## ORIGINAL RESEARCH

# Incidence and Timing of Thrombosis After the Norwood Procedure in the Single-Ventricle Reconstruction Trial

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**BACKGROUND:** Thrombosis is common in infants undergoing staged surgeries for single-ventricle congenital heart disease. The reported incidence and timing of thrombosis varies widely, making it difficult to understand the burden of thrombosis and develop approaches for prevention. We aimed to determine the timing and cumulative incidence of thrombosis following the stage I Norwood procedure and identify clinical characteristics associated with thrombosis.

**METHODS AND RESULTS:** We analyzed data from the Pediatric Heart Network Single Ventricle Reconstruction trial from 2005 to 2009 and identified infants with first-time thrombotic events. In 549 infants, the cumulative incidence of thrombosis was 21.2% (n=57) from stage I through stage II. Most events occurred during stage I (n=35/57, 65%), with a median time to thrombosis of 15 days. We used a Cox proportional hazards model to estimate the association of clinical variables with thrombosis. After adjusting for baseline variables, boys had a higher hazard of thrombosis (adjusted hazard ratio [HR], 2.69; 95% CI, 1.44–5.05; *P*=0.002), non–hypoplastic left heart syndrome cardiac anatomy was associated with a higher early hazard of thrombosis (adjusted HR, 3.93; 95% CI, 1.89–8.17; *P*<0.001), and longer cardiopulmonary bypass time was also associated with thrombosis (per 10-minute increase, adjusted HR, 1.07; 95% CI, 1.01–1.12; *P*=0.02). Lower oxygen saturation after the Norwood procedure increased the hazard for thrombosis in the unadjusted model (HR, 1.08; 95% CI, 1.02–1.14; *P*=0.011).

**CONCLUSIONS:** Thrombosis affects 1 in 5 infants through Stage II discharge, with most events occurring during stage I. Male sex, non–hypoplastic left heart syndrome anatomy, longer cardiopulmonary bypass time, and lower stage I oxygen saturation were associated with thrombosis.

**Key Words:** congenital heart disease ■ hypoplastic left heart syndrome ■ pediatrics ■ single ventricle ■ thrombosis

Infants with hypoplastic left heart syndrome (HLHS) and other morphologically related single right ventricle conditions require a series of reconstructive cardiac surgeries to survive.[1,2] The first surgery (Norwood procedure) typically takes place in the neonate and consists of a complex reconstruction of the aorta with proximal aortopulmonary anastomosis and division of the main pulmonary artery. In addition, it requires the placement of a systemic-to-pulmonary shunt to provide controlled pulmonary blood flow either in the form of a right ventricle-to-pulmonary artery (Sano) shunt or a subclavian-to-pulmonary artery (modified Blalock-Taussig) shunt. This surgery is followed by the stage II (Glenn) procedure at around 6 months of age and includes diversion of the superior vena cava flow directly into the pulmonary arterial system. The treatment path culminates in a Fontan type of procedure in early childhood, aiming to incorporate the inferior vena cava flow in the pulmonary circulation, thus completing the separation of the systemic venous from the pulmonary venous and the arterial circulation.[3,4] While staged surgical reconstructions have contributed to improved survival and quality of life, increased life span highlights the

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## CLINICAL PERSPECTIVE

### What Is New?

- One in 5 infants with single right ventricle congenital heart disease experience thrombosis through Stage II discharge, with most events occurring during the Stage I hospitalization.
- Male infants and those with non–hypoplastic left heart syndrome anatomy, longer cardiopulmonary bypass time, and lower stage I oxygen saturation are more likely to experience thrombosis.

### What Are the Clinical Implications?

- Our results highlight the need to identify early risk factors for thrombosis in order to guide time- and risk-targeted thromboprophylaxis in this high-risk population.

### Nonstandard Abbreviations and Acronyms

| | |
|---|---|
| **HLHS** | hypoplastic left heart syndrome |
| **mBTS** | modified Blalock-Taussig shunt |
| **PHN** | Pediatric Heart Network |
| **RVPAS** | right ventricle to pulmonary artery shunt |
| **SVR** | single ventricle reconstruction |

presence of morbidities. Among these, thrombosis is common and is further associated with increased mortality and morbidity.[5–7]

Pediatric congenital heart disease (CHD) is associated with higher risk for thrombosis attributable to alterations in blood flow, hypercoagulable state, surgery, use of central vascular lines, and foreign vascular material.[5,8–10] Infants with single-ventricle physiology CHD undergoing staged surgical reconstruction are among the pediatric patients at highest risk for thrombosis, with prior reports estimating that up to 50% of patients will experience thrombosis during the reconstruction process.[10–12] In one single-ventricle cohort, thrombosis was the primary or secondary cause of death in 21% and 24% of infants, respectively.[12] Shunt thrombosis is known to be a leading cause of mortality in this population, with up to 40% mortality [6]. Morbidities associated with thrombosis in children with single-ventricle CHD include cardioembolic stroke, pulmonary embolism, superior vena cava syndrome, difficult vascular access, postthrombotic syndrome, and increased healthcare usage.[8,10,13–15]

Prevention of thrombosis, an approach termed *thromboprophylaxis,* is not universally standardized because of lack of high-level evidence and varies by institution, surgeon, or cardiologist. Pharmacologic thromboprophylaxis in the single-ventricle population with aspirin, warfarin, and low-molecular-weight heparin have all been shown to reduce the risk for thrombosis, but thrombosis is still common, and evidence to further guide targeted thromboprophylaxis is very limited.[11,16] The reported incidence and timing of thrombosis varies widely in the literature, as most studies include heterogeneous patient populations that span several decades. An updated, detailed characterization of the incidence and timing of thrombosis in the single-ventricle population is a crucial first step in progress toward targeted thromboprophylaxis.

To address the wide variation in reported incidence and timing of thromboembolic events in infants with single right ventricle CHD, we used the Pediatric Heart Network (PHN) SVR (Single Ventricle Reconstruction) trial public data set to determine the timing and cumulative incidence of thrombosis following stage I and stage II surgical reconstructions and identify clinical characteristics associated with thromboembolic events. This analysis makes use of the largest prospective study in infants with single-ventricle CHD to inform future prospective studies and development of standardized, evidence-based guidelines for targeted thromboprophylaxis in this population.

## METHODS

### Study Design

Publicly available data from the National Institutes of Health/National Heart, Lung, and Blood Institute PHN SVR) trial were used to perform this retrospective cohort study. Access to the data was granted by the PHN, and data sets were downloaded on January 16, 2018. Anonymized data and materials have been made publicly available by the PHN and can be accessed at http://www.pediatricheartnetwork.org/ForResearchers/PHNPublicUseDatasets/SingleVentricleReconstruction-SVR.aspx. The design and rationale for the SVR trial have been described in prior publications.[17,18] From 2005 to 2009, the SVR trial compared 12-month transplant-free survival in infants with HLHS and related anatomy who were prospectively randomized to receive a modified Blalock-Taussig shunt (mBTS) or a right ventricle-to-pulmonary artery shunt (RVPAS) during the Norwood procedure, and the results have been discussed in detail.[19–21] The Institutional Review Board at each of the participating PHN centers approved the protocol

for the SVR trial, and informed consent was provided for each patient at the participating institution by a parent or guardian. Additionally, Institutional Review Board approval was obtained at Emory University for the purposes of this study. The primary outcome in this study was the experience of a first-time thrombotic event. A newer iteration of this study (SVR III) expands the monitoring of this cohort until the Fontan stage at 2 to 6 years of age, but these data have not yet been released for public use.

## Study Population

Inclusion criteria for the SVR trial have been published[18] and include infants with single right ventricle physiology conditions such as HLHS and morphologically related single right ventricle. All patients had a planned stage I Norwood and did not have any other associated genetic anomalies or medical conditions that would be likely to prohibit them from the stage I Norwood procedure and subsequent planned surgical reconstructions. A total of 920 newborns were screened for enrollment, and 549 were included in the original analysis of the SVR trial. Of the 549 patients who were randomized, no infants were excluded from analysis for the purpose of this study.

## Data Collection and Measurements

Thrombosis was defined as any event characterized by complication codes reported in the original SVR trial and included thrombus/thromboembolism, superior vena cava occlusion, and inferior vena cava occlusion. The SVR trial protocol did not mandate screening for asymptomatic thrombosis; therefore, the presence of thrombosis was determined by the standard of care at each participating PHN institution. Stroke was not included in the definition of thrombosis because of the inability to differentiate between ischemic and embolic stroke.

Study participants were evaluated at trial enrollment, pre-Norwood, stage I Norwood hospitalization discharge, before stage II hospitalization, stage II hospitalization discharge, and at the 14-month end-of-trial follow-up. Data collected included historical and pertinent variables that were available in the public use data set. Thrombus location, method of thromboprophylaxis, and details of thrombosis management for each patient were not explicitly reported in the trial.

The presence of thrombosis was recorded at each time point with time zero defined as the day of the stage I Norwood procedure. Echocardiographic data were obtained at trial enrollment, stage I Norwood hospitalization discharge, before stage II hospitalization, and the 14-month end-of-trial follow-up. Shunt type was defined as the shunt type present at stage I hospital discharge. Data were analyzed through the 14-month follow-up, when all participants had completed the stage II reconstruction. Because each infant progressed through the staged time points at different times, we report the cumulative incidence function estimates of thrombosis at 60, 120, and 300 days to represent the overall, general time points for which infants have completed stage I, are pre–stage II surgery, or are post–stage II surgery, respectively.

Baseline characteristics include demographic information, gestational age, birth weight and percentile, and anatomic diagnosis. Surgical characteristics include weight and weight $Z$ score at stage I Norwood surgery, total cardiopulmonary bypass time, total deep hypothermic circulatory arrest time, cooling time, stage I Norwood shunt type (mBTS or RVPAS), mBTS diameter, RVPAS diameter, lowest hematocrit and temperature (C) during stage I Norwood hospitalization, aprotinin administration, steroid administration, and extracorporeal membrane oxygenation during the stage I Norwood surgery. Clinical characteristics include stage I nutrition (formula or breast milk), heart catheterization needed before stage I Norwood surgery, baseline and post–stage I Norwood right ventricle ejection fraction, oxygen saturation at stage I and stage II hospitalization discharge, number of medications at stage I Norwood discharge, and number of complications during the stage I Norwood hospitalization. Hospital length of stay includes total intensive care unit and hospital lengths of stay for the stage I hospitalization.

## Statistical Analysis

Descriptive statistical analyses were performed to characterize the study population by calculating means with SDs for normally distributed continuous variables, median with interquartile ranges (IQRs) for nonnormally distributed continuous variables with skewed distribution, or count and proportions (frequencies) for categorical variables. Summary statistics were also calculated for thrombosis and nonthrombosis groups. Less than 5% of data were missing for each variable analyzed, and only complete case analysis was performed.

Independent variables (baseline, surgical, and other clinical characteristics) were compared between thrombosis and nonthrombosis groups to identify variables associated with a first-time thrombotic event. Chi-square and Fisher's exact test were used for categorical variables, and Wilcoxon rank-sum test was used for continuous variables.

The association between independent variables (baseline, surgical, and other clinical characteristics)

and time to thrombosis was analyzed with Cox regression analysis. A Cox proportional hazards regression model that included clinically relevant variables or variables with a *P* value <0.20 was used to estimate the hazard ratios (HRs) for thrombosis. Time zero was the day of the stage I Norwood procedure, and time-to-event data were determined as the time to (1) a patient's first thrombotic event in days, (2) death, (3) study withdrawal or lost to follow-up, or (4) the end of the 14-month study period. Because some of the events occurred early in the follow-up period, the hazard was not proportional with time for some outcomes of interest when stratified. For these outcomes, Heaviside functions were used to estimate the effect of stratification during different phases of follow-up (eg, <30 days versus >30 days). Effect of stratification on the hazard of thrombosis was quantified with the use of HRs with 95% CIs. Because death was considered a competing event for thrombosis, competing-risk analysis was performed to model the probability over time for 2 mutually exclusive end points after Norwood procedure: death and thromboembolic event, with the remaining patients being alive without thrombosis. The cumulative incidence function for thromboembolic events following the stage I Norwood procedure was reported using the Fine and Gray method for competing risks.[22,23] Variables were included in the adjusted model for clinical relevance (shunt type) or if the *P* value was <0.05.

To determine the association between risk of thrombosis and hospital length of stay, total length of intensive care unit and hospital stays were compared using the Wilcoxon rank-sum test.

Statistical analyses were performed using SAS software v 9.4 (SAS Institute, Cary, NC), and statistical significance was assessed at the 0.05 level.

# RESULTS

## Patient Characteristics

In the SVR trial, 549 infants underwent the stage I Norwood procedure and were randomized to receive the mBTS (n=275) or RVPAS (n=274). The majority of infants were White (n=436; 79.4%), term born (n=483, 88.0%) boys (n=340, 61.9%), with a median gestational age of 38 weeks (IQR, 37–39 weeks) and median birth weight of 3.1 kg (IQR, 2.9–3.4 kg). The predominant anatomic diagnosis was HLHS in 86% (n=474) of the infants, with the remaining cardiac anomalies listed in Table 1.

A total of 167 (30.4%) infants died during the study period; 16.4% died during the stage I hospitalization, 10.7% in the time between stage I hospitalization discharge and stage II reconstruction, and 3.3% during stage II hospitalization. All surviving infants following the stage I Norwood procedure went on to complete the stage II surgery. The details of patient enrollment, randomization, and follow-up can be found in the original trial publication.[19]

## Frequency and Timing of Thrombosis

A total of 57 patients (57/549; 10.4%) experienced a first-time thrombotic event between the stage I Norwood procedure and stage II hospitalization discharge (Table 2). Thirty-five of 57 (61%) of all thrombotic events occurred during the stage I hospitalization period. Seven more patients experienced thrombotic events during interstage I, and 15 patients experienced thrombotic events during stage II hospitalization.

## Baseline, Surgical, and Clinical Characteristics Associated With Thrombosis

Baseline characteristics associated with thrombosis include male sex and non-HLHS anatomy. Surgical characteristics associated with thrombosis include prolonged cardiopulmonary bypass time and the lack of aprotinin administration during the stage I Norwood procedure. Stage I Norwood shunt type was not associated with thrombosis. Clinical characteristics associated with thrombosis include lower stage I Norwood discharge oxygen saturation (Table 1). Additionally, the development of thrombosis during the stage I hospitalization was associated with prolonged intensive care unit stay (median, 27 versus 13 days; IQR, 13-46 versus 9–25 days; *P*<0.01) and overall length of hospital stay (median, 36 versus 23 days; IQR, 26–58 days versus 15–38 days; *P*<0.01), respectively (Table 1).

## Survival Analysis and Cumulative Incidence Function

During stage I hospitalization, 35 of the 549 infants who underwent the stage I Norwood procedure experienced a thrombotic event (Table 2). The median time to thrombosis was 15 days (IQR, 7–22 days), and 33 of 35; 94%) experienced the thrombotic events within 28 days (Figure 1). The cumulative incidence of thrombosis at 28 days was significantly higher for those with non-HLHS anatomy when compared with those with HLHS anatomy (16.5% versus 5.4%; HR, 3.2; 95% CI, 1.6–6.6; *P*<0.01) in a competing risks model. There was no statistical difference in thrombosis at 28 days based on sex or shunt type.

Through stage II hospital discharge, an additional 22 patients experienced a thrombotic event, for a total of 57 first-time thrombotic events during the study period. Cumulative incidence function estimates of thrombosis at 60, 120, and 300 days were 6.9%, 8.7%, and 21.2%, respectively (Figure 2A). The cumulative incidence of

**Table 1. Characteristics of the Study Population From the Pediatric Heart Network Single Ventricle Reconstruction Trial and Variables Associated With Thrombosis**

| | | Total (N=549) | Thrombosis (N=57; 10.4%) | | No Thrombosis (N=492; 89.6%) | | P Value |
|---|---|---|---|---|---|---|---|
| Demographic and baseline characteristics | | | | | | | |
| Age at randomization, d | | 5.0± 4.0 | | ... | … | | … |
| Gestational age, wk | | 38 (37 to 39) | 38 | (38–39) | 38 | (37 to 39) | 0.84 |
| Birth weight, g | | 3.1 (2.9 to 3.4) | 3.1 | (2.9–3.4) | 3.2 | (2.8 to 3.5) | 0.96 |
| Birth weight percentile | | | | | | | 0.49 |
| <30% | | 277 (50.5) | 33 | (57.9) | 244 | (49.6) | |
| 30%–70% | | 190 (34.6) | 17 | (29.8) | 173 | (35.2) | |
| >70% | | 82 (14.9) | 7 | (12.3) | 75 | (15.2) | |
| Sex | | | | | | | <0.01 |
| Male | | 340 (61.9) | 45 | (78.9) | 294 | (60.0) | |
| Female | | 209 (38.1) | 12 | (21.1) | 197 | (40.0) | |
| Race or ethnic group | | | | | | | 0.12 |
| White | | 436 (79.4) | 50 | (89.3) | 386 | (79.1) | |
| Black | | 86 (15.7) | 6 | (10.7) | 80 | (16.4) | |
| Other | | 27 (4.9 ) | 0 | (0.0) | 22 | (4.5) | |
| Anatomic diagnosis | | | | | | | 0.01† |
| Hypoplastic left heart | | 474 (86.3) | 44 | (77.2) | 430 | (87.4) | |
| Other* | | 75 (13.7) | 13 | (22.8) | 62 | (12.6) | |
| Surgical characteristics | | | | | | | |
| Weight at Norwood, kg | | 3.2 (2.8 to 3.5) | 3.1 | (2.8 to 3.4) | 3.2 | (2.8 to 3.5) | 0.82 |
| Weight at Norwood, Z score | | -0.5 (–1.3 to 0.1) | −0.7 | (–1.2 to 0.02) | −0.5 | (–1.3 to 0.2) | 0.55 |
| Randomized shunt type | | | | | | | 0.74 |
| mBTS | | 275 (50.0) | 29 | (50.9) | 239 | (48.6) | |
| RVPAS | | 274 (50.0) | 28 | (49.1) | 253 | (51.4) | |
| Total bypass time, min | | 139 (105 to 171) | 145 | (119 to 184) | 137 | (104 to 169) | 0.045† |
| Total DHCA time, min | | 35 (14 to 47) | 36 | (15 to 53) | 34 | (13 to 46) | 0.17 |
| Cooling time, min | | 30 (20 to 40) | 28 | (21 to 40) | 30 | (20 to 41) | 0.65 |
| mBTS diameter, mm | | 3.5 (3.5 to 4.0) | 3.5 | (3.5 to 4.0) | 3.5 | (3.5 to 3.5) | 0.48 |
| RVPAS diameter, mm | | 5.0 (5.0 to 6.0) | 6.0 | (5.0 to 6.0) | 5.0 | (5.0 to 6.0) | 0.07 |
| Lowest hematocrit (%) | | 29 (27 to 32) | 30 | (26 to 33) | 29 | (27 to 32) | 0.99 |
| Lowest temperature, C | | 17 (16 to 18) | 17 | (16 to 18) | 17 | (16 to 18) | 0.80 |
| Aprotinin administered | | 427 (77.8) | 38 | (66.7) | 389 | (79.1) | 0.03† |
| Steroids given | | 498 (90.7) | 53 | (93.0) | 445 | (90.4) | 0.53 |
| ECMO during Norwood hospitalization | | 35 (6.4) | 1 | (1.8) | 34 | (6.9) | 0.16 |
| Clinical characteristics | | | | | | | |
| Stage I nutrition | | | | | | | 0.25 |
| Formula | | 332 (76.1) | 35 | (83.3) | 297 | (75.4) | |
| Breast milk | | 204 (46.8) | 18 | (42.9) | 186 | (47.2) | |
| Catheterization before stage I | 39 (7.2) | 2 | (3.5) | 37 | (7.6) | 0.41 | |
| Ejection fraction at baseline | | | | | | 0.06 | |
| <40% | 257 (74.9) | 28 | (93.3) | 229 | (73.2) | | |
| 40.1%–49.9% | 36 (10.5) | 1 | (3.3) | 35 | (11.2) | | |
| >50.0% | 50 (14.6) | 1 | (3.3) | 49 | (15.7) | | |
| Ejection fraction after Norwood | | | | | | 0.88 | |
| <40% | 237 (80.9) | 28 | (84.8) | 209 | (80.4) | | |
| 40.1%–49.9% | 27 (9.2) | 3 | (9.1) | 24 | (9.2) | | |

*(Continued)*

**Table 1.  Continued**

|  |  | Total (N=549) | Thrombosis (N=57; 10.4%) |  | No Thrombosis (N=492; 89.6%) |  | P Value |
|---|---|---|---|---|---|---|---|
| >50.0% |  | 29 (9.9) | 2 | (6.1) | 27 | (10.4) |  |
| CPR during stage I hospitalization |  | 97 (17.8) | 14 | (24.6) | 83 | (17.0) | 0.16 |
| Stage I ICU length of stay, d |  | 14 (9–28) | 27 | (13–46) | 13 | (9–25) | <0.01† |
| Stage I hospital length of stay, d |  | 24 (16–41) | 36 | (26–58) | 23 | (15–38) | <0.01† |
| Stage I oxygen saturation, % |  | 82 (80–85) | 80 | (79–84) | 83 | (80–86) | 0.02† |
| Number of significant complications during stage I |  | 2 (1–4) | 5 | (2–6) | 2 | (1–4) | <0.01† |
| Number of stage I discharge medications |  | 5 (4–7) | 6 | (4–7) | 5 | (4–6) | 0.03 |
| Stage II oxygen saturation, % |  | 80 (77–84) | 80 | (77–82) | 80 | (77–84) | 0.26 |
| Alive at stage I hospital discharge |  | 459 (83.6) | 50 | (84.8) | 409 | (83.9) | 0.89 |
| Alive at 12-month follow-up |  | 380 (69.2) | 38 | (6.9) | 342 | (3.5) | 0.85 |

Values reported as median (IQR, 25th–75th percentile) or n (%). CPR indicates cardiopulmonary resuscitation; DHCA, deep hypothermic circulatory arrest; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; mBTS, modified Blalock-Taussig shunt; and RVPAS, right ventricle to pulmonary artery shunt.

*Other: Critical aortic stenosis (n=5; 0.9%), single right ventricle with systemic outflow obstruction (n=23; 4.2%), univentricular heart with systemic outflow obstruction (n=31; 5.6%), straddling mitral valve with left ventricle hypoplasia and outflow obstruction (n=1; 0.2%), functional single right ventricle (n=15; 2.7%).

†Statistically significant values.

thrombosis at 300 days was significantly higher in boys compared with girls (29.9% versus 8.8%; HR, 2.4; 95% CI, 1.3-4.6; P<0.01; Figure 2B), and in infants with non-HLHS anatomy compared with infants with HLHS anatomy (21% versus 16%; HR, 2.1; 95% CI, 1.1–3.9; P=0.02; Figure 2C).

Cox proportional hazards regression models were used to estimate the association of statistically significant or relevant clinical variables with the time to thrombosis. The adjusted and unadjusted HRs for thrombosis are shown in Table 3. Lower oxygen saturation after the Norwood procedure increased the hazard for thrombosis in the unadjusted model (HR, 1.08; 95% CI, 1.02–1.14; P=0.011). After treating death as a competing event, boys had a higher hazard of

thrombosis (adjusted HR, 2.69; 95% CI, 1.44–5.05; P=0.002) after adjusting for cardiac anatomy, cardiopulmonary bypass time, and type of shunt. Non-HLHS cardiac anatomy was associated with higher early hazard of thrombosis (<30 days post-Norwood), although that difference was not significant beyond 30 days (adjusted early HR, 3.93; 95% CI, 1.89–8.17; P<0.001 versus adjusted late HR, 0.72; 95% CI, 0.17–3.02; P=0.654). Finally, cardiopulmonary bypass time was significantly associated with time to thrombosis (per 10-minute increase, adjusted HR, 1.07; 95% CI, 1.01–1.12; P=0.02). Variables such as cardiac shunt type and birth weight were not associated with the time to thrombosis (Table 3).

**Table 2.  Timing and Number of Thromboembolic Events From Stage I Through Stage II Hospital Discharge in the SVR Trial**

|  | Stage I Hospitalization | Interstage I | Stage II Hospitalization |
|---|---|---|---|
| SVC occlusion | 1 | 0 | 0 |
| IVC occlusion | 1 | 0 | 0 |
| Thrombus | 33 | 7 | 15 |
| Total first-time thromboembolic events | 35 | 7 | 15 |

IVC indicates inferior vena cava; SVC, superior vena cava; and SVR, single ventricle reconstruction.

## DISCUSSION

Thrombosis is a frequent complication following staged surgical reconstruction in infants with single-ventricle CHD who undergo staged surgical reconstructions and leads to significant mortality and morbidity. Reports on the incidence and timing of thrombosis vary widely, making it difficult to develop targeted thromboprophylaxis.[5,10–12] In the largest reported prospective cohort of infants undergoing single-ventricle reconstruction, we provide an update to the literature by investigating the cumulative incidence and timing of thrombotic events through stage II and identifying factors associated with thrombosis.
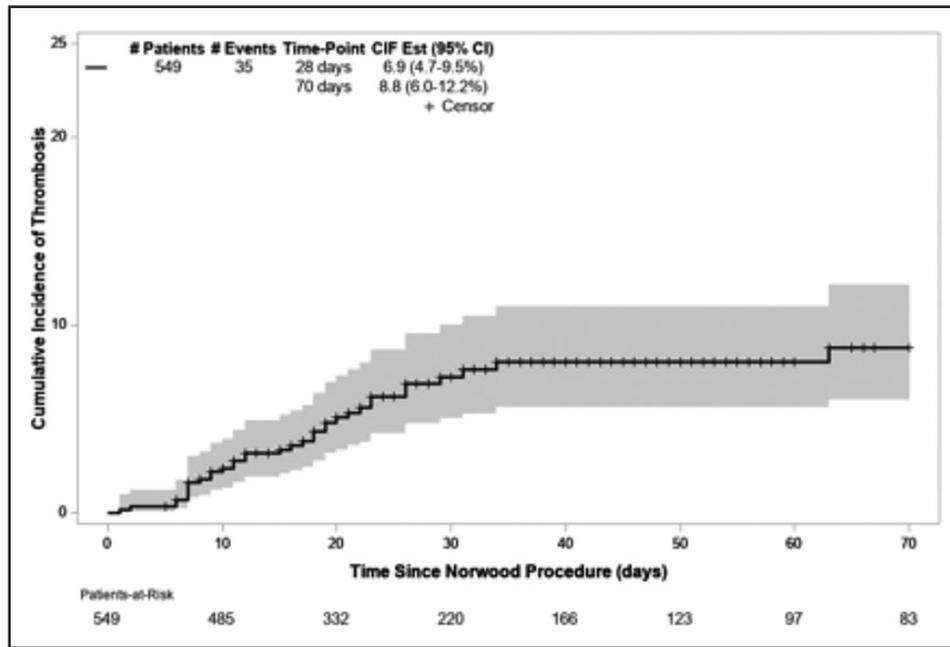
**Figure 1.  Cumulative incidence function (CIF) for thromboembolic events during stage I Norwood hospitalization.**

## Frequency and Timing of Thrombosis

The majority of thrombotic events occurred during stage I hospitalization. This finding is generally consistent across the medical literature and is attributable to additional known risk factors such as neonatal age and drastic alterations in blood flow when compared with subsequent reconstructions. We also show that the median time to thrombosis during the stage I hospitalization was 15 days, highlighting a potential time-based strategy for studying thromboprophylaxis in the immediate, high-risk postoperative period.

The cumulative incidence of thrombosis through stage II hospital discharge was 21.2%, which is notably lower than the overall incidence of 40% to 50% reported by Manlhiot et al.[12] Our finding may be explained by a different definition of thrombosis, as our study did not include asymptomatic thrombosis, or differences in surgical techniques and methods of thromboprophylaxis. Our study is unique in that we also model the cumulative incidence of thrombosis using a competing risks model, in which the overall cumulative incidence is 21.2%, but still lower than prior reports. Through stage II discharge, boys and infants with non-HLHS anatomy were more likely to experience thrombosis, again highlighting the concept of targeted thromboprophylaxis toward higher-risk individuals. It is important for future studies to investigate the underlying etiology of these differences in risk.

In our study, we report that 78.9% of infants with thrombosis were boys. Male sex has been associated with thrombosis in both the pediatric and adult literature, but the underlying mechanism has not yet been fully determined.[24] In a meta-analysis by Mahajerin et al[25] of pediatric patients with hospital-acquired venous thromboembolism, male sex was the most prevalent risk factor associated with thrombosis. In another large study by Raffini et al[26] using the Pediatric Health Information System, 55% of pediatric patients with venous thromboembolism were boys. The increased risk for thrombosis in those with non-HLHS anatomy is also unknown. Infants with non-HLHS anatomy are more likely to have asplenia or functional asplenia and are thought to have an increased risk for thrombosis because of the thrombocytosis that is associated with asplenia.[27]

We identified several other notable characteristics associated with thrombosis on multivariable analysis including longer cardiopulmonary bypass time and lower stage I hospitalization discharge oxygen saturation. Decreased baseline ejection fraction was not included because of missing data >5% but was significant in the univariable model, suggesting a trend toward significance. We hypothesize that decreased cardiac function leads to poor perfusion and blood flow, predisposing toward thrombosis, but further studies are needed. While these characteristics are not directly modifiable risk factors, they provide insight into at-risk individuals for the purposes of targeted thromboprophylaxis and future investigation. Of interest to the primary trial comparing transplant-free survival between stage I Norwood shunt
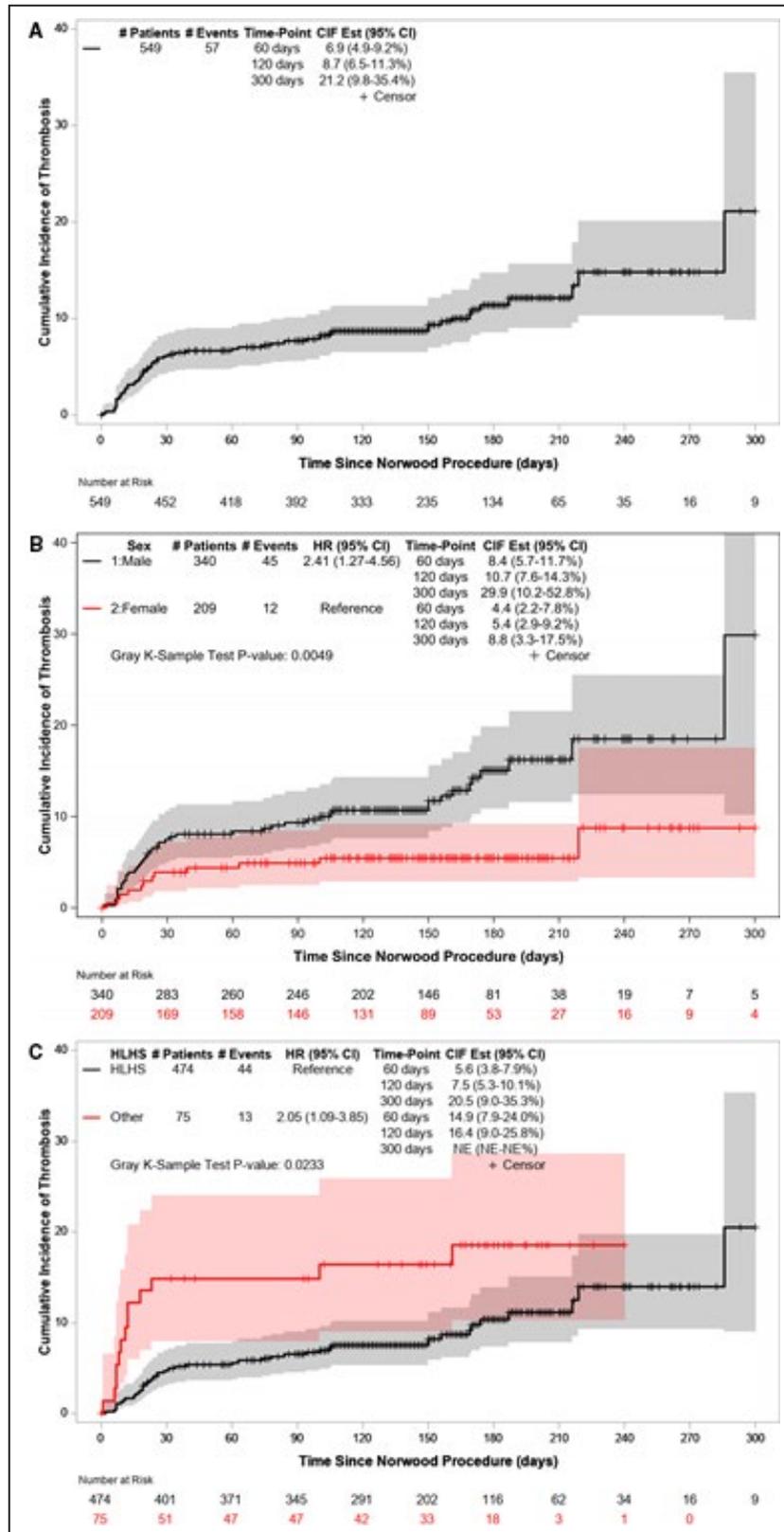
**Figure 2. Cumulative incidence function (CIF) for thromboembolic events following stage I Norwood procedure through stage II hospital discharge.**
(**A**) Overall, (**B**) stratified by sex, (**C**) stratified by cardiac anatomy. HR indicates hazard ratio; and HLHS, hypoplastic left heart syndrome.

**Table 3.** Association of Relevant Clinical Characteristics With Thrombosis Timing in Cox Proportional Hazards Regression Analysis

| Characteristic | HR (95% CI) | P value | aHR (95% CI) | P Value |
|---|---|---|---|---|
| Male sex (vs female) | 2. 41 (1.3–4.6) | 0.007* | 2.69 (1.44–5.05) | 0.002* |
| Other anatomy (vs HLHS) | | | | |
| <30 d | 3.40 (1.64–7.03) | 0.001* | 3.93 (1.89–8.17) | <0.001* |
| ≥30 d | 0.64 (0.15–2.69) | 0.54 | 0.72 (0.17 – 3.02) | 0.65 |
| Bypass time (by 10 min increase) | 1.04 (1.00–1.07) | 0.041* | 1.07 (1.01 – 1.12) | 0.022* |
| RVPAS (vs mBTS) | 1.09 (0.65 – 1.84) | 0.74 | 1.06 (0.63–1.80) | 0.82 |
| Stage I Norwood oxygen saturation (by 1% decrease) | 1.08 (1.02–1.14) | 0.011* | … | **…** |
| Low birth weight (<2500 g) | 1.05 (0.50–2.21) | 0.96 | … | … |

Values reported as median (IQR, 25th–75th percentile) or n (%). aHR indicates multivariable adjusted hazard ratio; HLHS, hypoplastic left heart syndrome; HR, univariable hazard ratio; IQR, interquartile range; mBTS, modified Blalock-Taussig shunt; and RVPAS, right ventricle to pulmonary artery shunt.
*Statistically significant values.

types, there was no significant difference in the incidence of any first-time thrombotic event between the mBTS and RVPAS groups.

Regarding clinical outcomes, thrombosis is associated with a 2-fold increase in stage I intensive care unit stay and a 13-day increase in the total stage I hospital length of stay. While the direction of association cannot be determined by our study and the results are subject to confounding variables, existing literature confirms that prolonged hospital length of stay is associated with increased risk of thrombosis and that thrombosis is associated with longer hospital stays and increased healthcare burden and expenditures.[10,25,28] More detailed subgroup analyses will help determine the direction and mechanism of this association. This finding, accompanied by our finding that the majority of thrombotic events occur in the early postsurgical period, emphasizes the need to focus on early thrombosis prevention.

There are many advantages related to the prospective design and structured approach provided by the original SVR trial, including the large sample size and the relative homogeneity of cardiac diagnoses and subsequent interventions. Limitations of this study include the retrospective analysis of the original data in which thrombosis was not the primary end point of the original trial. It is important to note that because the location of the thrombus (arterial, venous, or shunt) was not reported in the trial, we report on the cumulative incidence of any type of thrombosis, and further inference about specific variables and the type of thrombosis cannot be assessed. Additionally, other pertinent details such as presence of a central line, shunt geometry imperfections, and the specific method of

thromboprophylaxis for each patient were not reported in the trial. Because of this, our assessment of risk factors associated with thrombosis is not comprehensive and limited to the available variables described in our study. This limitation highlights the importance of designing future studies assessing thrombosis to collect more thrombosis-specific information. Finally, analysis of recurrent thrombotic events was not discussed in this study because recurrent events were not clearly measured in the trial.

## CONCLUSIONS

In conclusion, the cumulative incidence of thrombosis through stage II hospital discharge was 21.2%, with the highest-risk period for thrombosis during stage I hospitalization and the majority of thrombotic events occurring within 15 days of the stage I Norwood procedure. Boys and infants with non-HLHS anatomy are more likely to experience thrombosis when compared with girls and infants with HLHS anatomy, respectively. Thrombosis is also associated with longer cardiopulmonary bypass time and lower stage I hospitalization discharge oxygen saturation. Additionally, thrombosis is associated with longer stage I intensive care unit and hospital lengths of stay. This work underscores the need to identify early risk factors and novel approaches to guide time and risk-targeted thromboprophylaxis.

## ARTICLE INFORMATION

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