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ORIGINAL RESEARCH

Angiotensin-Converting Enzyme Inhibitor Prescription for Patients With Single Ventricle Physiology Enrolled in the NPC-QIC Registry

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BACKGROUND: The routine use of angiotensin-converting enzyme inhibitors (ACEI) during palliation of hypoplastic left heart syndrome is controversial. We sought to describe ACEI prescription in the interstage between stage 1 palliation (stage I Norwood procedure) discharge and stage 2 palliation (stage II superior cavopulmonary anastomosis procedure) admission using the NPC-QIC (National Pediatric Cardiology Quality Improvement Collaborative) registry.

METHODS AND RESULTS: Analysis of all patients (n=2180) enrolled in NPC-QIC from 2008 to 2016 included preoperative anatomy, risk factors, and echocardiographic data. ACEI were prescribed at stage I Norwood procedure discharge in 38% of patients. ACEI prescription declined from 2011 to 2016 compared with pre-2010 (36.8% versus 45%; P=0.005) with significant variation across centers (range 7–100%; P<0.001) and decreased prescribing rates associated with increased center volume (P=0.004). There was no difference in interstage mortality (P=0.662), change in atrioventricular valve regurgitation (P=0.101), or change in ventricular dysfunction (P=0.134) between groups. In multivariable analysis of all patients, atrioventricular septal defect (odds ratio [OR], 1.84; 95% CI, 1.28–2.65) or double outlet right ventricle (OR, 1.47; CI, 1.02–2.11), and preoperative mechanical ventilation (OR, 1.37; 95% CI, 1.12–1.68) were associated with increased ACEI prescription. In multivariable analysis of patients with complete echocardiographic data (n=812), ACEI prescription was more common with at least moderate atrioventricular valve regurgitation (OR, 1.88; 95% CI, 1.22–2.31).

CONCLUSIONS: ACEI prescription remains common in the interstage despite limited evidence of benefit. ACEI prescription is associated with preoperative mechanical ventilation, double outlet right ventricle, and atrioventricular valve regurgitation with marked inter-center variation. ACEI prescription is not associated with reduction in mortality, ventricular dysfunction, or atrioventricular valve regurgitation during the interstage.

Key Words: angiotensin-converting enzyme inhibitor ■ hypoplastic left heart syndrome ■ learning health system ■ quality improvement ■ single ventricle

Hypoplastic left heart syndrome (HLHS) is a complex and high-risk heart defect that requires intensive early intervention. It is also rare, affecting an estimated 1 in every 4344 live-born infants annually in the United States. Most infants with HLHS undergo a series of 3 palliative cardiac surgeries: stage I Norwood procedure (S1P) within a few days of birth, stage II superior cavopulmonary anastomosis procedure (S2P) at 4 to 6 months, and stage III (Fontan) procedure at 2 to 4 years. Mortality during the interstage—the period between discharge following S1P and admission for S2P—was common, previously occurring in 10% to 15% of infants with HLHS.[1,2] Patterned on the Institute of Medicine's Learning Healthcare System framework, the NPC-QIC (National Pediatric Cardiology Quality Improvement Collaborative) was designed as a community for collaborative innovation. Because of the high risk of interstage mortality, founders of the NPC-QIC

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CLINICAL PERSPECTIVE

What Is New?

- Angiotensin-converting enzyme inhibitor (ACEI) prescribing patterns in the interstage period of hypoplastic left heart syndrome palliation vary widely between congenital heart centers.
- Publication of randomized controlled trial findings showing no benefit of ACEI use did not have a dramatic effect on prescribing behavior, and interstage ACEI prescription remains common.
- ACEI prescription during the interstage is not associated with reduction in mortality, ventricular dysfunction, or atrioventricular valve regurgitation in the interstage.

What Are the Clinical Implications?

- Universal prescription of ACEI during the interstage is not supported by evidence from randomized controlled trials or large retrospective cohort studies, and congenital cardiologists should consider modifying ACEI prescribing behaviors in patients with less than moderate atrioventricular valve regurgitation and less than moderate ventricular dysfunction.
- Further studies to identify populations who benefit from ACEI in the interstage are needed.

Nonstandard Abbreviations and Acronyms

ACEI	angiotensin-converting enzyme inhibitor
AVSD	atrioventricular septal defect
AVVR	atrioventricular valve regurgitation
DORV	double-outlet right ventricle
HLHS	hypoplastic left heart syndrome
ISV	Infant Single Ventricle trial
NPC-QIC	National Pediatric Cardiology Quality Improvement Collaborative
REDCap	Research Electronic Data Capture database
S1P	stage I Norwood procedure
S2P	stage II superior cavopulmonary anastomosis procedure

were driven to change the prognosis of HLHS by engaging all stakeholders in innovation through local observation and data sharing. Between 2008 and 2016, phase I of the NPC-QIC assembled the largest ever cohort of infants with HLHS.[3,4]

Angiotensin-converting enzyme inhibitors (ACEI) were frequently prescribed to infants with single ventricle disease based on adult studies showing improvements in cardiac index and reductions in regurgitant volume when treating systemic atrioventricular valve regurgitation (AVVR) with afterload reduction.[5–8] To study potential benefits in infants with single ventricle physiology, the ISV (Infant Single Ventricle) trial randomized 230 infants across 10 centers with single ventricle physiology to receive ACEI or placebo. Infants with non-HLHS single ventricle variants were included. The primary end point, weight-for-age *z* score, was not different between the ACEI and placebo groups at 14 months of age. There were no significant differences in heart failure status, ventricular ejection fraction, or developmental scores. The authors concluded that the study did not support the routine use of ACEI in the single ventricle population.[9] Following this study, Zak et al[10] published their results in 2017 after surveying pediatric cardiologists nationwide to evaluate their ACEI prescribing behaviors after ISV publication. They showed that self-reported prescribing decreased significantly.[10] Aside from this small self-reported survey, it is currently unclear what effect the publication of the ISV trial results in July 2010 had on the prescribing patterns of physicians caring for infants with single ventricle variants in the interstage.

We hypothesized that the perceptions of ACEI prescribing behaviors represented in self-reported data may be discordant with objective prescribing data, and therefore that ACEI prescription remains common during the interstage. Using the NPC-QIC registry, we described ACEI prescription during the interstage, including associations with patient and center factors. Additionally, we evaluated associations between ACEI prescription and interstage mortality, weight gain, and cardiac function.

METHODS

Because of the sensitive nature of the data collected for this study, requests to access the data set from qualified researchers trained in human subject confidentiality protocols may be sent to NPC-QIC at info@npcqic.org.

Study Setting and Population

All patients included in NPC-QIC phase 1 registry (July 2008–July 2016) were eligible for inclusion in our analysis. To qualify for enrollment in the NPC-QIC phase 1 registry, an infant must: (1) be born with HLHS or variant single ventricle disease, (2) undergo staged palliation down the single ventricle pathway with either Norwood procedure or hybrid variant at a participating center, and (3) survive and be discharged from S1P hospitalization before S2P or transplantation. Enrollment for NPC-QIC phase 1 was initiated at the time of discharge after S1P. At the close of phase 1, 60 congenital heart centers were participating.[11]

Site participation in the NPC-QIC is managed by the individual institutional review boards at each site. Patients consent to retrospective data collection from the S1P hospitalization and prospective data collection until S2P discharge at the time of discharge from S1P. Site-level deidentified data are entered into a web-based Research Electronic Data Capture (REDCap) database. Site self-audits are performed biannually and must demonstrate enrollment and data entry for 95% of eligible patients. Data quality control is performed via REDcap system programmed edit checks for out-of-range values, discrepant data, and incorrect data types. SAS (SAS Institute Inc) reports check for logical consistency of outcome variables and are reported to participating centers on a monthly basis. NPC-QIC sites are deidentified before provision of the research data set by the NPC-QIC data management team.

Study Design and Statistical Analysis

Data Collection

We performed a retrospective cohort analysis using variables available in the data registry that may associate with or confound the use of ACEI including demographic factors, birth data, presence of preoperative risk factors, postoperative complications, and length of stay. Weights were converted to a weight-for-age *z* score using World Health Organization normative data. AVVR and ventricular dysfunction were qualitatively assessed by each site via echocardiography at S1P discharge and the most proximal interstage visit to S2P admission. Categorical variables were created by splitting patients into groups with less than moderate and moderate or worse AVVR or ventricular dysfunction. All statistical analysis was performed in SAS (SAS Institute Inc).

Outcomes

Our primary outcome was the prescription of ACEI at the time of discharge from S1P. Secondary outcomes included interstage mortality, interstage growth, and interstage progression of ventricular dysfunction or AVVR.

Descriptive and Bivariate Analysis

Continuous variables were summarized using median values with interquartile range and categorical variables were summarized using frequencies and percentages. Bivariate analysis was performed with chi-square and Wilcoxon rank sum test as appropriate. Interstage outcomes were assessed as change over time from S1P discharge to S2P admission with McNemar test. Interstage mortality was analyzed using Kaplan–Meier methods. In all analyses, the significance level was defined as 0.05.

Multivariable Analysis of ACEI Prescription

ACEI prescription was modeled using a generalized linear mixed model with variance matrix blocked by treatment center, maximum likelihood estimation technique, and Gauss-Hermite quadrature likelihood approximation. The model included characteristics that were significant in bivariate analysis and clinically relevant. A secondary generalized linear mixed model was performed on patients with complete echocardiographic data at both S1P discharge and S2P admission. In all analyses, the significance level was defined as 0.05. When reporting odds ratios (ORs), 95% CIs are also reported.

Center Variation in ACEI Prescription

Rates of ACEI prescription across centers were compared. Analysis of surgical center characteristics associated with ACEI prescription was performed on the entire NPC-QIC phase 1 cohort of 60 centers. We then divided the centers based on the year of first patient enrollment and isolated centers that enrolled their first patient before publication of the ISV trial. This early center group was then used for pre-post ISV analysis to reduce the effect of changing center mix over time as new surgical centers were added to the registry.

Along with the classical statistical analysis, we used statistical process control methodology to evaluate change in the process of ACEI prescription over time across NPC-QIC centers. A quarterly p-chart[12] was created demonstrating the collaborative-wide use of ACEI, annotated with the timing of the publication of the ISV trial. Funnel plots are a common statistical quality improvement tool,[13] employed in our analysis to demonstrate ACEI prescription by center and year of S1P.

Ethics Statement

The authors assert that all procedures contributing to this work comply with the ethical standards of the US Code of Federal Regulations 45 CFR 46 on the protection of human subjects and with the Helsinki Declaration of 1975, as revised in 2008. This study has been approved by the institutional review board at Cincinnati Children's Hospital Medical Center. The authors had full access to the data and take full responsibility for its integrity. All authors have read and agree to the article as written.

RESULTS

Descriptive and Bivariate Analysis

Patient Characteristics

A total of 2180 patients from 60 participating congenital heart surgical centers met inclusion criteria

Table 1. Demographics and Bivariate Analysis of Preoperative Patient and Hospitalization Characteristics Associated With ACEI Prescription

	Cohort Total	No Prescription, No. (%)	ACEI Prescription, No. (%)	*P* Value
Sex				0.930
Men	1356	853 (63)	503 (37)	
Women	824	516 (63)	308 (37)	
Birth era*				0.005
2008–2010	348	192 (55)	156 (45)	
2012–2016	1598	1010 (63)	588 (37)	
Gestational age				0.750
<37 wk	192	117 (61)	75 (39)	
≥37 wk	1994	1240 (62)	754 (38)	
Annual center volume				0.004
<5	465	258 (55)	207 (45)	
5 to 15	1385	887 (64)	498 (36)	
>15	332	208 (63)	124 (37)	
Anatomic variant				<0.001
HLHS	1675	1050 (63)	625 (37)	
DORV	131	72 (55)	59 (45)	
AVSD	126	61 (48)	65 (52)	
DILV	102	75 (74)	27 (26)	
Other	149	96 (64)	53 (36)	
Stage 1 palliation type				0.08
Norwood/Sano	1234	793 (64)	441 (36)	
Norwood/BTS	677	392 (58)	285 (42)	
Hybrid	177	110 (62)	67 (38)	
DKS/BTS	80	47 (59)	33 (41)	
Norwood shunt type†				0.036
Norwood/Sano	1234	793 (64)	441 (36)	
Norwood/BTS	677	392 (58)	285 (42)	
Preoperative risk factors				
Extracorporeal membrane oxygenation	22	8 (37)	14 (63)	0.613
Arrhythmia	60	27 (45)	33 (55)	0.129
Acidosis	381	157 (41)	224 (59)	0.044
Mechanical ventilation	534	235 (44)	299 (56)	<0.001
Renal insufficiency	101	45 (45)	56 (55)	0.073

ACEI indicates angiotensin-converting enzyme inhibitor; AVSD, atrioventricular septal defect; BTS, Blalock-Taussig shunt; DILV, double inlet left ventricle; DORV, double outlet right ventricle; and HLHS, hypoplastic left heart syndrome.

*2011 excluded to allow for diffusion of ISV (Infant Single Ventricle) trial results after publication.

†Patients undergoing hybrid operation or Damus-Kaye-Stansel (DKS) procedure were excluded for shunt type comparison.

for enrollment in phase 1 of the NPC-QIC registry. Summary demographic data for included patients are provided in Table 1. There was a male predominance (62%) and the most common anatomic variant was HLHS (76%). The majority of patients underwent S1P with a Norwood procedure with a right ventricular to pulmonary artery (Sano) shunt (57%). The median age at discharge was 36 days (interquartile range, 25–54) with a median weight of 3.6 kg (interquartile range, 3.2–4.1 kg). ACEI was prescribed in 829 (38%) patients at discharge and 93% of these patients were still prescribed an ACEI at S1P admission. The overall interstage mortality rate was 6.8%.

Patient Predictors of ACEI Prescription

In bivariate analysis of preoperative patient and hospital characteristics (Table 1), there was no association between sex (P=0.930), gestational age (P=0.750), or S1P palliation type (P=0.080) with prescription of ACEI at S1P discharge. Preoperative risk factors that were not significantly associated include

Table 2. Bivariate Analysis of Postoperative Hospitalization Characteristics Associated With ACEI Prescription

	N*	No Prescription, No. (%) or Median [Interquartile Range]	ACEI Prescription, No. (%) or Median [Interquartile Range]	*P* Value
Extracorporeal membrane oxygenation	2180	64 (4.7)	45 (5.4)	0.471
Reoperation	2180	251 (18.6)	184 (22.2)	0.040
Interventional catheterization	2150	284 (21.3)	163 (19.9)	0.450
Postoperative dialysis	2180	58 (4.3)	47 (5.7)	0.140
AVVR (≥moderate)	954	89 (14.7)	85 (24.5)	<0.001
Ventricular dysfunction (≥moderate)	982	27 (4.3)	14 (4.1)	0.609
Weight *z* score at S1P discharge	2170	−1.8 [±1.2]	−2 [±1.3]	0.002
Age at S1P discharge	2180	32 d [23–49]	41.5 d [29–60]	<0.001

Comparison performed with chi-square test. ACEI indicates angiotensin-converting enzyme inhibitor; AVVR, atrioventricular valve regurgitation; and S1P, stage I Norwood procedure.

*Number of patients with available data for each characteristic.

extracorporeal membrane oxygenation (*P*=0.613), arrhythmia (*P*=0.129), and renal insufficiency (*P*=0.073). Preoperative acidosis (59%, *P*=0.044) and mechanical ventilation (56%, *P*<0.001) were associated with increased rates of ACEI prescription. Patients with double-outlet right ventricle (DORV) (45%, *P*<0.001) and atrioventricular septal defect (AVSD) (52%, *P*<0.001) anatomic variants were more likely to receive ACEI prescription as were patients undergoing Norwood with Blalock-Taussig shunt when compared with Norwood with Sano shunt (42% versus 36%, *P*=0.036).

Table 2 lists bivariate analysis of the postoperative hospitalization characteristics. There was no difference in postoperative rates of extracorporeal membrane oxygenation (*P*=0.471), interventional catheterization (*P*=0.450), renal failure (*P*=0.140), or incidence of at least moderate ventricular dysfunction as assessed on S1P discharge echocardiography (*P*=0.609). Birth year was not significantly associated with differences in prescribing rates, but when phase 1 was broken into pre- and post-ISV cohorts by birth year, there was significantly less prescribing in those infants born after 2011 (45% versus 36%, *P*=0.005).

Interstage Outcomes

Analysis of the interstage and S2P admission data showed no difference in interstage mortality between those patients prescribed ACEIs compared with those who were not (*P*=0.662). Kaplan–Meier curves for the 2 groups are shown in Figure 1. There was no difference in interstage growth between the groups (median change in *z* score 0.37 versus 0.31, *P*=0.992).

Multivariable Analysis of ACEI Prescription

Significant variables from bivariate analysis were used to create a multivariable logistic regression model (Table 3) of ACEI prescription. Notably, at least moderate ventricular dysfunction was not a significant predictor of ACEI prescription in bivariate analysis and was not included in the multivariable model. Independent patient-associated predictors of ACEI prescription included AVSD (OR, 1.85; 95% CI, 1.28–2.65) and DORV (OR, 1.47; 95% CI, 1.02–2.11) anatomic variants (versus HLHS as the reference group) and the presence of preoperative mechanical ventilation (OR, 1.37; 95% CI, 1.12–1.68).

Secondary Multivariable Analysis of ACEI Prescription

For the 812 patients who had complete S1P and S2P echocardiographic assessment data, AVSD anatomic variant was not significant (OR, 1.67; 95% CI, 0.89–2.76), but at least moderate AVVR was significantly associated with ACEI prescription (OR, 1.76; 95% CI, 1.22–2.31). Preoperative mechanical ventilation (OR,

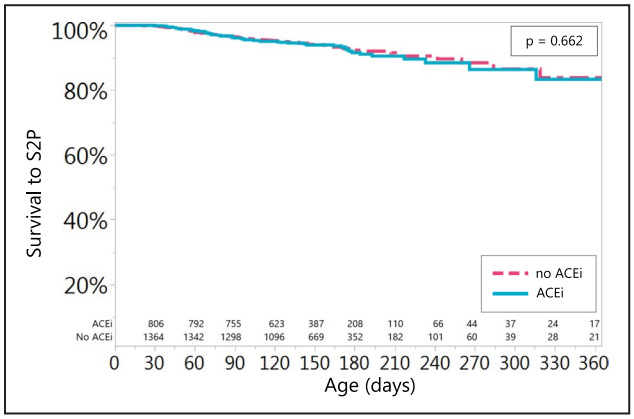

Figure 1. Kaplan–Meier analysis for all-cause interstage mortality using log-rank test.
ACEI indicates angiotensin-converting enzyme inhibitor; and S2P, stage II superior cavopulmonary anastomosis procedure.

Table 3. Multivariable Logistic Regression Model of Variables Associated With ACEI Prescription at S1P Discharge in All 2180 Patients

	Odds Ratio	95% CI
AVSD* (vs HLHS)	1.85	1.28 to 2.65
DORV* (vs HLHS)	1.47	1.02 to 2.11
Preoperative mechanical ventilation*	1.37	1.12 to 1.68
S1P reoperation	1.26	0.92 to 1.58
Weight for age *z* score	1.07	0.99 to 1.16
S1P renal insufficiency	1.23	0.82 to 1.86
Preoperative acidosis	1.87	0.86 to 4.08
Age at S1P surgery	0.99	0.91 to 1.10
Sano shunt (vs BTS)	0.82	0.63 to 1.07

ACEI indicates angiotensin-converting enzyme inhibitor; AVSD, atrioventricular septal defect; BTS, Blalock-Taussig shunt; DORV, double outlet right ventricle; HLHS, hypoplastic left heart syndrome; and S1P, stage I Norwood procedure.

*Statistically significant. Comparison performed with a generalized linear mixed model with variance matrix blocked by treatment center, maximum likelihood estimation technique, and Gauss-Hermite quadrature likelihood approximation.

Table 4. Multivariable Logistic Regression Model of Variables Associated With ACEI Prescription at S1P Discharge in 812 Patients With Complete Echocardiographic Data

	Odds Ratio	95% CI
DORV* (vs HLHS)	1.88	1.05 to 3.34
AVVR* (≥moderate vs ≤mild)	1.76	1.22 to 2.31
Preoperative mechanical ventilation*	1.63	1.15 to 2.28
AVSD (vs HLHS)	1.67	0.89 to 2.76
Predischarge reoperation	1.22	0.87 to 1.72
Weight-for-age *z* score	1.05	0.93 to 1.17
S1P renal insufficiency	0.84	0.41 to 1.76
Preoperative acidosis	1.02	0.72 to 1.54
Age at S1P surgery	1.00	0.94 to 1.07
Sano shunt (vs BTS)	0.74	0.48 to 1.16

ACEI indicates angiotensin-converting enzyme inhibitor; AVSD, atrioventricular septal defect; AVVR, atrioventricular valve regurgitation; BTS, Blalock-Taussig shunt; DORV, double outlet right ventricle; HLHS, hypoplastic left heart syndrome; and S1P, stage I Norwood procedure.

*Statistically significant. Comparison performed with a generalized linear mixed model with variance matrix blocked by treatment center, maximum likelihood estimation technique, and Gauss-Hermite quadrature likelihood approximation.

1.63; 95% CI, 1.15–2.28) and DORV (OR, 1.88; 95% CI, 1.05–3.34) anatomy remained significant (Table 4). There was no difference in improvement or worsening of AVVR (P=0.101) or ventricular dysfunction (P=0.134) (Figure 2).

Center Variation in ACEI Prescription

There was marked variation across centers in rates of ACEI prescription at discharge (range 7–100%, median 35%; interquartile range, 14.6–55.4%). Increasing annual center volume (P=0.004) was associated with decreased ACEI prescription. Figure 3 is a funnel plot that shows variation of prescribing rates across center size and grouped by era of entry into the NPC-QIC registry. To eliminate the effect of center mix change over time, early centers that enrolled patients before 2011 were isolated, and prescribing behaviors inside this early center group were compared before and after the publication of ISV results. Figure 4 shows no significant change in the prescribing rates of ACEI in the early center group (P=0.169) post-ISV publication. When comparing the post-ISV publication prescribing rates in the early center group versus the late center group, we found that the late centers prescribed significantly fewer ACEI at S1P discharge (early cohort 40.2% versus late cohort 31.5%, P<0.001) (Figure 5).

To evaluate for change in prescribing patterns over time, we also employed statistical process control methodology. When treating prescription of ACEI as a process measure, there was no detectable signal for special cause variation using the Western Electric 3-sigma and Anhøj rules,[14,15] indicating stable prescription rates over time after publication of ISV results (Figure 6).

DISCUSSION

This study demonstrates that ACEI prescription remains common in the interstage with over one third of interstage patients still prescribed an ACEI at S1P discharge. Although the prescription rate was lower for those infants born in 2011–2016 as compared with the pre-2010 cohort, we found no evidence of decreases in ACEI prescription in centers with both pre- and post-ISV registry data. As evidenced by the lack of special cause variation, we did not identify a temporal relationship between changes in ACEI prescribing and publication of the ISV trial results. We also found that intercenter practice variation was widely prevalent. ACEI prescription was independently associated with preoperative mechanical ventilation and a diagnosis of AVSD or DORV. For those patients undergoing a Norwood procedure, shunt type was significant in bivariate analysis though fell out of significance in the regression model, likely as a result of center-specific surgical and prescribing practices. In the subgroup analysis of patients with complete echocardiographic data, we found that AVVR rather than AVSD was an independent

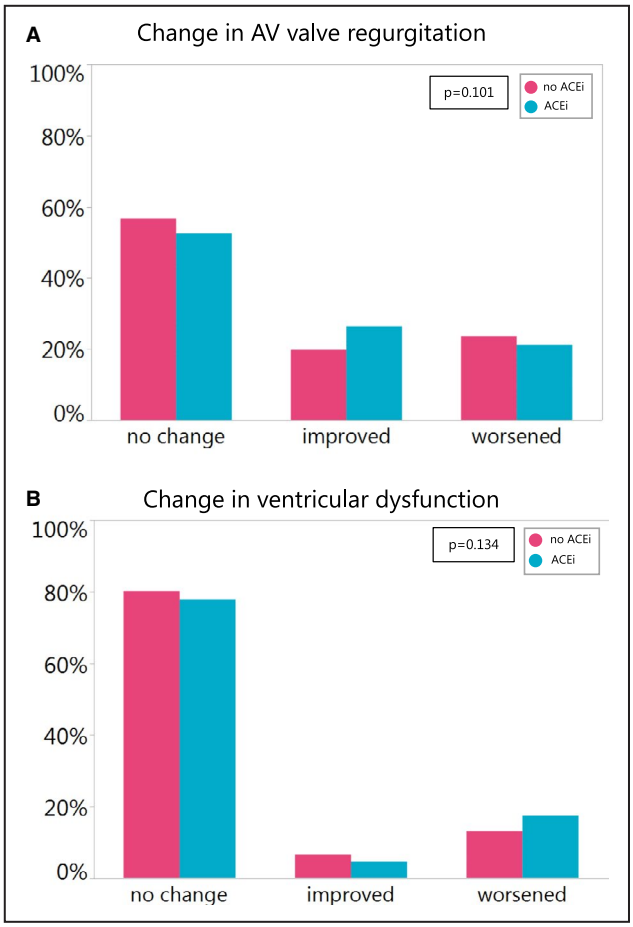

Figure 2. Change in atrioventricular valve regurgitation (A) and ventricular dysfunction (B) over the interstage.
Patients were assessed by echocardiography at the time of discharge from stage I Norwood procedure and categorized into none, mild, moderate, or severe. Interstage change was reassessed by echocardiography at stage II superior cavopulmonary anastomosis procedure readmission. Comparison performed using McNemar test.

predictor of ACEI prescription. This group showed no difference in progression or improvement of weight-for-age *z* score, AVVR, or ventricular dysfunction over the interstage period.

The continued use of ACEI in the interstage after ISV publication may be driven by the high incidence of systemic AVVR during single ventricle palliation and its associated poor prognosis. ACEI use in the interstage has historically been driven by standard practice derived from studies in adults with systemic AVVR. Treatment of systemic AVVR with afterload reduction has been supported by well-established studies in adults with mitral regurgitation. Improvement in cardiac index and reductions in regurgitant volume and end-diastolic ventricular pressure with nitroprusside have been shown, especially in the setting of left ventricular dysfunction.[5,6] However, the acute effects of ACEI administration are less consistent, showing improvement

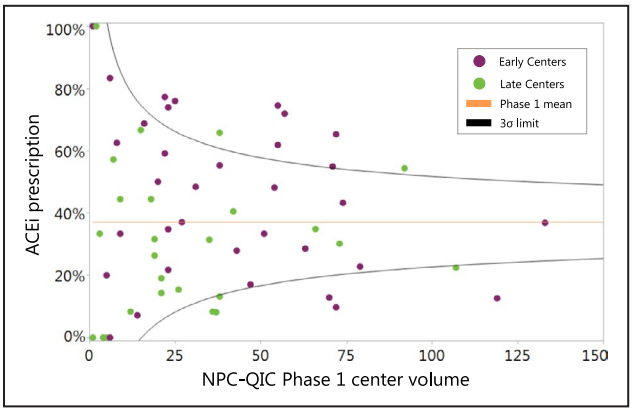

Figure 3. Variation in rates of angiotensin-converting enzyme inhibitor (ACEI) prescription at stage I Norwood procedure discharge.
Centers enrolling their first patient before 2011 are indicated as early centers, and those enrolling their first patient in 2011 or later are indicated as late centers. NPC-QIC indicates National Pediatric Cardiology Quality Improvement Collaborative.

in regurgitant fraction with no change in cardiac index or systolic ventricular function.[7] In the adult literature, chronic ACEI therapy has been most effective in symptomatic patients with left ventricular dysfunction.[8] The ISV trial, published in 2010, was the Pediatric Heart Network's attempt to provide insight into the use of ACEIs during the interstage period.

Consistent with the ISV results, our secondary analysis found no difference in clinically relevant outcomes

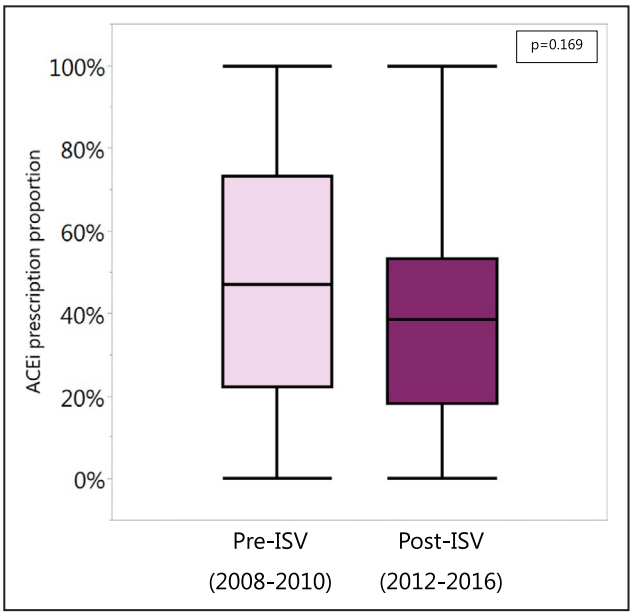

Figure 4. Chi-square comparison of the prescribing rates for angiotensin-converting enzyme inhibitor (ACEI) at stage I Norwood procedure discharge among National Pediatric Cardiology Quality Improvement Collaborative centers with data available both before and after the publication of the ISV (Infant Single Ventricle) trial.

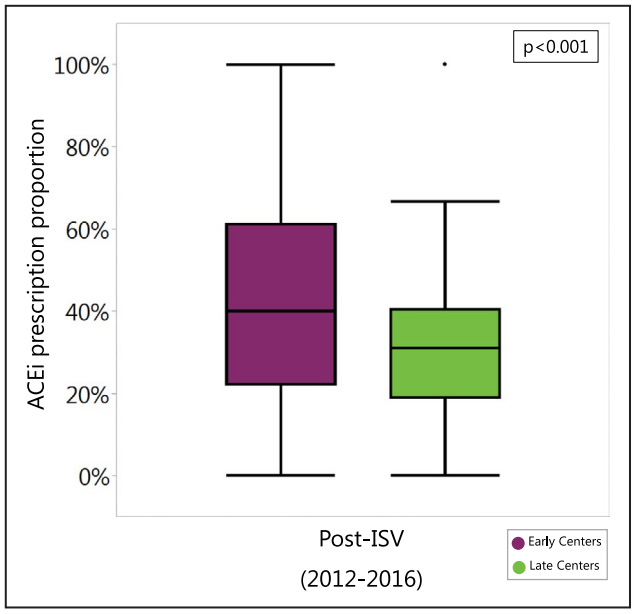

Figure 5. Chi-square comparison of the post-ISV (Infant Single Ventricle) trial prescribing rates for angiotensin-converting enzyme inhibitor (ACEI) at stage I Norwood procedure discharge among National Pediatric Cardiology Quality Improvement Collaborative centers who enrolled their first patient prior to 2011 (early centers) and those first enrolling in 2011 or later (late centers).

in patients who were prescribed ACEI compared with those who were not. While patients with at least moderate AVVR were prescribed ACEI more frequently, we found no evidence that prescription of ACEI modified their elevated risk of interstage morbidity or mortality. However, our power to detect differences in this group is limited by the small number of patients with at least moderate AVVR. The independent association with preoperative mechanical ventilation was a surprising finding and represents an opportunity for further investigation. We must consider whether this association is related to uncorrected illness severity, era effect, or covariation with other center-dependent practice patterns that were not addressed by our a priori statistical analysis plan.

With the addition of our findings, we now have further evidence suggesting little benefit of ACEI therapy in patients with single ventricle physiology who have mild or no AVVR and mild or no ventricular dysfunction. We feel it is reasonable to reinforce the conclusion drawn by the ISV trial investigators who found no evidence to support the routine use of ACEI in the interstage single ventricle population. We hypothesize that many pediatric cardiologists continue to prescribe ACEI during the interstage, even in the absence of data in congenital heart disease to support its use, as a result of the perception of minimal risk of side effects, theoretical evidence for management of pulmonary over circulation, and the paucity of other effective medical therapies for AVVR and ventricular dysfunction in the interstage.

Our analysis highlights that the impact of high-powered, well-designed negative trial results on the prescription of ACEI has been limited in scope and slow to propagate through the community of congenital cardiologists. Previous research has identified the difficulty in publication and distribution of negative research findings, especially those that go against the prevailing scientific paradigm of the time.[16] Zak et al reported that the majority of respondents modified their prescribing practices, but 28% of respondents thought the results of the ISV trial were unhelpful in clinical decision-making, most commonly because of small sample size, irrelevant end points, disagreement with trial design and the interpretation of trial results.[10] This resistance is borne out of the prescribing practices identified in our report, although resistance to change seems more common in general practice patterns captured within the NPC-QIC registry than by the self-reported practices as described by Zak and colleagues. The discrepancy in findings between Zak et al and our analysis may be attributable to the low survey response rate noted in their report, a common problem in survey cohorts. It is reasonable to assume that those with strong positive or negative feelings towards the ISV results were more likely to be respondents resulting in a study cohort that represents a biased sample of congenital cardiologists.

In terms of center-related ACEI prescribing practices, the finding that there is wide variation across NPC-QIC centers is in keeping with multiple prior studies documenting differences in care practices for infants with HLHS.[17–19] However, because NPC-QIC aims to improve outcomes by reducing variation in care, it is somewhat surprising that such wide variation exists within the learning network. It is important to note that NPC-QIC has never specifically recommended that centers change their ACEI prescription practices. The driver of different prescribing rates between the early and late centers in NPC-QIC is unclear. There was no difference in the anatomic variant mix and preoperative risk factor prevalence between the early and late centers. Patients were more commonly treated in larger centers with 27% of patients undergoing stage 1 palliation at a center with an annual volume of >15 patients per year compared with 9% of patients being treated at large centers in the early center group. We speculate that one factor may be the shifts in the rate at which interstage patients were discharged home. The intense focus on interstage survival may have increased the number of patients who remained hospitalized for the duration of the interstage, thereby changing the patient population

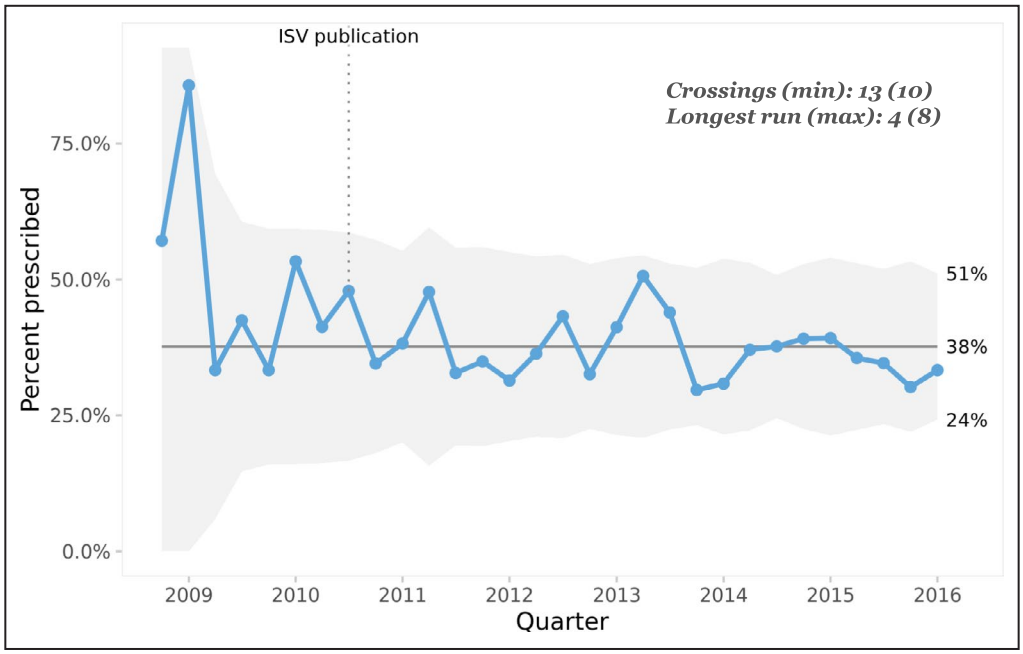

Figure 6. Statistical process control analysis of angiotensin-converting enzyme inhibitor prescribing across the entire National Pediatric Cardiology Quality Improvement Collaborative (phase 1).

The threshold of special cause variation met when: (1) any point falls outside 3 SDs from the mean, (2) the longest run above or below the mean exceeds the upper 95% prediction limit, or (3) the number of points crossing the midline falls below the 95% prediction limit. This analysis shows no special cause variation; the process remains in control almost 6 years after initial publication of the ISV (Infant Single Ventricle) trial results.

that qualified for enrollment during later years of phase 1 data collection.

Study Limitations

Three limitations to our study must be addressed. First, phase 1 of NPC-QIC excluded the highest-risk patients with single ventricle physiology who remain hospitalized during the interstage or who die before hospital discharge. These highly resource-intensive patients are a key group of patients who need further study to guide their management.

The second limitation of our study is the lack of data or incomplete collection for important surgical and clinical variables such as detailed echocardiographic, physiologic, and laboratory data; intraoperative complications; shunt size; or outcomes past S2P admission. While answering questions regarding specific surgical variables, perioperative risk factors, or biomarkers will not be possible with the current registry data collection, phase 2 of NPC-QIC has been designed to study the HLHS population, including those not discharged in the interstage, through the first year of life. We strongly support other efforts to better understand the complex nature of single ventricle palliation and feel that the collaborative learning that occurs within the NPC-QIC would be an excellent testbed for future investigations.

Last, the global aim of NPC-QIC is to change practice through sharing data to improve the care for patients with HLHS. Because of this overarching goal, it is possible that ongoing quality improvement work in the collaborative may have affected the study outcomes over time. It is important to reiterate here that NPC-QIC has not developed any improvement projects that focus on the use of ACEI during the interstage but has targeted feeding and nutrition practices resulting in increasing interstage weight for age *z* score change over time.

CONCLUSIONS

Our analysis of the NPC-QIC phase 1 registry found that ACEI prescription remains common in the interstage and was not dramatically impacted by ISV trial publication. ACEI prescription is associated with preoperative mechanical ventilation and DORV and AVSD anatomic variants. AVVR at S1P discharge is an independent predictor in those patients with complete echocardiographic data. ACEI prescription is not associated with reduction in mortality, ventricular dysfunction, or AVVR in the interstage. Universal prescription of ACEI during the interstage is not supported by evidence from randomized controlled trials or large retrospective cohort studies. Further work to

identify subpopulations who benefit from ACEI in the interstage is needed.

ARTICLE INFORMATION

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Disclosures

None.

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