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ORIGINAL RESEARCH

CONGENITAL HEART DISEASE

Systemic Sirolimus Therapy Is Associated With Reduced Intervention Frequency in Pulmonary Vein Stenosis

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ABSTRACT

BACKGROUND Early clinical outcomes data for adjunctive systemic sirolimus therapy (SST) for moderate to severe pediatric pulmonary vein stenosis (PVS) are promising but limited.

OBJECTIVES The authors aimed to characterize a cohort of patients treated with SST to determine if SST was associated with a reduction in frequency of PVS interventions.

METHODS Medical records of 45 patients with PVS treated with SST for ≥1 month from 2015 to 2022 were retrospectively reviewed. PVS intervention rates pre-SST and on-SST were compared using generalized Poisson mixed models, accounting for paired intervals within each patient. In addition to an unadjusted model, an adjusted model accounted for age at interval start, PVS type, sex, prematurity, and concurrent antiproliferative therapy. Mean number of PVS interventions per patient over time (mean cumulative function) were also compared for these intervals in an unpaired fashion. Kaplan-Meier estimates were used to quantify survival over time.

RESULTS Median per-patient PVS intervention rate (interventions/year) was 5 pre-SST and 1.7 on-SST, significantly lower on-SST in the unadjusted and adjusted models ($P < 0.001$, both). Patients accrued an increased cumulative number of interventions over time pre-SST compared to on-SST by mean cumulative function ($P < 0.001$). Median duration of SST was 1.7 years and median follow-up time from SST initiation was 2.7 years. There were 6 mortalities at a median of 1.1 years (range, 4.4 months-6.5 years) following SST initiation.

CONCLUSIONS SST was associated with a reduction in frequency of PVS interventions. Prospective studies are warranted to determine potential causality, delineate patient- and vein-level outcomes, and determine optimal therapeutic duration. (JACC Adv. 2024;3:101401) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

ISS = in-stent stenosis

PVS = pulmonary vein stenosis

SST = systemic sirolimus therapy

Pediatric pulmonary vein stenosis (PVS) is an uncommon disorder, occurring in native vessels of normal and abnormal hearts as well as surgically repaired veins. Despite aggressive operative and catheter-based interventions, disease progression and recurrence are common, and mortality remains high, particularly early in the course of disease.[1-6] Affected veins demonstrate intimal hyperplasia with myofibroblast-like cell proliferation and extracellular matrix deposition.[7,8] Investigation continues into the role of various receptor tyrosine kinase pathways in the pathogenesis of PVS,[8-10] yielding potential therapeutic targets. Several medications have been proposed as adjunctive therapies to mitigate the underlying proliferative mechanisms of PVS.[11] Among these, the mammalian target of rapamycin inhibitor sirolimus shows promise given its mechanistic targets, success of sirolimus-eluting stents in animal models,[10,12] and positive results in other proliferative vascular pathologies.[13-18]

Current clinical data supporting effectiveness in achieving goals of systemic sirolimus therapy (SST) for PVS are limited to small single-center studies with short-term follow-up.[19-23] Early results demonstrated reduced rate of in-stent stenosis (ISS) growth,[19] survival benefit with SST over untreated controls,[20] and reduced frequency of catheterization.[21] The safety profile of sirolimus has been previously investigated in other pediatric populations.[16-18] While mild side effects are relatively common, serious adverse events are rare in the published experiences with PVS.[19-21] Important aspects of therapy such as optimal treatment duration and dosing, indications for initiation and cessation, and utility of combination therapies remain poorly delineated.

In this retrospective study, we aimed to determine the patient-level impact of SST on PVS intervention frequency. We also characterize a large cohort of patients receiving SST for PVS to establish current practices, report outcomes, and highlight remaining knowledge gaps.

METHODS

DESIGN AND TERMINOLOGY. This study was conducted following approval by the Baylor College of Medicine Institutional Review Board (protocol H-44390, approved 6/1/2021 with waiver of informed consent given minimum risk). The Texas Children's Hospital (Houston, Texas) PVS database (containing 401 patients managed at the institution between January 1995 and December 2022) was screened for patients who received SST. Medical records, including from outside institutions when available, through August 2023 were retrospectively reviewed. Exclusion criteria were no interventions at Texas Children's Hospital and primary indication for SST unrelated to PVS (determined by clinical notes; eg, treatment of vascular malformations/lymphatic disorders or transplant immunosuppression in the absence of clinically significant PVS). Patients who did not complete at least 1 month of SST (discontinued within 30 days and subsequently died or did not resume therapy) were excluded to allow adequate time to observe therapeutic effects.

The primary endpoint was PVS intervention frequency (number of interventions during interval/length of interval in years). PVS interventions included operative PVS repair (excluding index repair of anomalous pulmonary venous connections) and catheter-based procedures (including balloon angioplasty, stent placement, and attempted or successful recanalization of atretic/occluded veins). To test our hypothesis that SST would be associated with reduced intervention frequency, the primary endpoint was compared between 2 intervals (**Central Illustration**): pre-SST (approximate date of PVS diagnosis until start of first course of SST lasting ≥30 days) and on-SST (start of SST until either last follow-up if SST was continuous or until SST cessation/interruption for >30 days). Pauses in therapy up to 30 days for acute indications were included in the on-SST interval. Subsequent intervals in patients who restarted SST were not analyzed except when explicitly stated.

Prematurity was defined as gestational age at birth <37 weeks. PVS types were assigned exclusively to each patient as either primary (diagnosed without prior pulmonary vein intervention) or post-repair (diagnosed following repair of anomalous pulmonary venous connections). Concurrent antiproliferative therapy was defined as ≥30 days of therapy during the interval of interest with immunosuppressive medications or other systemic medical

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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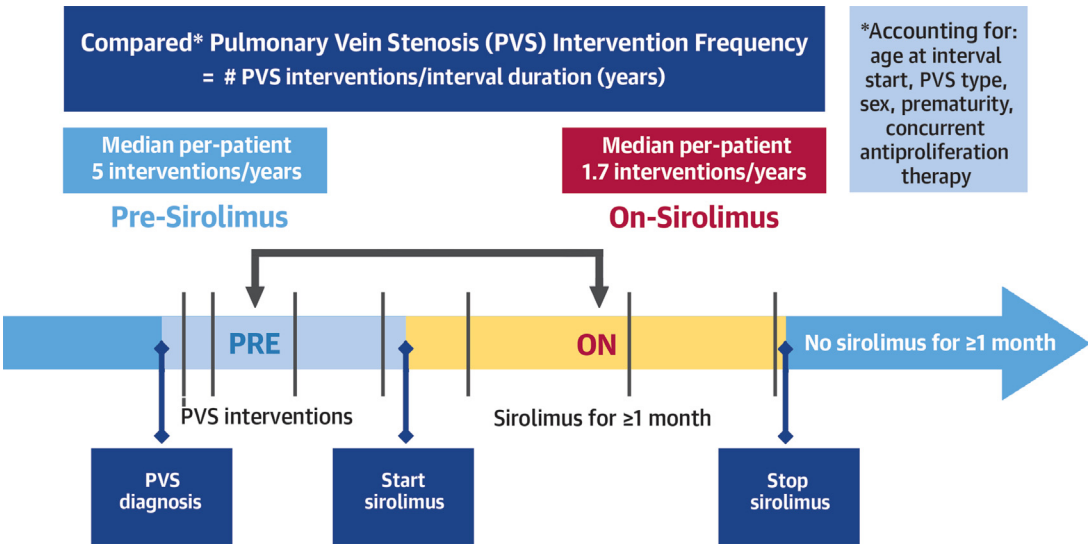
CENTRAL ILLUSTRATION **Systemic Sirolimus Therapy for PVS Is Associated With less Frequent Interventions**



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Our analysis compared PVS intervention frequency during treatment with systemic sirolimus therapy ("on-sirolimus") with patients' intervention frequency prior to starting sirolimus therapy. Our model also accounts for several patient and disease factors that may influence intervention frequency. Abbreviation as in Figure 1.

adjuncts for PVS (imatinib mesylate [Gleevec, Novartis Inc], bevacizumab [Avastin, Genentech Inc], or losartan).

Nonmutually exclusive indications for SST initiation were defined as follows: extensive disease (history of PVS in 4-5 veins pre-SST), refractory disease (≥3 PVS interventions pre-SST), progressive disease (new involvement of previously unobstructed veins or upstream progression of disease at last catheterization pre-SST), primary prevention of ISS (new stents placed at last catheterization pre-SST), and secondary prevention of ISS (narrowing within prior stents reported at last catheterization pre-SST). When counting number of affected veins, common vessels were counted as 2 veins; eg, stenosis in right upper and left common pulmonary veins (giving rise to a left upper and left lower pulmonary vein) was considered 3-vessel disease. Indications for cessation of the first course of SST (nonmutually exclusive) were subjectively assessed from clinical notes and categorized as: disease stabilization, disease progression (worsening disease extent or severity), infection, parent preference or noncompliance, perioperative wound healing, and medication side effects.

Hemodynamic data were obtained from the last catheterization pre-SST and either the last catheterization prior to stopping first course of SST or most recent catheterization (if treated continuously through most recent follow-up). If interventions were performed, preintervention values were utilized when available.

CURRENT CLINICAL PRACTICES. Patients with PVS commonly seek care over their lifetimes at multiple institutions. Some patients in this cohort began SST at outside centers prior to transfer to Texas Children's Hospital. At our institution, SST has been utilized off-label since 2015 as medical adjunctive therapy for severe and/or recurrent PVS, without rigidly defined selection criteria. Therapeutic goals include reduction in rate of ISS, slowing disease progression, and reducing the number or frequency of procedures. Decision to initiate SST and duration of therapy is individualized based on interdisciplinary discussion at a multidisciplinary PVS team meeting, involving interventional cardiology, patient's primary cardiologist, and hematology-oncology/vascular anomalies specialists. Patients' families are counseled regarding risks, benefits, and uncertainties surrounding SST for

TABLE 1 Patient Characteristics

Demographics	
Total included patients	45 (100%)
Male	26 (58%)
Premature	14 (31%)
Nonpulmonary vein CHD	37 (82%)
Single ventricle[a]	11 (24%)
TAPVC	15 (33%)
Supracardiac	8
Cardiac	1
Infracardiac	3
Mixed	3
PAPVC	4 (9%)
Type of PVS	
Primary	29 (64%)
Post-repair	16 (36%)
Age at first PVS intervention, d	127 (76-224) [29-2,171]
Time from PVS diagnosis to first intervention, d	10 (1-42) [0-886]
Pre-SST PVS intervention modalities	
Any operative	20 (44%)
Any catheter-based	42 (93%)
Any stent	38 (84%)
SST initiation	
Number of diseased veins at SST initiation	4 (3-5) [1-5]
1	1 (2%)
2	6 (13%)
3	12 (27%)
4	11 (24%)
5	15 (33%)
Bilateral PVS	35 (78%)
History of atretic vein(s)	31 (69%)
Indications for SST initiation	
Extensive disease (4-5 veins)	26 (58%)
Refractory disease (≥3 interventions)	24 (53%)
Progressive disease	24 (53%)
Primary prevention ISS (new stent)	19 (42%)
Secondary prevention ISS (prior ISS)	22 (49%)
SST initiated at TCH	40 (89%)
Follow-up	
Age at last follow-up, y	4.9 (2.7-6.4) [0.5-10.8]
Time from SST start to last follow-up, y	2.7 (1.2-3.9) [0.1-8.2]
Stopped SST >30 d	20 (44%)
Indications for cessation SST (first course)	n = 20
Stabilization	5 (25%)
Progressive disease	2 (10%)
Infection	6 (30%)
Side effects	0 (0%)
Wound healing	5 (25%)
Parental preference	5 (25%)
Multiple courses of SST	10 (22%)
On SST at last follow-up[b]	34 (76%)
Deceased	6 (13%)

Values are n (%), median (IQR, 25th-75th percentile) [minimum-maximum]. [a]At birth. 2 patients underwent transplant prior to starting SST. [b]Either continuously or after restarting.

CHD = congenital heart disease; ISS = in-stent stenosis; PAPVC = partial anomalous pulmonary venous connection; PVS = pulmonary vein stenosis; SST = systemic sirolimus therapy; TAPVC = total anomalous pulmonary venous connection; TCH = Texas Children's Hospital.

PVS by hematology-oncology and interventional cardiology to obtain informed consent for treatment. Generally, patients are trialed on therapy for approximately 1 year, if tolerated, and continued indefinitely until their disease clinically stabilizes (reduced intervention frequency, improved symptoms, stable vein caliber), substantial side effects are experienced, and/or due to patient/family preference. Timing of surveillance and interventional catheterization is also individualized, utilizing a team-based approach and algorithm similar to that described by Vanderlaan et al.[11]

Initiating dose and monitoring protocol was based on a multidisciplinary institutional consensus for sirolimus administration for PVS. Patients receive enteral sirolimus twice daily at 0.4 mg/m^2/dose if <6 months old or 0.8 mg/m^2/dose if >6 months old. Dosage is titrated to a target trough level (drawn prior to morning dose) of 8 to 12 ng/mL. Baseline laboratory studies (complete blood count with differential, complete metabolic panel, lipid panel, and trough sirolimus level) are repeated monthly for patients <2 years old and every 3 months for patients ≥2 years. In-person or telehealth visits with the provider managing SST (vascular anomalies hematology-oncology team at our institution) are recommended at least every 3 months. Therapy is temporarily held for active infection or febrile illness (until fever-free for viral or completed antibiotic therapy for bacterial infections). We consider holding SST peri-operatively to minimize interference with wound healing with interval surveillance and evaluation for resumption of therapy 4 to 6 weeks post-operatively. Prophylaxis against *Pneumocystis jirovecii* pneumonia and avoidance of live vaccines are standard practices.

STATISTICAL ANALYSIS. Summary statistics and survival analyses were conducted using STATA, version 17 (StataCorp LLC). Continuous and categorical variables are summarized as median (25th-75th percentile) or frequency (percentage of total or at risk), respectively, unless otherwise indicated. Paired continuous variables were compared via Wilcoxon signed rank test. Kaplan-Meier survival estimates with 95% CIs were used to describe survival over time. Survival was analyzed separately starting from: 1) time of PVS diagnosis, with patients becoming at risk at the time of SST initiation (left truncation); and 2) time of SST initiation.

Poisson generalized mixed models were utilized to compare the PVS intervention rates for pre-SST

versus on-SST phases while accommodating paired phases within the same patient. This comparison was made unadjusted and after controlling for age at the start of the interval, PVS type, sex, prematurity, and concurrent antiproliferative therapy. Covariates for adjusted analysis were selected a priori based on clinical relevance to reintervention frequency or PVS prognosis.[1,2,5] An additional model evaluated expanded data, including interventions through last follow-up and multiple courses of SST; this model evaluated PVS intervention rates by whether the patient was taking SST and time from PVS diagnosis. The GLMMIX procedure in SAS, version 9.4 (SAS Institute Inc) was used to fit the Poisson generalized mixed models.

Recurrent event analysis was performed in R, version 4.3.2 (R Foundation for statistical computing) utilizing the reda and reReg packages. Mean number of PVS interventions per patient over time (mean cumulative function) were described by Nelson-Aalen estimates with 95% CIs and compared using the pseudo-score test.[24-26] Notably, this nonparametric method does not account for pairing of pre-SST and on-SST intervals in the same patients. A 2-sided 0.05 significance level was utilized for all hypothesis tests.

RESULTS

BASELINE CHARACTERISTICS AND THERAPEUTIC INDICATIONS. Characteristics for the 45 included patients are summarized in Table 1. Earliest PVS diagnosis was in 2013 and earliest SST initiation was in 2015. Type of PVS was primary in 29 patients (64%), including 3 patients with partial anomalous pulmonary venous connections and stenotic normally connected veins prior to repair. Sixteen patients (36%) had post-repair PVS: 15 with repaired total anomalous pulmonary venous connections and 1 with repaired partial anomalous pulmonary venous connections. Nonpulmonary venous congenital cardiac lesions were present in 37 (82%) patients. Of 11 patients born with single ventricle lesions, 3 underwent heart transplantation: 2 started SST post-transplantation, and 1 patient was transplanted after their first course of SST (held for wound healing and resumed postoperatively).

All patients had multivessel PVS except 1 patient with extensive upstream segmental disease in a single vein and difficult central venous access (limiting transcatheter interventions). Interventional strategies pre-SST are outlined in Table 1. Thirty-six patients (80%) had 2 or more interventions pre-SST.

Median age at SST initiation was 1.1 years (range, 1.2 months-8.1 years), and median time from PVS diagnosis to SST initiation was 6.1 months (range, 14 days-7.7 years) (Table 2). Median duration of the first course of SST was 1.7 years (range, 36 days-7.5 years) (Table 2). SST was stopped in 20 patients

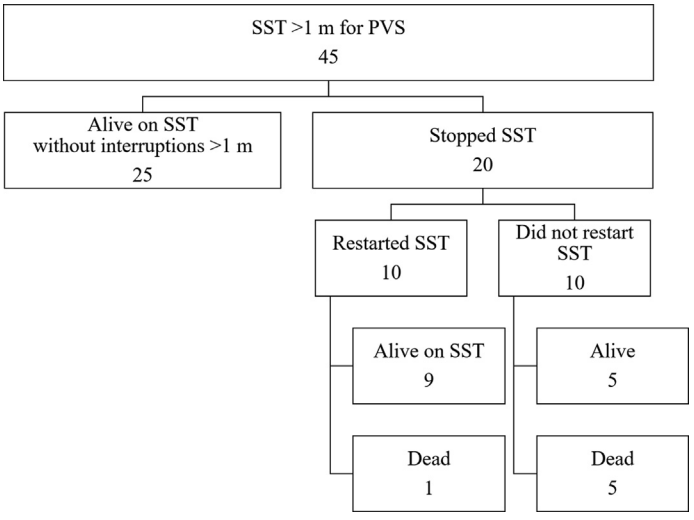
TABLE 2 Per-Patient PVS Intervention Frequency

	Pre-SST	On-SST
Age at interval start	3.6 m (2.1 m-5.7 m) [6 d-5.9 y]	1.1 y (5.9 m-2.4 y) [1.2 m-8.1 y]
Interval duration	6.1 m (2.8 m-1.8 y) [14 d-7.7 y]	1.7 y (8.0 m-2.7 y) [1.2 m-7.5 y]
Number PVS interventions	3 (2-5) [0-18]	2 (1-4) [0-15]
Interventions/y	5.0 (2.3-10.6) [0-48.7]	1.7 (0.8-2.8) [0-10.1]
Antiproliferative therapy >30 d	6 (13%)	5 (11%)
Time between interventions[a]	2.9 m (1.4 m-4.6 m) [10 d-10.2 m] n = 36	5.7 m (3.8 m-7.9 m) [1.4 m-10.2 m] n = 28

Values are n (% total) or median (25th-75th percentile) [minimum-maximum]. Pre-SST: PVS diagnosis until SST started. On-SST: start sirolimus until sirolimus stopped for ≥30 days (first course, if multiple courses). [a]for those with ≥2 interventions during the interval.

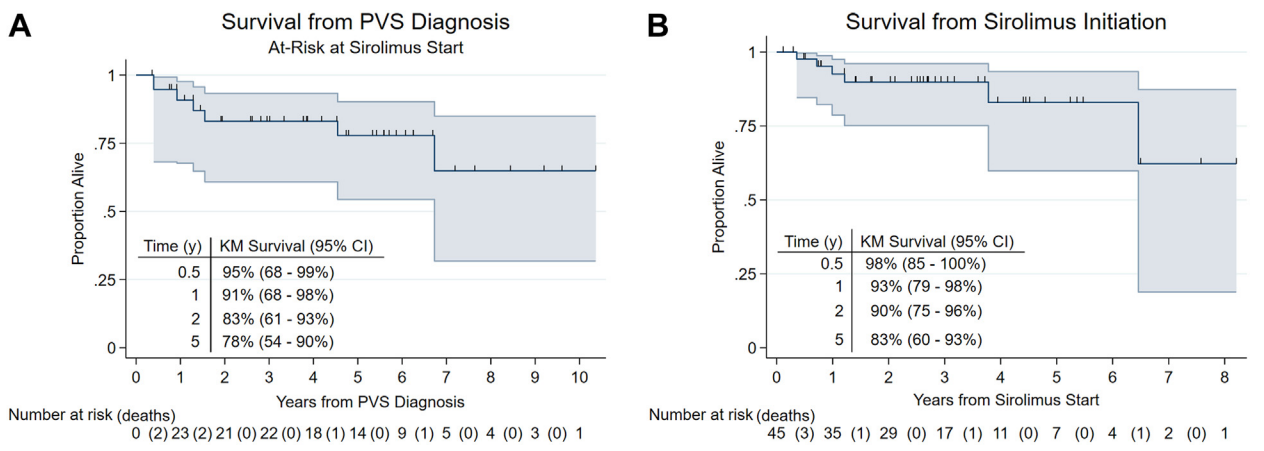
Abbreviations as in Table 1.

FIGURE 1 Therapy Cessation and Outcomes



Flow chart summarizing number of patients in the included cohort, whether they had interruptions of at least 1 month in therapy, whether or not they had multiple courses of SST, and their status at follow-up. PVS = pulmonary vein stenosis; SST = systemic sirolimus therapy.

FIGURE 2 Survival



Kaplan-Meier (KM) survival curves with 95% CI shaded, tick marks indicating right-censored observations at last follow-up. Number at risk below graphs with number of failures shown in parentheses. Estimated survival with 95% CI shown for selected times. (A) Survival from pulmonary vein stenosis (PVS) diagnosis, with subjects becoming at risk at the time of systemic Sirolimus therapy (SST) initiation (left truncation). Estimates at each time point reflect survival for included patients who had started SST by that time. (B) Survival from sirolimus initiation. Note, patients who completed <30 days SST were excluded.

(44%), 10 of whom subsequently restarted SST (Table 1 and Figure 1) a median of 93.5 days (range, 31 days-2.4 years) following cessation. Of those who restarted SST (n = 10), the indications for discontinuation of the first course were wound healing (n = 2), parental preference or noncompliance without other indication (n = 3), infection (n = 2), and progressive disease (n = 1). Five patients who stopped therapy remained alive without a second course; their indications for discontinuation were disease stabilization (n = 4) and progressive disease (n = 1).

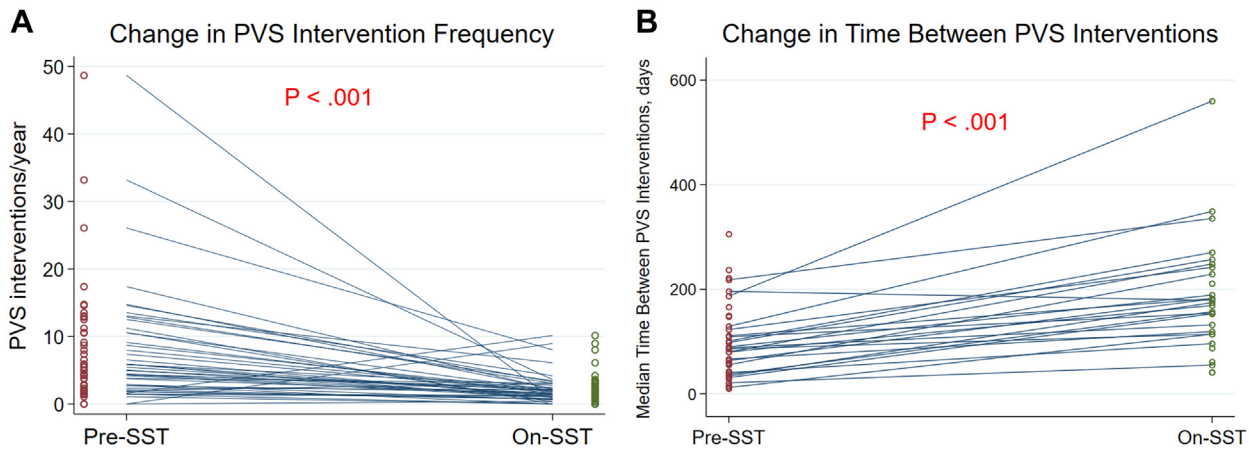
SURVIVAL. Six patients (13%) who completed at least 30 days of SST died, all after stopping SST and in the setting of infections preceding their deaths (additional details in Supplemental Table 1). Two had heterotaxy and single ventricle. Indications for SST cessation for the deceased patients were infection (n = 5) and stable disease (n = 1). Median time to death was 1.1 years (range, 4.4 months-6.5 years) from SST initiation, 1.4 years (range, 4.8 months-6.7 years) from PVS diagnosis, and 39.5 days (range, 12 days-4.8 years) from last dose of SST. Median duration of first SST course for deceased patients was 7.7 months (range, 3 months-3.7 years).

Estimated survival from PVS diagnosis for the included cohort (excluding those who died or stopped therapy within 30 days), accounting for patients becoming at risk at the time of SST initiation, was 90.8% (67.6% to 97.6%) at 1 year and 77.9% (54.4% to 90.2%) at 5 years (Figure 2A). Estimated survival from SST initiation was 92.6% (78.7% to 97.6%) at 1 year and 83.0% (59.8% to 93.4%) at 5 years (Figure 2B).

INTERVENTION FREQUENCY. Median per-patient PVS intervention frequency was significantly higher pre-SST (5 interventions/year) compared to on-SST (1.7 interventions/year; $P < 0.001$) (Table 2, Figure 3). Similarly, median per-patient time between interventions also significantly increased ($P < 0.001$, n = 28 patients with ≥2 interventions in each interval) (Table 2, Figure 3). Four patients (9%) had higher reintervention frequency on-SST compared to pre-SST: 2 patients had no interventions prior to starting SST, 1 patient discontinued SST due to PVS progression (5 interventions/2.5 years pre-SST; 8 interventions/2.7 years on-SST), and 1 patient had a short follow-up duration but remains on SST (1 intervention/7.7 months pre-SST; 1 intervention/36 days on-SST).

Pooled PVS intervention rates were 3.0 interventions/person-year pre-SST (total 176 interventions/58.2 years) and 1.6 interventions/person-year on-SST (total 146 interventions/92.1 years), representing a significant decrease in the intervention rate while on-SST in the unadjusted Poisson generalized mixed model analysis ($P < 0.001$). In the multivariate model controlling for age at start of the interval, PVS type, sex, prematurity, and concurrent antiproliferative therapy, the PVS intervention rate

FIGURE 3 Reintervention Frequency



Slope plots depict change in (A) intervention frequency (number of interventions during the interval/duration of interval in years) with generalized poisson mixed model *P* value and (B) median time between interventions with sign rank *P* value (red indicates $P < 0.05$, both). Overlayed dot plots show values pre-SST (diagnosis to start of sirolimus, red) and on-SST (first course, green). Abbreviations as in **Figure 1**.

remained significantly higher pre-SST than on-SST ($P < 0.001$) (Supplemental Table 2). No other covariates were significantly associated with reintervention rate in the adjusted model (Supplemental Table 2).

The mean cumulative functions of PVS interventions pre-SST versus on-SST significantly differed ($P < 0.001$) (**Figure 4**); on average, patients accrued more interventions over time pre-SST compared to on-SST. The mean number of PVS interventions per patient was 2.6 (2.0-3.1, n = 23 at risk) 6 months after PVS diagnosis (pre-SST) and 1.1 (0.8-1.4, n = 37 at risk) after 6 months of SST (on-SST). The mean number of PVS interventions per patient was 3.8 (3.0-4.7, n = 16 at risk) 1 year after PVS diagnosis and 2.1 (1.6-2.5, n = 30 at risk) after 1 year of SST. Recurrent PVS interventions by patient, including those with multiple courses of SST, are visualized in an event plot (Supplemental Figure 1).

Evaluating across the entirety of patients' follow-up and including multiple courses of SST, our additional Poisson generalized mixed model estimated that after adjusting for time since PVS diagnosis, intervention rate was 3.7 interventions/person-year while not taking SST compared to 2.1 interventions/person-year while taking SST ($P = 0.001$). Accounting for whether the patient was taking SST, each additional year since PVS diagnosis was associated with a significant decrease in the intervention rate ($P < 0.001$), with model-estimated intervention rates of 3.0 interventions/person-year 1 year after diagnosis, 2.5 interventions/person-year 2 years after diagnosis, and 2.0 interventions/person-year 3 years after diagnosis.

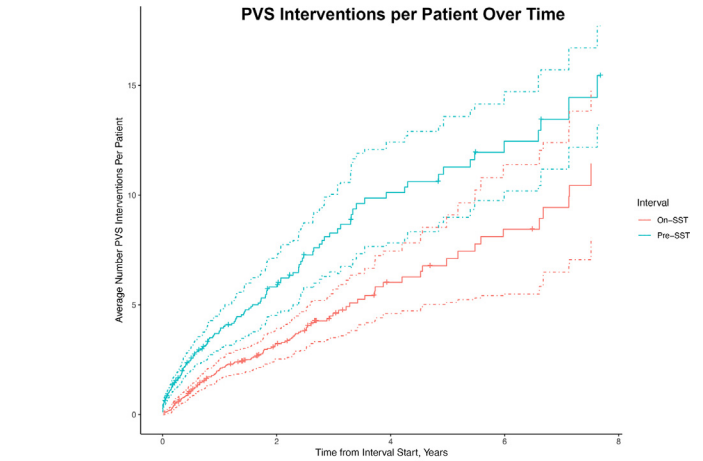
HEMODYNAMICS. Changes in hemodynamics from pre-SST to last on-SST are presented in **Table 3** and **Figure 5**. For single ventricle patients, there was no difference in pulmonary vascular resistance ($P = 0.59$). However, for biventricular patients, pulmonary vascular resistance, right ventricular systolic pressure, relative right ventricular to systemic systolic pressure, and mean pulmonary artery pressures were significantly lower on-SST ($P = 0.006$, 0.006, <0.001, and 0.002, respectively).

DISCUSSION

This retrospective analysis of a large cohort of patients receiving SST for PVS demonstrated a reduction in frequency of interventions while treated with SST compared to prior to therapy. The effect persisted in multivariable regression analysis after accounting for several patient-level factors relating to disease prognosis and while accounting for time since diagnosis. We observed reasonable short- to mid-term survival and favorable hemodynamic changes among these patients with moderate to severe disease, reflecting a realistic snapshot of current clinical practices.

Early clinical results with sirolimus as an adjuvant medical therapy targeting the pathogenic mechanisms of PVS have been promising, leading many centers to add SST to their armamentarium for aggressive multivessel PVS. Retrospective studies of patients receiving SST in addition to standard

FIGURE 4 Mean Cumulative Functions



Plot of mean cumulative function of PVS interventions (average number of PVS interventions per patient) over time in years from the start of the interval (PVS diagnosis for pre-SST, start of sirolimus for on-SST) by interval (pre-SST in orange, on-SST in blue). Vertical ticks represent censored data points (started sirolimus for pre-SST, stopped SST or last follow-up while continuously on SST for on-SST). Dashed lines represent 95% CIs. Pseudo-score *P* value shown. Abbreviations as in Figure 1.

therapies have demonstrated an association with superior survival,[20] slowed progression of ISS,[19] reduction in frequency and duration of catheterization,[21] and stabilization or improvement in vessel pathology.[21-23] Despite these encouraging results, significant knowledge gaps and variability remain in current clinical practice with SST for PVS. Sample sizes are small given the rarity of severe PVS and recent adoption of off-label SST in this population. Follow-up remains restricted to short-term outcomes. Furthermore, dosing regimens, therapeutic duration, concurrent therapies, surveillance and interventional strategies, and metrics for success differ between and within institutions. The number of factors that likely impact outcomes in these complex patients currently outstrips the power of existing studies to definitively detect and attribute benefits to SST alone.

REDUCED INTERVENTION FREQUENCY. In our study of 45 patients, median operative or interventional catheterization frequency was 5/year for patients (3/person-year) pre-SST and 1.7/year (1.6/person-year) while receiving SST. Existing literature detailing intervention frequency during SST for PVS is limited to small series. Our findings complement those of Shorofsky et al whose cohort of 10 patients had less frequent diagnostic or interventional catheterizations on-SST (median 2/year) compared with pre-SST (median 3/year).[21] Patel et al[20] reported a pooled catheter intervention rate of 3.7/person-year for 15 patients receiving SST for severe PVS, though this may include interventions prior to as well as during SST.

The association between SST and reduced intervention frequency is encouraging; however, retrospective studies cannot prove causality. While our adjusted analysis utilizes patients' pre-SST disease trajectory as their own control and accounts for several factors that may affect interventional frequency, other unmeasured factors likely impact reintervention frequency over time. For example, we did not account for concurrent pulmonary hypertensive therapies, types of interventions, or vein-level characteristics. Furthermore, intervention frequency may not always correlate to disease severity.

Reintervention frequency also tends to decrease over time[5] for PVS survivors, potentially due to patient growth, accumulated effects of repeated interventions, and veins reaching a threshold size.[6] Our data did support a significant decrease in intervention frequency over time, independent of treatment with SST. However, we found that even accounting for time since diagnosis, taking SST was associated with a lower intervention rate than not taking SST.

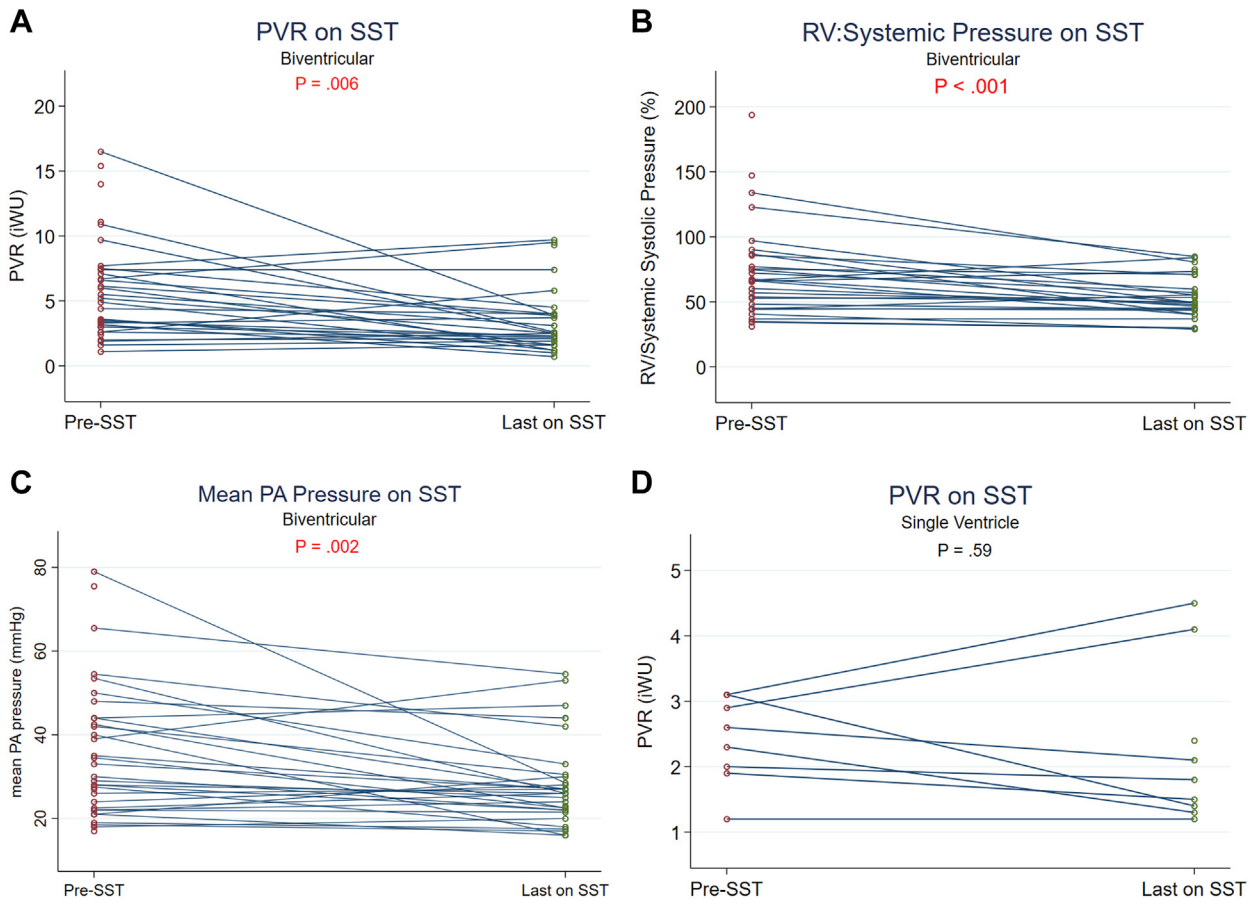
Implicit bias of the clinical team might also have contributed to less frequent intervention during SST. Though difficult to quantify, the Texas Children's PVS

TABLE 3 Hemodynamics

	Pre-SST	On-SST[a]	Paired Difference (On-Pre)	*P* Value[b]
PVR (single ventricle), iWU	2.5 (2.0-3) [1.2-3.1] n = 8	1.8 (1.4-2.4) [1.2-4.5] n = 9	−0.3 (−0.8, +0.6) [-1.7, +1.4] n = 8	0.59
PVR (biventricular), iWU	5.1 (3-7.45) [1.1-16.5] n = 32	2.5 (1.9-4) [0.7-9.7] n = 29	−1.9 (−3, +0.3) [-12.6, +3.2] n = 27	**0.006**
RV/systemic systolic pressure (biventricular), %	66 (45-85) [31-194] n = 31	52 (44-71) [29-85] n = 30	−10 (−25, −1) [-53, +17] n = 26	**<0.001**
RV systolic pressure (biventricular)	50.5 (38-68) [23-126] n = 30	45.5 (36-55) [22-89] n = 28	−6.5 (−15.5, 0) [-30, +29] n = 24	**0.006**
Mean PA pressure (biventricular)	30 (22.4-44) [17-79] n = 33	26 (22-30.3) [16-54.5] n = 32	−5.5 (−12, +1) [-50.5, +14] n = 30	**0.002**

Values are median (25th-75th percentile) [minimum-maximum]. n = number non-missing. See slope plots of selected parameters (Figure 5). [a]On-SST values obtained from last catheterization prior to stopping SST for at least 30 d, or if continuously using, the most recent catheterization on SST. [b]Signed rank test for differences between matched pairs only. Exact *P* value, **bold** denotes <0.05.
iWU = indexed Woods units (WU/m^2); PA = pulmonary artery; PVR = pulmonary vascular resistance; RV = right ventricle; other abbreviation as in Table 1.

FIGURE 5 Hemodynamics



Slope plots depict changes in hemodynamic parameters from last catheterization pre-SST to last catheterization on first course of SST for biventricular (A to C) and single ventricle (D) patients. Sign rank *P* value shown, red indicates $P < 0.05$. iWU = indexed Woods units (WU/m^2); PA = pulmonary artery; PVR = pulmonary vascular resistance; RV = right ventricle; other abbreviation as in Figure 1.

team maintains an aggressive approach to frequency of catheterization and intervention, preferring to intervene whenever feasible. Discussions in the catheterization laboratory and in multidisciplinary PVS team meetings aim to assure a consistent approach and minimize bias of the performing interventionalist.

SURVIVAL. While direct comparison of survival is limited due to inclusion criteria, existing studies of PVS provide context to our descriptive analysis. Survival in our high-risk cohort of patients was encouraging compared to published reports of survival as low as 50% to 70% at 2 years from first PVS intervention.[1,4-6] In our cohort, 83% of patients who started sirolimus within 2 years of PVS diagnosis were alive at 2 years from diagnosis. This contrasts with the 100% survival at median follow-up of 2.2 years reported by Patel et al[20] for patients receiving SST for severe PVS. Without a control group, we cannot evaluate or attribute a survival benefit to SST, and multiple factors are likely driving the positive contemporary trends in PVS survival. The relative contributions of aggressive interventional strategies,[3-6,19,20] SST,[20] and other era-related advances in practices and therapies[11] are difficult to determine in a heterogeneous retrospective cohort. Furthermore, patients who discontinued SST within 30 days and either died or did not resume therapy were excluded, potentially biasing the favorable survival results.

Notably, all mortalities were preceded by infection, though proximate cause of death was not always sepsis. The role of immunosuppression due to SST in the outcome in these patients who died in the setting of infectious processes remains unclear, but its

contribution cannot be ruled out. Our study was not intended to capture all potential side effects or short gaps in therapy for acute infection. Many patients with PVS have concomitant chronic lung disease, pulmonary hypertension, other comorbidities, and generalized frailty predisposing them to infections. We recommend holding sirolimus in the setting of acute febrile illness or suspicion of active systemic infection, avoidance of live vaccines, and prescribing infectious prophylaxis (though evidence is lacking for the effectiveness of the latter).[27] Parental education, communication with the prescribing team, and partnership with primary care providers is vital to promote appropriate practices and precautions for these vulnerable patients.

WHO SHOULD BE TREATED WITH SST FOR PVS, AND FOR HOW LONG? Indications for initiating and stopping therapy vary in the literature and continue to evolve as collective experience and evidence with SST for PVS accumulates. SST is largely being utilized in patients with moderate-severe PVS with multivessel disease or requiring repeated interventions.[19-23] Utilization of standardized measures of disease severity and surveillance algorithms[20,21] will facilitate ongoing evaluation of therapeutic benefits. Advanced imaging technologies such as intravascular ultrasound,[28] optical coherence tomography,[21] and magnetic resonance imaging[22,29] hold promise to augment our understanding and quantification of disease progression. A team-based multidisciplinary approach[11,19-21] remains key to implementing and monitoring multimodal therapeutic regimens in these complex patients.

The ideal duration of therapy remains unclear. Callahan et al[19] observed benefits for ISS with courses as short as 8 weeks. However, Shorofsky et al[21] noted favorable vascular remodeling in patients on SST by optical coherence tomography followed by recurrence of intimal proliferation after cessation. Longer-term follow-up is required to delineate disease trajectory following discontinuation of SST and to determine burden of side effects with longer therapeutic durations. In our series with a median follow up of 2.7 years post-SST initiation, half of patients who discontinued therapy were restarted on a subsequent course, and our median duration of first course of therapy was 1.7 years. In the absence of rigorous data, as long as patients remain free from contraindications and serious side effects, it may be reasonable to continue therapy for at least 1 year. We propose that patients over 2 years old with favorable hemodynamics, decreased reintervention frequency, and whose veins have grown or been stented to a threshold diameter >7 mm[6] might be trialed off therapy with close monitoring for disease progression.

STUDY LIMITATIONS. While our analysis suggests an association between SST and reduced intervention frequency, this interpretation should be contextualized by several additional limitations. Diagnostic catheterizations without interventions were not counted in this analysis, so procedural burden to patients may be underestimated. Patients with short interval durations (particularly pre-SST) resulted in several outliers with inflated frequency values. This may have impacted results since Poisson generalized mixed model estimates are sensitive to extreme values. However, supplemental nonparametric methods such as the Wilcoxon signed rank test and pseudo-score comparison of mean cumulative functions yielded congruent significant results. With limited data regarding a patient's disease course pre-SST, it is difficult to understand the aggression or progressiveness of a patient's disease. However, in the setting of severe stenosis and understanding the insidious, progressive nature of disease, SST initiation in these scenarios retains a favorable risk-benefit profile. It is generally well tolerated and offers a theoretical benefit by targeting theorized underlying disease mechanism of PVS.[8-10] A transparent risk-benefit discussion and informed consent is undertaken with parents for this reason. Given the evolving science related to PVS, we felt it was pertinent to include these patients to reflect contemporary practice and to assist in decision-making for similar patients.

In our aim to capture a large and diverse clinical experience with SST for PVS, we were limited to less-granular data. Patients with PVS often transfer care between institutions throughout their lives and/or undergo interventions at our referral center while monitored in the interim at outside practices closer to their residence. Reliably complete drug levels during SST were not routinely attainable; therefore, patient nonadherence and subtherapeutic drug levels are not accounted for in this study. Nonetheless, practice variation among and within institutions, patient movement, and variable therapeutic levels reflect a realistic snapshot of this complex population, rendering reasonable expectations for implementation of SST in the current PVS practice environment.

Furthermore, the study is limited by absence of a control group. Given the heterogeneity of PVS phenotypes, generating a matched cohort with similar patterns and severity of disease in a small affected population was not feasible. By comparing

intervention frequency prior to initiation of SST, each patient was self-matched, mitigating much of the variability which is difficult to quantify between patients.

Our inclusion criteria could introduce selection bias by excluding patients who died before or within 30 days of SST initiation and patients whose PVS was not severe enough to warrant SST. Lack of standardized criteria for SST initiation further compounds selection bias. A standardized multi-institutional prospective clinical trial would provide more definitive data regarding the indications, benefits, and risks for SST for patients as well as individual veins. Such trials could facilitate identification and inclusion of an appropriate contemporary untreated control group to elucidate therapeutic benefits of SST. However, randomization may not be feasible due to ethical concerns about withholding potentially beneficial therapy in a population with poor prognosis and limited therapeutic options.

CONCLUSIONS

SST was associated with decreased PVS intervention frequency compared to pre-sirolimus, accounting for age at the start of the interval, PVS type, sex, prematurity, and concurrent antiproliferative therapy. Survival was reasonable compared with reported literature for patients with severe disease, and favorable hemodynamic changes were observed in patients with biventricular anatomy. Prospective studies are warranted to evaluate the potential causal impact on outcomes at the patient and vein levels.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Systemic sirolimus is an emerging adjunctive medical therapy targeting the underlying pathogenesis of PVS. In this retrospective study, SST was associated with reduced frequency of interventions compared with prior to therapy, both in unadjusted analysis and after controlling for clinically relevant covariates via multivariable regression analysis.

TRANSLATIONAL OUTLOOK 1: Prospective, multi-institutional clinical trials with standardized therapeutic regimens are needed to definitively assess safety, quantify benefits, and determine ideal dosing strategies for systemic sirolimus and other adjuvant medical therapies for PVS. Identifying appropriate control cohorts will also further these aims.

TRANSLATIONAL OUTLOOK 2: Further development and validation of models similar to the Poisson generalized mixed regression in this study could create tools to inform decision-making and family counseling when considering SST for PVS. Models taking into account patient demographic and disease-related factors might be able to accurately predict an individual's benefits of therapy or anticipated disease trajectory following cessation.

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APPENDIX For supplemental tables and a figure, please see the online version of this paper.