of ACE-I therapy to improve interstage failure is likely multifactorial. It is possible that interstage

TABLE 1 Baseline characteristics among participants with complete data, Model 2 (N = 1 446)

	ACE-I		
	Yes N = 569	No N = 877	*P* value*
Age at Norwood procedure, mean±SD (days)	10.7 (26.9)	11.1 (88.7)	0.91
Sex, *n* (col%)			
Female	211 (37.1)	347 (39.6)	0.34
Male	358 (62.9)	530 (60.4)	
Race, *n* (col%)			
White	426 (74.9)	660 (75.3)	
African American	75 (13.2)	138 (15.7)	0.11
Other	68 (11.9)	79 (9.0)	
Primary cardiac diagnosis, *n* (col%)			
Aortic atresia with mitral atresia	177 (31.1)	307 (35.0)	
Aortic atresia with mitral stenosis	109 (19.2)	164 (18.7)	0.38
Aortic stenosis with mitral stenosis	88 (15.5)	138 (15.7)	
Other	195 (34.3)	268 (30.6)	
Preoperative risk factors, *n* (col%)			
Yes	103 (18.1)	88 (10.0)	<0.01
No	466 (81.9)	789 (90.0)	
Postoperative risk factors, *n* (col%)			
Yes	62 (10.9)	59 (6.7)	<0.01
No	507 (89.1)	818 (93.3)	
Renal problems, *n* (col%)			
Yes	92 (16.2)	79 (9.0)	<0.01
No	477 (83.8)	798 (91.0)	
Major organ system abnormalities, *n* (col%)			
Yes	55 (9.7)	53 (6.0)	0.01
No	514 (90.3)	824 (94.0)	
Type of operative procedure, *n* (col%)			
Norwood with Blalock-Taussig shunt	204 (35.8)	248 (28.3)	
Norwood with RV-PA conduit	272 (47.8)	501 (57.1)	<0.01
Hybrid Norwood	54 (9.5)	69 (7.9)	
Other	39 (6.8)	59 (6.7)	
Need for cardiac reoperation, *n* (col%)			
Yes	126 (22.1)	164 (18.7)	0.11
No	443 (77.9)	713 (81.3)	

*Student's *t*-test or Pearson's chi-square.

failure may be due to noncardiac causes such as feeding difficulties, genetic problems, and comorbidities[23] and so would not be affected by ACE-I therapy. Another explanation may be the physiologic action of ACE-I. Because ACE-I decrease blood pressure,[24] the therapy may compromise coronary artery filling, which may interfere with blood flow to the myocardium, resulting in myocardial ischemia, impaired ventricular function, and arrhythmias.

Although there is no evidence in the literature, nor from our study, that supports the use of ACE-I therapy during the interstage period in children with single ventricle defects, a high proportion of this population is discharged on this therapy (39% in our study). Physicians may believe that ACE-I therapy will be helpful based on the demonstrated salutary effect ACE-I therapy has in children (1 month–14 years) with heart failure; ACE-I drugs lower aortic pressure, systemic vascular resistance, and atrial pressure in these children.[15] ACE-I therapy has also been associated with reduced ventricular dilation, which improves the prognosis in patients with heart failure.[25,26] The differential effects of ACE-I in children with heart failure when compared with infants with single ventricle defects may suggest age-related differences in pharmacodynamics or end-organ response.

4.2 | Use of propensity-score method

Propensity score matching was used to reduce the possibility of confounding by indication. This type of confounding is usually a concern in observational pharmaco-epidemiologic studies when individuals who are prescribed a medication are inherently different from those who do not take the medication. In our sample, infants who were discharged

TABLE 2 Baseline characteristics in propensity-score matched cohort, Model 3 (N = 1 104)

	ACE-I		
	Yes N = 552	No N = 552	Risk Difference (|*d*|)
Sex, *n* (col%)			
Female	202 (36.6)	217 (39.3)	0.07
Male	350 (63.4)	335 (60.7)	0.04
Race, *n* (col%)			
White	416 (75.4)	424 (76.8)	0.02
African American	74 (13.4)	68 (12.3)	0.08
Other	62 (11.2)	60 (10.9)	0.03
Primary cardiac diagnosis, *n* (col%)			
Aortic atresia with mitral atresia	173 (31.3)	172 (31.2)	<0.01
Aortic atresia with mitral stenosis	109 (19.7)	116 (21.0)	0.06
Aortic stenosis with mitral stenosis	85 (15.4)	75 (13.6)	**0.12**
Other	185 (33.5)	189 (34.2)	0.02
Preoperative risk factors, *n* (col%)			
Yes	90 (16.3)	85 (15.4)	0.06
No	462 (83.7)	467 (84.6)	0.01
Postoperative risk factors, *n* (col%)			
Yes	55 (10.0)	51 (13.5)	0.08
No	497 (90.0)	501 (90.8)	<0.01
Renal problems, *n* (col%)			
Yes	80 (14.5)	74 (13.4)	0.08
No	472 (85.5)	478 (86.6)	0.01
Major organ system abnormalities, *n* (col%)			
Yes	48 (8.7)	51 (9.2)	0.06
No	504 (91.3)	501 (90.8)	<0.01
Type of operative procedure, *n* (col%)			
Norwood with Blalock-Taussig shunt	193 (35.0)	189 (34.2)	0.02
Norwood with RV-PA conduit	269 (48.7)	265 (48.0)	0.05
Hybrid Norwood	53 (9.6)	56 (10.1)	**0.13**
Other	37 (6.7)	42 (7.6)	0.01
Need for cardiac reoperation, *n* (col%)			
Yes	119 (21.6)	125 (22.6)	0.05
No	433 (78.4)	427 (77.4)	0.01

TABLE 3 Association between ACE-I and interstage failure

		Total *n* (col %)	Failure *n* (row %)	Success *n* (row %)	Odds ratio (95% CI)	*P* value
Model 1[a]	ACE-I					
	Yes	585 (39.3)	78 (13.3)	507 (86.7)	1.44 (1.04, 1.99)	0.03
	No	902 (60.7)	87 (9.6)	815 (90.4)	1.00 (Ref)	
Model 2[b]	ACE-I					
	Yes	569 (39.3)	72 (12.6)	497 (87.4)	1.37 (0.98, 1.91)	0.07
	No	877 (60.7)	84 (9.6)	793 (90.4)	1.00 (Ref)	
Model 3[c]	ACE-I					
	Yes	552 (50)	71 (12.9)	481 (87.1)	1.29 (0.88, 1.95)	0.18
	No	552 (50)	58 (10.5)	494 (89.5)	1.00 (Ref)	

[a]Unadjusted logistic regression model with original sample (N = 1 487).
[b]Unadjusted logistic regression model including only participants with complete data (N = 1 446).
[c]Conditional logistic regression with propensity-score matched pairs adjusting for primary cardiac diagnosis and operative procedure (N = 1 104).

on ACE inhibitors were more likely to have preoperative and postoperative risk factors (moderate-to-severe atrioventricular valve regurgitation, moderate-to-severe ventricular dysfunction, arrhythmia, or aortic coarctation, hypertension, the need for a ventricular assist device, and the need for extracorporeal membrane oxygenation), renal problems and major organ system abnormalities. Severity of the disease among patients who received ACE inhibitors may lead to poorer outcomes in this group, compared to those who were not discharged on ACE inhibitors. Therefore, propensity score matching was used to balance exposure groups, such that disease severity was no longer the major cause of poor interstage outcomes among children discharged on ACE inhibitors. Although our adjusted result was not statistically significant, the estimate of effect supported poorer outcomes in those discharged on ACE inhibitors, even after controlling for baseline differences between exposure groups.

4.3 | Strengths and limitations

This study has several limitations. Our study is based on data collected with the aim of improving quality of care, and not specifically to address the question that we explore. The conditions reported in medical records and used in the NPC-QIC registry were not corroborated, so nondifferential misclassification cannot be ruled out. Further our study is not a randomized clinical trial. It is possible that there was selection bias in the patients who participated in the NPC-QIC registry. Some infants who were included in the registry could not be included in our propensity-score analyses (Model 3) due to missing data. Although there were no differences in most of the baseline covariates between participants with complete data and those with missing covariates, we saw differences in the type of operative procedure and the need for reoperation. Children with missing information were more likely to undergo reoperation (34% vs. 20%; $P = 0.04$) and 'other' type of operative procedure (24% vs. 7%; $P < 0.01$). In addition, our analyses did not account for various combinations of drugs, medication changes or discontinuation of ACE-I during the interstage period. As with any observational study, the possibility of residual confounding still exists.

Our study has a number of strengths. First, to our knowledge this is the first study to examine the association between ACE-I therapy and interstage failure in children with single ventricle defects. We are unaware of any prior studies that evaluated interstage failure as a composite outcome defined as death, heart transplantation or not being a candidate for the second operation. Second, despite the observational nature of our study, we used propensity scores to reduce the possibility of confounding by indication. Third, the sample size was large compared to prior studies investigating the effects of ACE-I therapy in children with single ventricle.

5 | CONCLUSION

ACE-I therapy did not demonstrate beneficial effect in infants with HLHS during the interstage period; in fact, there is a suggestion that ACE-I therapy may be detrimental. Further investigations, preferably properly powered randomized studies, are warranted to evaluate the effect of ACE-I therapy on interstage failure.

ACKNOWLEDGMENT

We acknowledge the contribution of Dr. Surbhi Leekha for comments on earlier versions of this manuscript.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest with the contents of this article.

AUTHOR CONTRIBUTIONS

Yimgang DP, Evans CF, and Rosenthal GL conceptualized the study. Yimgang DP and Sorkin JD identified the statistical analysis plan. Yimgang DP led data analysis and manuscript writing. Sorkin JD and Abraham DS participated in data analysis and interpretation. Rosenthal GL supervised the study. Abraham DS, Evans CF, Rosenthal GL, and Sorkin JD critically reviewed and edited the article. All authors read and approved the final version of the article.

ORCID

Doris P. Yimgang MPH http://orcid.org/0000-0002-3909-4839

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How to cite this article: Yimgang DP, Sorkin JD, Evans CF, Abraham DS, Rosenthal GL. Angiotensin converting enzyme inhibitors and interstage failure in infants with hypoplastic left heart syndrome. *Congenital Heart Disease*. 2018;13:533–540. https://doi.org/10.1111/chd.12622