# Digoxin Use Is Associated With Reduced Interstage Mortality in Patients With No History of Arrhythmia After Stage I Palliation for Single Ventricle Heart Disease

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***Background***—Interstage mortality (IM) remains significant after stage 1 palliation (S1P) for single-ventricle heart disease (SVD), with many deaths sudden and unexpected. We sought to determine whether digoxin use post-S1P is associated with reduced IM, utilizing the multicenter database of the National Pediatric Cardiology Quality Improvement Collaborative (NPCQIC).

***Methods and Results***—From June 2008 to July 2013, 816 infants discharged after S1P from 50 surgical sites completed the interstage to stage II palliation, transplant, or IM. Arrhythmia during S1P hospitalization or discharge on antiarrhythmic medications were exclusions (n=270); 2 patients were lost to follow-up. Two analyses were performed: (1) propensity-score adjusted logistic regression with IM as outcome and (2) retrospective cohort analysis for patients discharged on digoxin versus not, matched for surgical site and other established IM risk factors. Of 544 study patients, 119 (21.9%) were discharged on digoxin. Logistic regression analysis with propensity score, site-size group, and digoxin use as predictor variables showed an increased risk of IM in those not discharged on digoxin (odds ratio, 8.6; lower confidence limit, 1.9; upper confidence limit, 38.3; *P*<0.01). The retrospective cohort analysis for 60 patients on digoxin (matched for site of care, type of S1P, post-S1P ECMO use, genetic syndrome, discharge feeding route, ventricular function, tricuspid regurgitation, and aortic arch gradient) showed 0% IM in the digoxin at discharge group and an estimated IM difference between the 2 groups of 9% (*P*=0.04).

***Conclusions***—Among SVD infants in the NPCQIC database discharged post-S1P with no history of arrhythmia, use of digoxin at discharge was associated with reduced IM. (***J Am Heart Assoc***. 2016;5:e002376 doi: 10.1161/JAHA.115.002376)

**Key Words:** cardiovascular disorders • cardiovascular surgery • congenital heart disease • mortality • quality improvement

Among congenital cardiac defects, patients with single-ventricle physiology remain the most complex and have the highest rates of associated morbidity and mortality. Children with hypoplastic left heart syndrome (HLHS) and other forms of left heart hypoplasia face the highest mortality rates, up to 30% to 45% in their first 4 years of life, with typical mortality rates of 15% to 20% occurring around the stage 1 palliation (S1P), and interstage mortality (IM) rates of 10% to 15% in survivors discharged to home before bidirectional Glenn operation (BDG).[1–4]

The causative factors for death after S1P remain various and complex. Older autopsy series in nonsurvivors after the Norwood type of S1P described a high rate of anatomical or functional issues causative of mortality, including circulatory collapse from systemic to pulmonary artery shunt compromise, occult recurrent aortic arch obstruction, restrictive atrial septae, severe valvular regurgitation, or ventricular dysfunction.[5] More recently, the technical outcome of S1P (the "technical performance score"), which includes some of the above anatomical issues, was predictive of survival, with those with better scores demonstrating improved survival after adjusting for preoperative risk status.[6,7]

However, the causes of IM among survivors of S1P discharged to home is less well characterized. A large

multicenter study among those discharged with subsequent IM identified several risk factors: patient related, such as history of preterm delivery and HLHS subtype with aortic and mitral atresia; surgically related, such as a Blalock-Taussig (BT) shunt (in those without significant atrioventricular valve regurgitation); and family related, such as census block poverty level.[4] However, the immediate cause of IM in these patients is often unclear; a recent registry study demonstrated that the majority die suddenly or unexpectedly at home or in emergency departments.[8] Given that many out-of-hospital deaths remain unexplained even after autopsy with no anatomical problems identified, occult arrhythmia leading to circulatory collapse has been suspected to be an important mechanism, but a difficult one to prove.

Digoxin, a cardiac glycoside medication derived from the Foxglove plant, has been used for centuries to treat congestive heart failure and has also been useful in the treatment of arrhythmias through effects on conduction at the atrioventricular node. Digoxin is used, by some clinicians, for treatment of infants with HLHS and other single-ventricle defects post-S1P, despite the absence of published evidence regarding efficacy on clinical outcomes in this setting. Given that one of the causes of IM post-S1P may be occult arrhythmia, we hypothesized that treatment with digoxin might result in improved interstage survival in patients with no history of documented arrhythmia. We thus sought to investigate whether treatment with digoxin at time of discharge was associated with a reduced risk of IM in a large cohort of survivors of S1P with no history of arrhythmia discharged to home from the National Pediatric Cardiology Quality Improvement Collaborative (NPCQIC).

## Methods

### Study Setting and Population

The NPCQIC was established in 2008, with goals to reduce mortality and improve the quality of life of infants with HLHS and single-ventricle disease (SVD) variants discharged to home during the interstage period between discharge from S1P and BDG or transplant. At the time of this study, NPCQIC had expanded into a nation-wide network of over 50 participating surgical centers in the United States and a database with over 800 infants enrolled. Participation in the NPCQIC is approved by institutional review boards (IRBs) at all participating centers. All infants followed at participating NPCQIC centers and meeting the criteria for enrollment into the registry are identified for potential enrollment. These criteria are: (1) diagnosis of SVD (such as HLHS) requiring S1P operation or similar variant and (2) survival to, and discharge from, the hospital before BDG or transplant. After verification of eligibility, consent is obtained and multiple data elements

are collected from the time of the patient's birth through discharge from their BDG operation or transplant. This site-level deidentified data are entered into a Web-based Research Electronic Data Capture (REDCap) database. Site self-audits are performed every 6 months and demonstrate that >95% of eligible infants at participating centers have been enrolled in the study and entered into the registry database. Data quality control is conducted using a combination of REDcap system programmed edit checks and Statistical Analysis System (SAS) reports. The programmed edit checks flags for discrepant data, out of range values, and incorrect data types in real time. SAS reports check the database for logical consistency of outcome variables, and reports are sent to participating sites on a monthly basis for data corrections.

This study was performed according to a protocol approved by the IRB of each participating institution, including the Committee for Clinical Investigation at Boston Children's Hospital (Boston, MA). 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.

### Study Design and Variables

We hypothesized that patients without a history of arrhythmia discharged on digoxin to the interstage had a lower mortality rate than those not discharged on digoxin. Therefore, patients with any history of arrhythmia during the S1P hospitalization, or discharged on a beta blocker or other antiarrhythmic medication besides digoxin were excluded, to control for potential confounders in this observational study. Potential predictor variables included data from birth to hospital discharge from S1P that were thought to relate to IM. This included patient demographic and anatomical factors, such as chromosomal anomalies and other associated organ system abnormalities, presence of preoperative risk factors, type of initial surgical palliation, and characterizations of postoperative hospitalization, such as length of intubation, requirement for extracorporeal membrane oxygenator (ECMO) use, major postoperative procedures, postoperative complications, and any necessary cardiac reoperation. Our outcome variable was IM, where no mortality was the endpoint of BDG or transplant.

### Statistical Analysis

Categorical variables were summarized using frequencies and percentages; continuous variables were summarized using medians with 25th and 75th percentiles. Univariate logistic regression was performed with each variable as the predictor and IM as the outcome; a similar univariate logistic regression was performed with each variable as the predictor and treatment with digoxin as the outcome to further identify variables for inclusion in the propensity score. Statistical

significance in the univariate analysis and clinical judgement were used to determine the variables to be included in the propensity score. Correlations among the variables considered for inclusion in the propensity score were examined to evaluate collinearity. A Kaplan-Meier survival curve was produced for comparing those discharged on digoxin to those not discharged on digoxin. A log-rank test was used to test for statistical significance with α=0.05.

Funnel plots, a common statistical quality improvement technique, were used to examine center variability in IM and percent of patients discharged on digoxin.[9] The control limits define the boundaries of common cause variation defined as normal and expected variation. Sites outside the control limits indicate special cause variation, which is a signal that care practices may be different at those sites from the collaborative as a whole. Three sigma control limits were used in the funnel plots.

Two complementary statistical analyses were conducted to evaluate the relationship between digoxin use in patients without a history of arrhythmia and IM: logistic regression with propensity score and a retrospective cohort analysis with a case-control framework. Both of these were selected in order to control for potential confounders. Discharge ventricular function, discharge tricuspid regurgitation, and discharge aortic arch gradient had 14%, 15%, and 18% missing data, respectively. For the following 2 statistical analyses, multiple imputation was performed using IVEware software (Survey Research Center, University of Michigan, Ann Arbor, MI)[10] to address this issue. Multivariate sequential regression was conducted with 10 cycles and 10 imputations to produce 10 data sets. Instead of filling in a single value for each missing value, 10 plausible values are represented in each of the 10 data sets. Analyses were run on each of the 10 data sets, and parameter estimates from each of these analyses were combined using a SAS procedure, which creates valid inferences for these parameters by weighting standard errors.

### Logistic regression

Logistic regression with a propensity score as a continuous covariate[11] was used to evaluate the relationship between digoxin use and IM. Propensity score analysis reduces the effects of confounding when using observational data to estimate treatment effects. Variables used to develop the propensity score for treatment with digoxin included type of S1P, post-S1P ECMO use, genetic syndrome, discharge feeding route, ventricular function, tricuspid regurgitation, and aortic arch gradient. The model used logistic regression with IM as the outcome variable and propensity score, site volume grouping (see below), and discharge on digoxin included as covariates. This approach allowed inclusion of all patients in the analysis leading to generalizability, assum-

ing the propensity score includes all relevant covariates and the relationship is correctly specified.

As a surrogate for site procedural volume and to control for site variation related to volume, sites were grouped into 3 categories: those enrolling an average of less than 5 infants/year in the registry, those enrolling 5 to <10/year, and those enrolling ≥10/year over the time period of center participation in the network. The quality of propensity scores was evaluated by examining distributions of propensity scores for those discharged on digoxin versus not. Estimates and SEs for each imputation were combined to generate valid statistical inferences.

### Retrospective cohort analysis

In addition, to further control for potential unmeasured center-specific confounders, a retrospective cohort study using a case-control framework was conducted. Patients were grouped into those discharged into the interstage period on digoxin versus not. For each group, patients were matched for surgical site (a mandatory match) and for 7 other potential confounders identified by clinicians as risk factors for IM and/or selection bias for treatment with digoxin (type of S1P, post-S1P ECMO use, genetic syndrome, discharge feeding route, discharge ventricular dysfunction, discharge tricuspid regurgitation, and aortic arch gradient). After matching by surgical site, if an exact match could not be found for 1 of the 7 risk factors, a patient discharged on digoxin was matched with a patient not on digoxin with the next less-serious level of the factor; we did not match a patient on digoxin with a patient with a more-serious level of factor(s). For example, if an exact match for a patient on digoxin with moderate ventricular dysfunction was not possible, only a match not on digoxin with a better degree of ventricular function was used. This creates the most conservative test of the association with digoxin use with IM. Fishers' exact test was performed, and estimates and SEs for each imputation were combined to generate valid statistical inferences. All statistical inferences were conducted at the 2-sided 5% level of significance and were performed using SAS 9.3 (SAS Institute Inc., Cary, NC).

## Results

### Patient Characteristics

A total of 816 patients from 50 participating surgical centers met inclusion criteria for the NPCQIC registry during the study period from June 2008 to July 2013; from this cohort, 257 patients were excluded from this analysis for history of arrhythmia during the S1P hospitalization (2 sites were excluded because all patients had a history of arrhythmia), 13 patients were excluded as they were discharged on a

beta-blocker or other antiarrhythmic medication, and 2 patients were excluded because the outcome of IM, BDG, or transplant was not known. Summary demographic information for the remaining 544 patients is listed in Table 1. Patients were predominantly male (60%); the majority (68%) had variants of HLHS; the most common type of S1P was the Norwood with a right ventricle to pulmonary artery conduit (52%); and the overall median S1P hospital length of stay was 33 days. A total of 119 patients (22%) were prescribed digoxin at hospital discharge. Follow-up data from the last clinic visit before reaching a clinical endpoint (IM, transplant, or BDG) demonstrated that 91% of infants on digoxin at S1P discharge continued to be prescribed digoxin, and 93% of those not on digoxin at S1P discharge remained off digoxin treatment. In the entire cohort, there were 44 interstage deaths (8% overall).

## Factors Associated With IM

In univariate logistic regression analysis without imputation, 3 factors were significantly associated with IM: type of S1P; post-operative ECMO use; and digoxin use at S1P discharge. Table 2 lists the results of univariate analysis for selected variables from a much larger list of candidate variables explored (see Data S1 for a complete list of variables investigated). Ventricular dysfunction, tricuspid regurgitation, aortic arch gradient, genetic syndrome, and feeding route at discharge were not significantly associated with IM. The lowest volume sites had significant increased IM over the medium and larger sites. Type of S1P was significantly associated with IM, with the lowest IM observed with the Norwood with right ventricle to pulmonary artery homograft and the highest IM with those treated with a Damus-Kaye-Stansel (DKS) and BT shunt. Treatment with postoperative ECMO was associated with higher IM (21% IM in those requiring ECMO). Finally, treatment with digoxin at discharge was associated with reduced IM: 1.7% IM in those on digoxin versus 9.9% in those not on digoxin ($P$=0.01). Figure 1 displays the Kaplan-Meier (K-M) survival analysis from time of S1P discharge, with statistically significant reduction in IM in those on digoxin compared to patients not on digoxin (K-M $P$-value, 0.01).

## Logistic Regression Analysis With Propensity Score

Relationships between digoxin use and variables included in the propensity score are displayed in Table 3. Although genetic syndrome, discharge ventricular dysfunction, and discharge tricuspid regurgitation did not demonstrate a significant association with digoxin use, clinical judgement indicated that it was important to include these variables in

**Table 1.** Patient Summary Information (n=544)

| Patient Parameters | Number (%) or Median [IQR] |
|---|---|
| Male | 325 (60) |
| Birth weight, kg | 3.2 [2.9, 3.5] |
| Gestational age, weeks | 39 [38, 39] |
| Primary cardiac diagnosis | |
| Hypoplastic left heart syndrome variant | 369 (68) |
| HLHS with MA/AA | 192 (35) |
| HLHS with MS/AS | 82 (15) |
| HLHS with MS/AA | 79 (15) |
| HLHS with MA/AS | 16 (3) |
| Double-outlet right ventricle with left-sided hypoplasia | 23 (4) |
| Double-inlet left ventricle | 26 (5) |
| Unbalanced AV canal | 23 (4) |
| Double-inlet right ventricle | 1 (<1) |
| Single ventricle | 14 (3) |
| Other | 85 (15) |
| Secondary diagnoses before S1P | |
| Restrictive atrial septum | 90 (17) |
| AV valve regurgitation* | 18 (3) |
| Ventricular dysfunction* | 12 (2) |
| Syndrome or genetic abnormality | 41 (8) |
| Major anomaly of other organ system | 49 (9) |
| S1P surgical variables | |
| Age at S1P, days | 5 [4, 8] |
| Type of S1P | |
| Norwood/BT shunt | 188 (35) |
| Norwood/RV to PA conduit | 285 (52) |
| Hybrid S1P | 51 (9) |
| DKS connection with BT shunt | 18 (3) |
| Hospital length of stay, days | 33 [23, 51] |
| Oxygen saturation at discharge (%) | 83 [80, 86] |
| Feeding route at discharge | |
| Oral only | 221 (41) |
| NG/NJ alone or with oral | 220 (41) |
| GT alone or with oral | 102 (19) |
| Home surveillance strategy at discharge | |
| None | 31 (6) |
| O₂ saturation and weight | 468 (86) |
| O₂ saturation only | 44 (8) |

AA indicates aortic atresia; AS, aortic stenosis; AV, atrioventricular; BT, Blalock-Taussig; DKS, Damus-Kaye Stansel; GT, gastric tube; HLHS, hypoplastic left heart syndrome; IQR, intraquartile range; MA, mitral atresia; MS, mitral stenosis; NG, nasogastric; NJ, nasojejunal; O₂, oxygen; PA, pulmonary artery; RV, right ventricle; S1P, stage 1 palliation. *Defined as ≥moderate.

**Table 2.** Factors Associated With Interstage Mortality in Univariate Analysis (n=544)

| Patient Variable | N | Mortality=No No. (%) | Mortality=Yes No. (%) | P Value |
|---|---|---|---|---|
| Discharged on digoxin | 544 | | | 0.01 |
| No | 425 | 383 (90.1) | 42 (9.9) | |
| Yes | 119 | 117 (98.3) | 2 (1.7) | |
| Site enrollment grouping* | 544 | | | 0.03 |
| Less than 5 patients/yr | 156 | 137 (87.8) | 19 (12.2) | |
| 5 to 9 patients/yr | 193 | 183 (94.8) | 10 (5.2) | |
| ≥10 patients/yr | 195 | 180 (92.3) | 15 (7.7) | |
| Type of S1P | 542 | | | 0.01 |
| Norwood/BT shunt | 188 | 172 (91.5) | 16 (8.5) | |
| Norwood/RV-PA conduit | 285 | 270 (94.7) | 15 (5.3) | |
| Hybrid S1P | 51 | 43 (84.3) | 8 (15.7) | |
| DKS connection with BT shunt | 18 | 13 (72.2) | 5 (27.8) | |
| Post S1P ECMO use | 540 | | | 0.05 |
| No | 521 | 481 (92.3) | 40 (7.7) | |
| Yes | 19 | 15 (78.9) | 4 (21.1) | |
| Discharge ventricular function | 467 | | | 0.45 |
| Normal-mild dysfunction | 451 | 418 (92.7) | 33 (7.3) | |
| ≥Moderate dysfunction | 16 | 14 (87.5) | 2 (12.5) | |
| Discharge tricuspid regurgitation | 461 | | | 0.61 |
| None-mild | 371 | 344 (92.7) | 27 (7.3) | |
| ≥Moderate | 90 | 82 (91.1) | 8 (8.9) | |
| Discharge aortic arch gradient†, mm Hg | 448 | | | 0.35 |
| 0 to 10 | 364 | 340 (93.4) | 24 (6.6) | |
| >10 | 84 | 76 (90.5) | 8 (9.5) | |
| Syndrome or genetic abnormality | 544 | | | 0.68 |
| No | 503 | 463 (92.0) | 40 (8.0) | |
| Yes | 41 | 37 (90.2) | 4 (9.8) | |
| Feeding route at discharge | 543 | | | 0.64 |
| Oral only | 221 | 203 (91.9) | 18 (8.1) | |
| NG/NJ alone or with oral | 220 | 201 (91.4) | 19 (8.6) | |
| GT alone or with oral | 102 | 95 (93.1) | 7 (6.9) | |

BT indicates Blalock-Taussig; DKS, Damus-Kaye Stansel; ECMO, extracorporeal membrane oxygenator; GT, gastric tube; NG, nasogastic; NJ, nasojejunal; PA, pulmonary artery; RV, right ventricle; S1P, Stage 1 Palliation.
*Average patient enrollment/year. See Methods.
†Excludes patients with hybrid S1P.
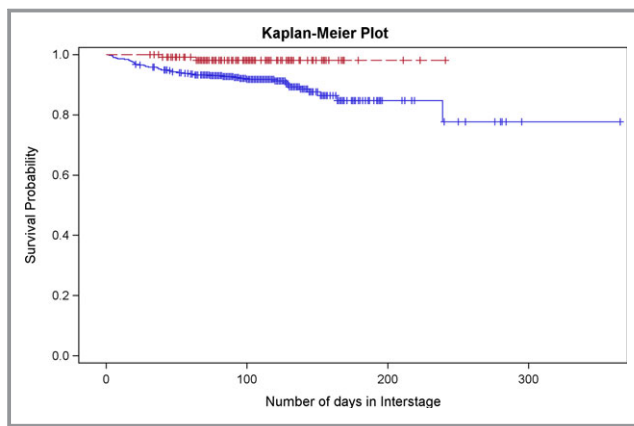


**Figure 1.** Survival by digoxin treatment. Kaplan-Meier survival analysis for 546 infants enrolled in the National Pediatric Cardiology Quality Improvement Collaborative registry with no history of arrhythmia discharged to home after stage 1 palliation. Patients treated with digoxin at hospital discharge (N=119; red line) had reduced interstage mortality compared to patients not on digoxin (N=427; blue line; K-M, *P*=0.01).

the propensity score. Figure 2 demonstrates the distribution of propensity scores between those on digoxin versus not on digoxin at discharge; as observed in the bar histograms as well as the percentage quintiles of propensity scores in the embedded table, the 2 populations demonstrate good overlap across the range of propensity scores. Propensity-score–adjusted multivariable regression demonstrated that patients not on digoxin at S1P discharge had an odds ratio (OR; 95% CI) of 8.6 (1.9, 38.2) for IM relative to those on digoxin at discharge (*P*<0.01). A sensitivity analysis was conducted using both tertiles and quintiles of the propensity score and results were consistent with our continuous covariate results.

## Retrospective Cohort Analysis

For the retrospective cohort analysis, ≈50% of patients on digoxin were able to be matched with patients not on digoxin, representing ≈44% of surgical sites. All patients were matched for site of care; ≈84% of patients were matched to ≥6 of 7 variables (type of S1P, post-S1P ECMO use, discharge ventricular function, tricuspid regurgitation, discharge aortic arch gradient, syndrome or genetic abnormality, and feeding route at discharge). The percentage in the digoxin group was 0% IM, and the estimated difference in mortality between the 2 groups is 9% (95% CI, 1, 17; *P*=0.04).

## Surgical Center, Digoxin Use, and IM

Variation among surgical centers is depicted in the funnel plots for IM (Figure 3) and digoxin use (Figure 4). Though no sites were outside the control limits for IM, 7 sites were

**Table 3.** Factors Associated With Digoxin at Discharge in Univariate Analysis (n=544)

| Patient Variable | N | Digoxin=No No. (%) | Digoxin=Yes No. (%) | *P* Value |
|---|---|---|---|---|
| Discharged on digoxin | 544 | 425 (78.1) | 119 (21.9) | |
| Site enrollment grouping* | 544 | | | <0.01 |
| Less than 5 patients/year | 156 | 120 (76.9) | 36 (23.1) | |
| 5 to 9 patients/year | 193 | 137 (71.0) | 56 (29.0) | |
| ≥10 patients/year | 195 | 168 (86.2) | 27 (13.8) | |
| Type of S1P | 542 | | | 0.01 |
| Norwood/BT shunt | 188 | 140 (74.5) | 48 (25.5) | |
| Norwood/RV-PA conduit | 285 | 235 (82.5) | 50 (17.5) | |
| Hybrid S1P | 51 | 32 (62.7) | 19 (37.3) | |
| DKS connection with BT shunt | 18 | 16 (88.9) | 2 (11.1) | |
| Post S1P ECMO use | 540 | | | <0.01 |
| No | 521 | 411 (78.9) | 110 (21.1) | |
| Yes | 19 | 10 (52.6) | 9 (47.4) | |
| Discharge ventricular function | 467 | | | 0.45 |
| Normal-mild dysfunction | 451 | 347 (76.9) | 104 (23.1) | |
| ≥Moderate dysfunction | 16 | 11 (68.8) | 5 (31.3) | |
| Discharge tricuspid regurgitation | 461 | | | 0.72 |
| None-mild | 371 | 282 (76.0) | 89 (24.0) | |
| ≥Moderate | 90 | 70 (77.8) | 20 (22.2) | |
| Discharge aortic arch gradient[†, mm Hg] | 448 | | | <0.01 |
| 0 to 10 | 364 | 297 (81.6) | 67 (18.4) | |
| >10 | 84 | 45 (53.6) | 39 (46.4) | |
| Syndrome or genetic abnormality | 544 | | | 0.99 |
| No | 503 | 393 (78.1) | 110 (21.9) | |
| Yes | 41 | 32 (78.0) | 9 (22.0) | |
| Feeding route at discharge | 543 | | | <0.01 |
| Oral only | 221 | 168 (76.0) | 53 (24.0) | |
| NG/NJ alone or with oral | 220 | 186 (84.5) | 34 (15.5) | |
| GT alone or with oral | 102 | 70 (68.6) | 32 (31.4) | |

BT indicates Blalock-Taussig; DKS, Damus-Kaye Stansel; ECMO, extracorporeal membrane oxygenator; GT, gastric tube; NG, nasogastric; NJ, nasojejunal; PA, pulmonary artery; RV, right ventricle; S1P, stage 1 palliation.
*Average patient enrollment/year. See Methods.
[†]Excludes patients with hybrid S1P.

outside the control limits for digoxin use at discharge from S1P, with 2 centers reporting 100% of patients discharged home on digoxin and 19 others with 0% of patients discharged on digoxin.
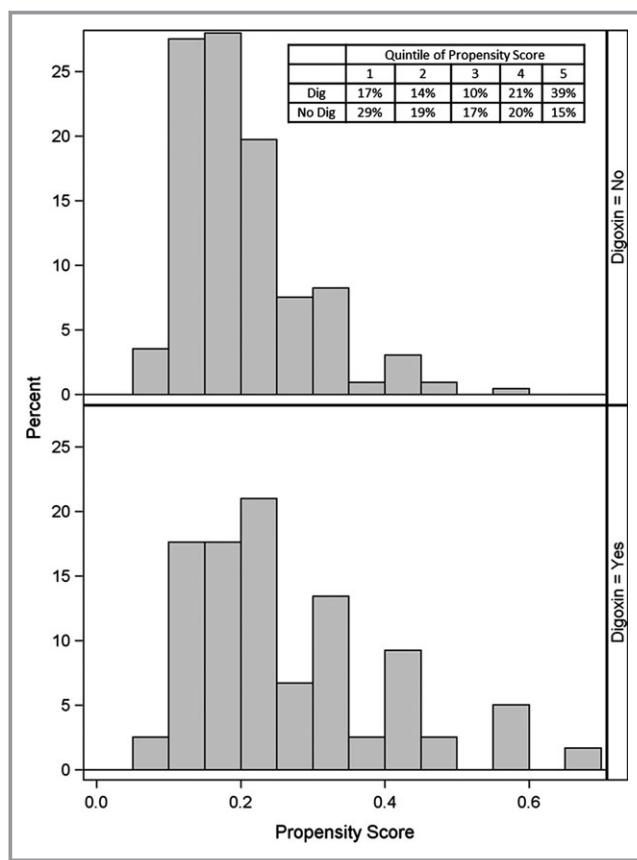


**Figure 2.** Propensity score distribution by digoxin treatment. Bar graph comparison of the distribution of propensity scores among the 544 infants in the study cohort. Upper panel shows the distribution of propensity scores for those not on digoxin at discharge and the lower panel the scores for infants on digoxin at discharge. Embedded table shows the percentage distribution of infants across the quintiles of propensity scores.

## Secondary Analyses: Exclusions

Survival analyses for the excluded patients with history of arrhythmia, as well as the entire NPCQIC registry cohort before exclusions are shown in Figures 5 and 6, respectively. After excluding patients on antiarrhythmia medication other than digoxin, among the 257 patients excluded for history of significant arrhythmia during the S1P, there was no statistically significant difference in mortality in those treated with digoxin versus not (Figure 5). In addition, this group of excluded patients had a similar interstage mortality to the entire NPCQIC cohort before any exclusions (Figure 6).

## Discussion

To our knowledge, this is the first large, multicenter study of digoxin use in a cohort of infants with SVD discharged to home post-S1P. We found that infants with no history of arrhythmia prescribed digoxin at hospital discharge had a lower rate of IM
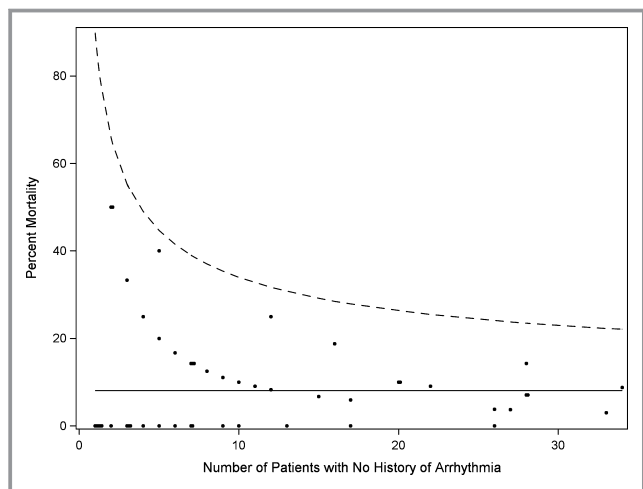
**Figure 3.** Interstage mortality by surgical site (n=50 centers). This figure shows interstage mortality (IM) among the 544 infants in the study cohort. Each small circle represents a surgical site, with the number of patients enrolled in the registry on the *x* axis and percent IM on the *y* axis. The curved line represents the upper 99.7% CI for statistical significance. The solid straight line represents the mean.

in univariate analysis, in a propensity-score–adjusted logistic regression model and in a retrospective cohort analysis with mandatory site-of-care matching. We also found marked intercenter variability in the use of digoxin in this setting, and for some centers, intracenter variability as demonstrated in Figure 4. Among those centers with significant intracenter variability in use of digoxin, the findings of the larger study held true, with lower IM among infants discharged on digoxin,
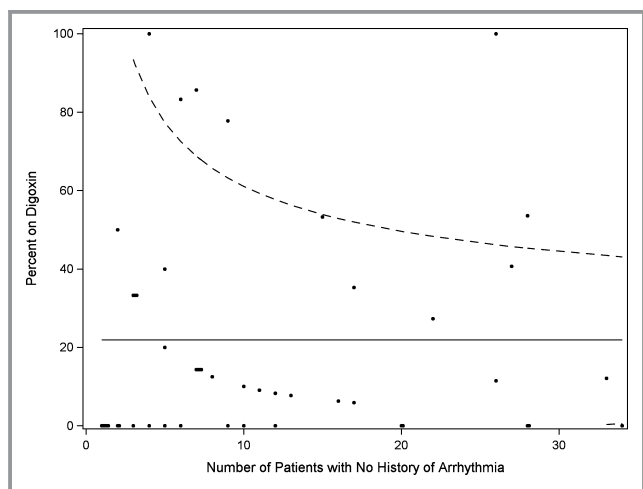


**Figure 4.** Digoxin use by surgical site (n=50 centers). This figure shows digoxin use at discharge among the 544 infants in the study cohort. Each small circle represents a surgical site, with number of patients in the study cohort on the *x* axis and percent on digoxin at hospital discharge on the *y* axis. Curved lines represent the 99.7% CI for statistical significance. The solid straight line represents the mean.
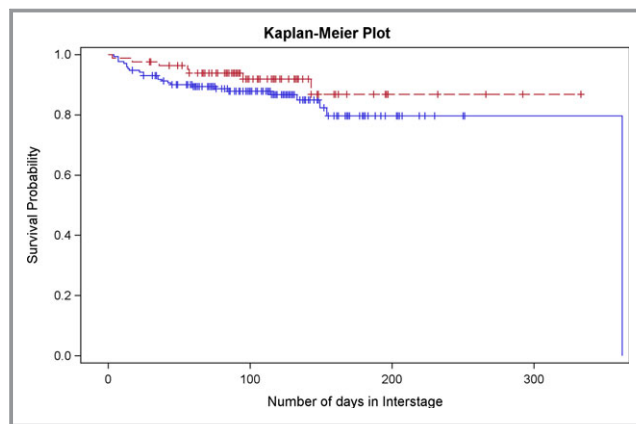


**Figure 5.** Survival analysis for excluded patients with history of arrhythmia by digoxin treatment status. Kaplan-Meier survival analysis for 257 infants enrolled in the National Pediatric Cardiology Quality Improvement Collaborative registry with history of arrhythmia during the stage 1 palliation hospitalization. Though patients treated with digoxin at hospital discharge (red line), compared to patients not on digoxin (blue line), had slightly different survival curves, the difference was not statistically significant.

although the sample sizes at each individual center are too small to allow for formal statistical analyses.

Though some patient- and procedure-related risk factors for IM have been identified from the NPCQIC database and in other large multicenter studies[4] (such as preterm delivery, type of S1P, and post-S1P use of ECMO), these factors offer little guidance to clinicians and families as to a given patient's risk of IM as a child enters the interstage period and may have little to do with the immediate cause of interstage death in this setting. As previously noted, a retrospective review of IM from the NPCQIC database demonstrated that a substantial proportion of patients died after sudden, unexpected events at home or in emergency departments.[8] Whereas occult
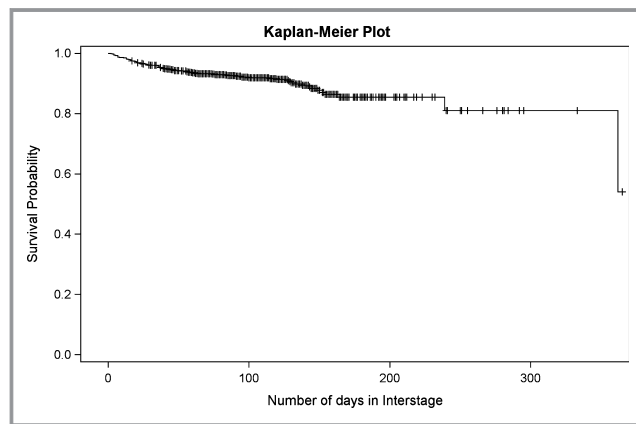


**Figure 6.** Survival analysis for entire cohort before exclusions. Kaplan-Meier survival analysis for all 816 infants enrolled in the National Pediatric Cardiology Quality Improvement Collaborative registry discharged to home after stage 1 palliation hospitalization.

arrhythmia leading to circulatory instability has been postulated as a potential immediate cause of death for these infants, this has not yet been proven. Interestingly, though patients with history of documented arrhythmia during the S1P hospitalization or those on other antiarrhythmia medications were purposely excluded from the current analysis, among the 270 patients excluded, 36% (77) of these patients were treated with digoxin alone at discharge, and there was no statistically significant association of medication group with IM (7.8% for those on digoxin alone, 10.4% for those on no antiarrhythmia medication, and 18.4% for those on other antiarrhythmia medications other than digoxin).

Our study offers some initial support for the occult arrhythmia hypothesis as a potential mechanism of IM, although, by no means, proof. Should these findings be confirmed with further research, many questions remain regarding the mechanism of action(s) of digoxin in this setting. In addition to its antiarrhythmia properties, digoxin has effects on the neurohormonal axis of heart failure, and thus the potential mechanism of action may be complex and multifactorial.

## Study Limitations

There are several limitations to this study, including the usual limitations when using retrospective registry data, such as the inability to independently verify registry data and the inability to collect any missing data points. The current study used the multiple imputation technique to minimize the latter issue, and, importantly, the findings of increased IM associated with no use of digoxin at discharge were consistent across all imputations. Whereas the number of patient variables collected between birth and time of discharge post-S1P is extensive in this database, there may be unmeasured confounders that could affect the results. In addition, there is no information collected in the registry on the precise indication for starting digoxin, the drug dosages used, and no data regarding actual patient/family adherence to giving the medication. Although our analysis was based upon digoxin use at S1P discharge and treatment crossover in the interstage period was possible and did occur, data from the last clinic visit before reaching an endpoint (BDG, IM, or transplant) showed that over 90% of infants in each group continued to be prescribed or not prescribed digoxin. Last, though the small number of events created a wide CI, the lower OR confidence limit of 1.9 is still a clinically relevant effect.

## Conclusions

In summary, in this study of a large, multicenter cohort of infants discharged to home post-S1P with no history of arrhythmia in the NPCQIC registry, use of digoxin at discharge was associated with reduced IM in both retrospective cohort and propensity-score–adjusted logistic regression analysis. We also found marked practice variation regarding digoxin use in this setting. Further research is needed to confirm this association and investigate the mechanism(s) of action.

## Disclosures

None.

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