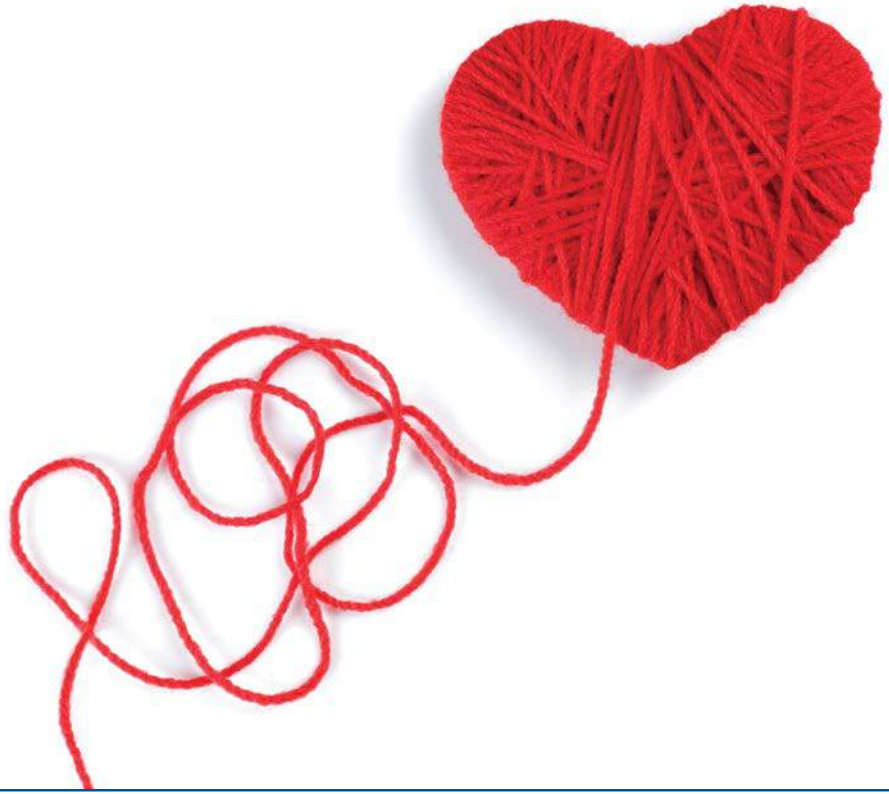
CARDIOLOGY 2023

IS PULMONARY VEIN STENOSIS A TREATABLE DISEASE?



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February 25th, 2023

Children's Hospital of Philadelphia
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Perelman School of Medicine
University of Pennsylvania

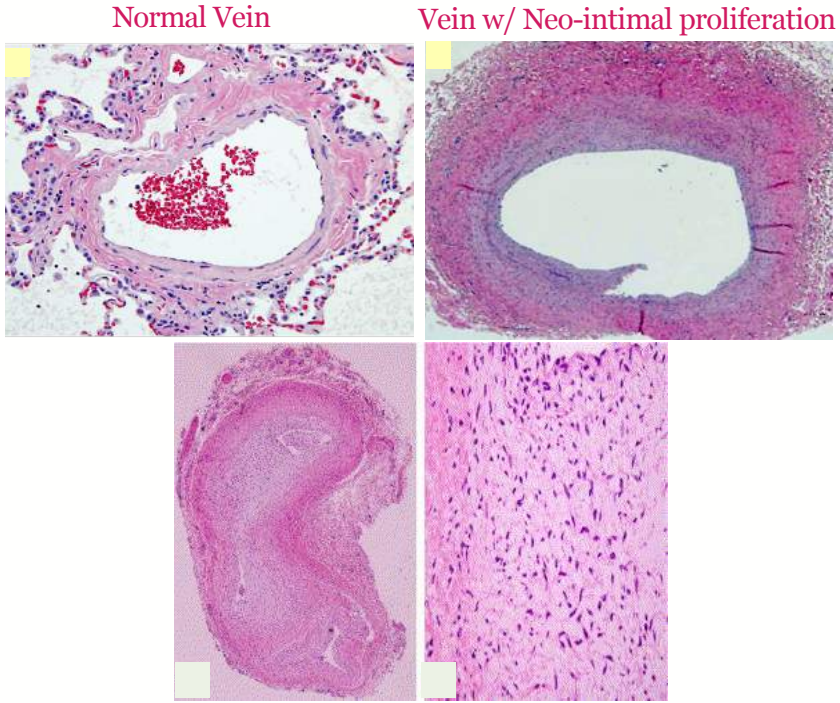
22CME0420/PPT/01-23

DISCLOSURES

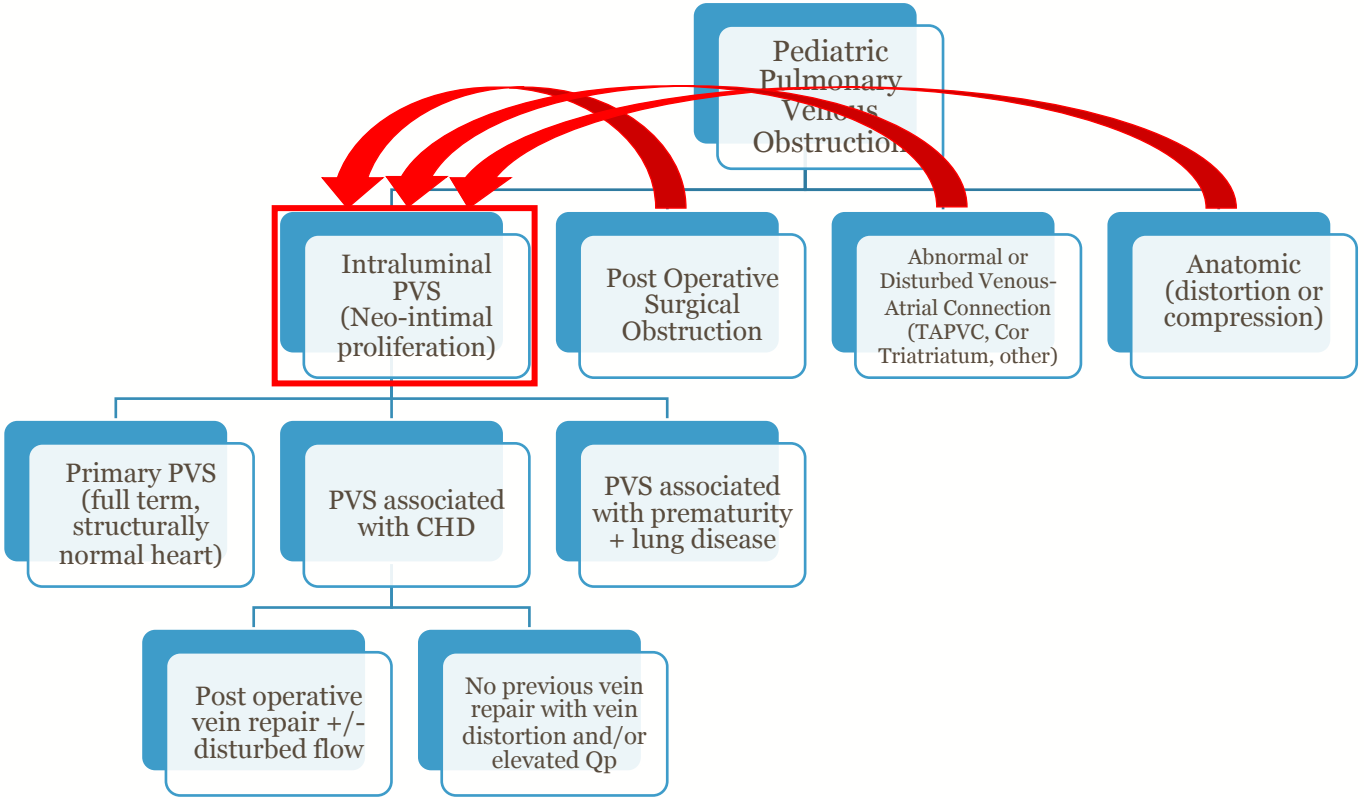
- None

WHAT IS INTRALUMINAL PVS?

- Disease of pulmonary vein Wall Thickening leading to luminal narrowing
- Neo-intimal hyperplasia (thickening of the intima) of myofibroblast-like cells in a loose myxocollagenous matrix[1,2]



1. Kovach AE, Magcala PM, Ireland CM, et al. Paucicellular Fibrointimal Proliferation Characterizes Pediatric Pulmonary Vein Stenosis: Clinicopathologic Analysis of 213 Samples from 97 Patients. Am J Surg Pathol 2017; 41(9): 1198-1204.
2. Sadr IM, Tan PE, Kieran MW, Jenkins KJ. Mechanism of pulmonary vein stenosis in infants with normally connected veins. *Am J Cardiol*. 2000;86(5):577-579, A10.

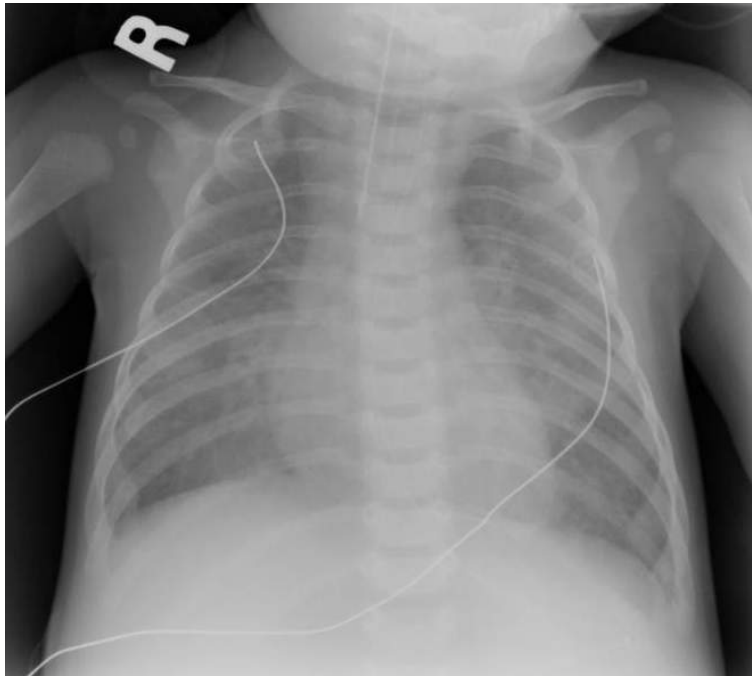

Pediatric Pulmonary Venous Obstruction
Intraluminal PVS (Neo-intimal proliferation)
Post Operative Surgical Obstruction
Abnormal or Disturbed Venous-Atrial Connection (TAPVC, Cor Triatriatum, other)
Anatomic (distortion or compression)
Primary PVS (full term, structurally normal heart)
PVS associated with CHD
PVS associated with prematurity + lung disease
Post operative vein repair +/- disturbed flow
No previous vein repair with vein distortion and/or elevated Qp

WHY IS PVS CHALLENGING?

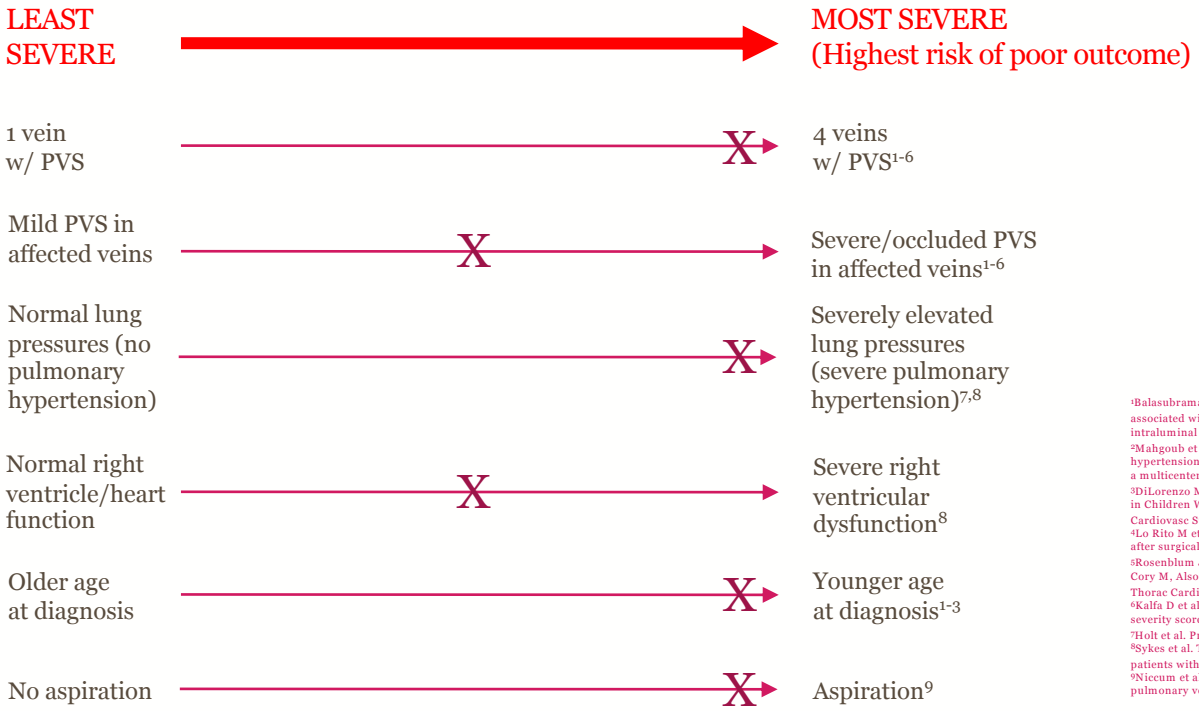
- PVS -> pulmonary venous hypertension -> pulmonary arterial hypertension -> right heart failure -> death
- Rare
- Not completely understood
- Restenosis after any intervention (surgery, cath, etc.) is common

IS PVS TREATABLE? -> CASE EXAMPLE

- Year = 2016
- 3-month-old ex full term with h/o poor growth presents with respiratory failure
  - Sibling died of respiratory failure
    - Autopsy: Multi-vessel PVS
- Testing confirms Multi-vessel PVS involving all veins



CASE EXAMPLE: PVS SEVERITY



[1]Balasubramanian et al. Bilateral disease and early age at presentation are associated with shorter survival in patients with congenital heart disease and intraluminal pulmonary vein stenosis. Congenit Heart Dis 2012 7(4):378-86.
[2]Mahgoub et al. Pulmonary vein stenosis of ex-premature infants with pulmonary hypertension and bronchopulmonary dysplasia, epidemiology, and survival from a multicenter cohort. Pediatr Pulmonol 2017 52(8):1063-70.
[3]DiLorenzo MP., Santo A., Rome JJ., et al. Pulmonary Vein Stenosis: Outcomes in Children With Congenital Heart Disease and Prematurity. Semin Thorac Cardiovasc Surg 2019;31(2):266–73.
[4]Lo Rito M et al. Pulmonary vein stenosis: severity and location predict survival after surgical repair. J Thorac Cardiovasc Surg 2016;151:657-66-2.
[5]Rosenblum JM, Altin HF, Gillespie SE, Bauser-Heaton H, Kanter KA, Sinha R, Cory M, Alsoufi B. Management outcomes of primary pulmonary vein stenosis. J Thorac Cardiovasc Surg 2020;159:1029-1036.e1.
[6]Kalfa D et al. Primary pulmonary vein stenosis: outcomes, risk factors, and severity score in a multicentric study. Ann Thorac Surg 2017;104:182-189.
[7]Holt et al. Primary pulmonary vein stenosis. Am J Cardiol 2007 99(4):568-72.
[8]Sykes et al. The impact of right ventricular pressure and function on survival in patients with pulmonary vein stenosis. Pulm Circ 2018;8(2).
[9]Niccum et al. Aspiration is associated with poor treatment response in pediatric pulmonary vein stenosis. Children 2021; 8, 783.

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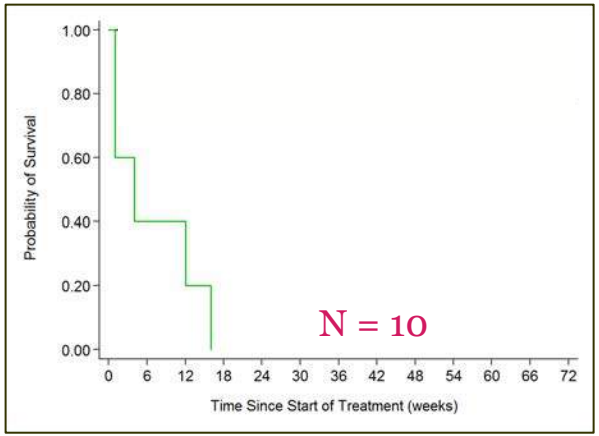
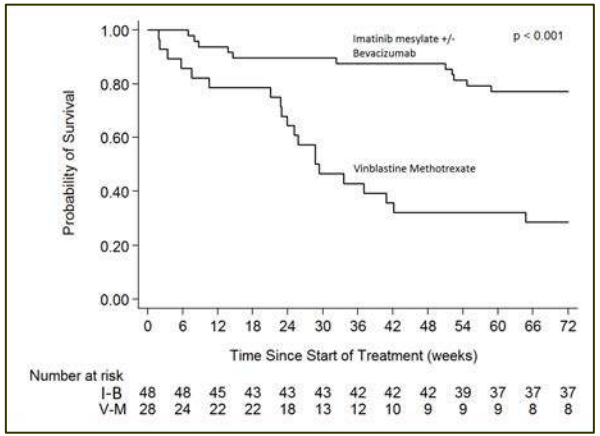
CASE EXAMPLE: OUTCOME

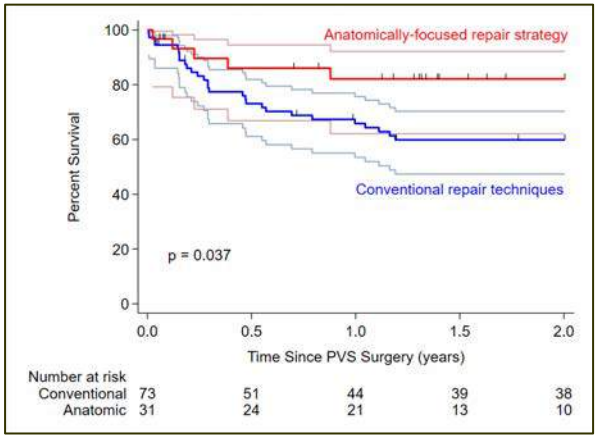
- 7 years later…

- Normal RV function
- Sub-systemic RVSP
- Meds: ASA, diuril, aldactone, O2 at night
- Annual Catheterization

DEMONSTRATE IMPROVEMENT (CENTER 1)







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Rehman, M., Jenkins, K. J., Juraszek, A. L., Connor, J. A., Gauvreau, K., Muneeb, M., Sena, L. M., Colan, S. D., Saia, T., & Kieran, M. W. (2011). A prospective phase II trial of vinblastine and methotrexate in multivessel intraluminal pulmonary vein stenosis in infants and children. *Congenital Heart Disease*, *6*(6), 608–623.

Callahan, R., Kieran, M. W., Baird, C. W., Colan, S. D., Gauvreau, K., Ireland, C. M., Marshall, A. C., Sena, L. M., Vargas, S. O., & Jenkins, K. J. (2018). Adjunct Targeted Biologic Inhibition Agents to Treat Aggressive Multivessel Intraluminal Pediatric Pulmonary Vein Stenosis. *The Journal of Pediatrics*, *198*, 29-35.e5.

Feins, E. N., Ireland, C., Gauvreau, K., Chávez, M., Callahan, R., Jenkins, K. J., & Baird, C. W. (2021). Pulmonary vein stenosis: Anatomic considerations, surgical management, and outcomes. *The Journal of Thoracic and Cardiovascular Surgery*. 6

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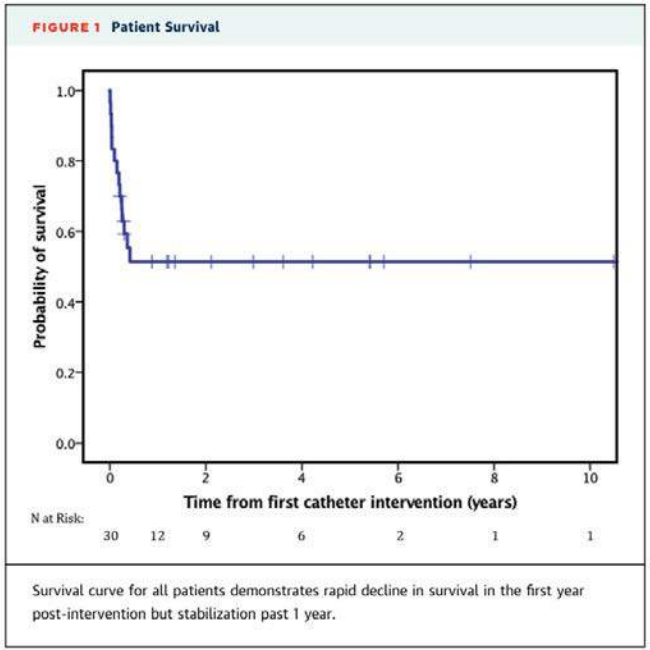
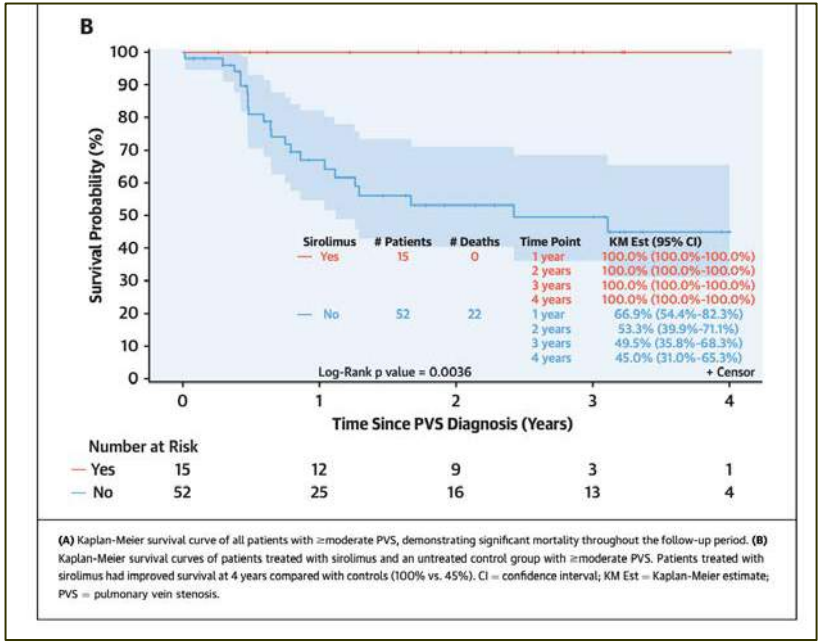
DEMONSTRATE IMPROVEMENT (CENTER 2)



Cory, M. J., Ooi, Y. K., Kelleman, M. S., Vincent, R. N., Kim, D. W., & Petit, C. J. (2017). Reintervention Is Associated With Improved Survival in Pediatric Patients With Pulmonary Vein Stenosis. *JACC: Cardiovascular Interventions*, *10*(17), 1788–1798.



Patel, J. D., Briones, M., Mandhani, M., Jones, S., Suthar, D., Gray, R., Pettus, J., McCracken, C., Thomas, A., & Petit, C. J. (2021). Systemic Sirolimus Therapy for Infants and Children With Pulmonary Vein Stenosis. *Journal of the American College of Cardiology*, *77*(22), 2807–2818.

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DEMONSTRATE IMPROVEMENT (CENTER 3)

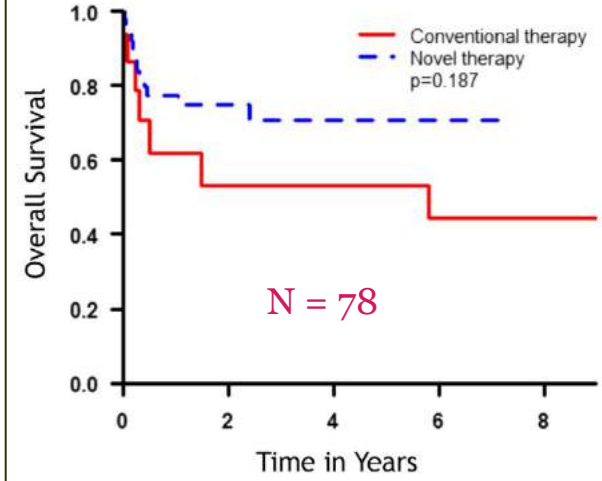


FIGURE 3 Survival curve comparing patients receiving conventional therapy using BMS alone (red) and novel therapy using a combination of DES and BMS (blue). BMS, bare metal stents; DES, drug-eluting stents [Color figure can be viewed at wileyonlinelibrary.com]

Khan, A., Qureshi, A. M., & Justino, H. (2019). Comparison of drug eluting versus bare metal stents for pulmonary vein stenosis in childhood. *Catheterization and Cardiovascular Interventions*, *94*(2), 233–242.

CULTURE SHIFT

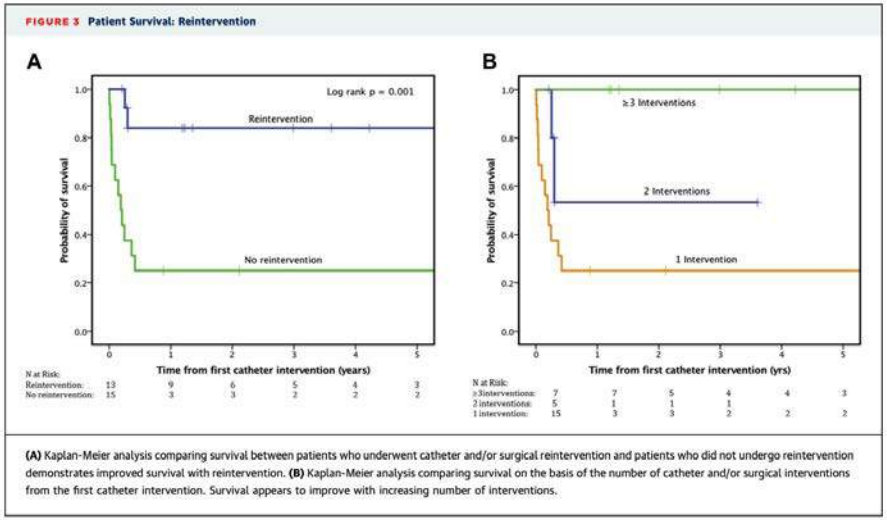
FATAL DISEASE

Application of new therapies

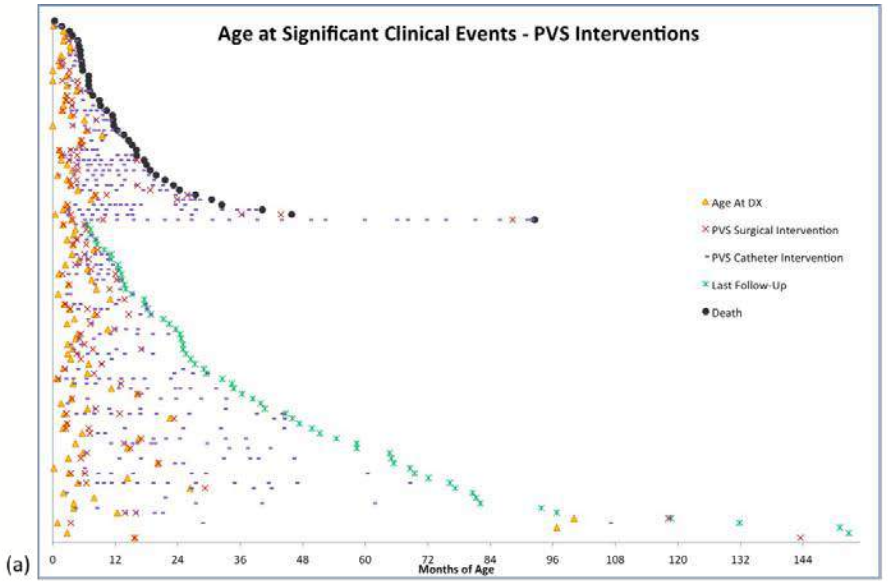
CHRONIC DISEASE

(with expectation of restenosis)

LIGHT AT THE END OF THE TUNNEL



Cory, M. J., Ooi, Y. K., Kelleman, M. S., Vincent, R. N., Kim, D. W., & Petit, C. J. (2017). Reintervention Is Associated With Improved Survival in Pediatric Patients With Pulmonary Vein Stenosis. *JACC: Cardiovascular Interventions*, *10*(17), 1788–1798.



Sykes MC, Ireland C, McSweeney JE, Rosenholm E, Andren KG, Kulik TJ. The impact of right ventricular pressure and function on survival in patients with pulmonary vein stenosis. Pulm Circ. 2018 Apr-Jun;8(2)

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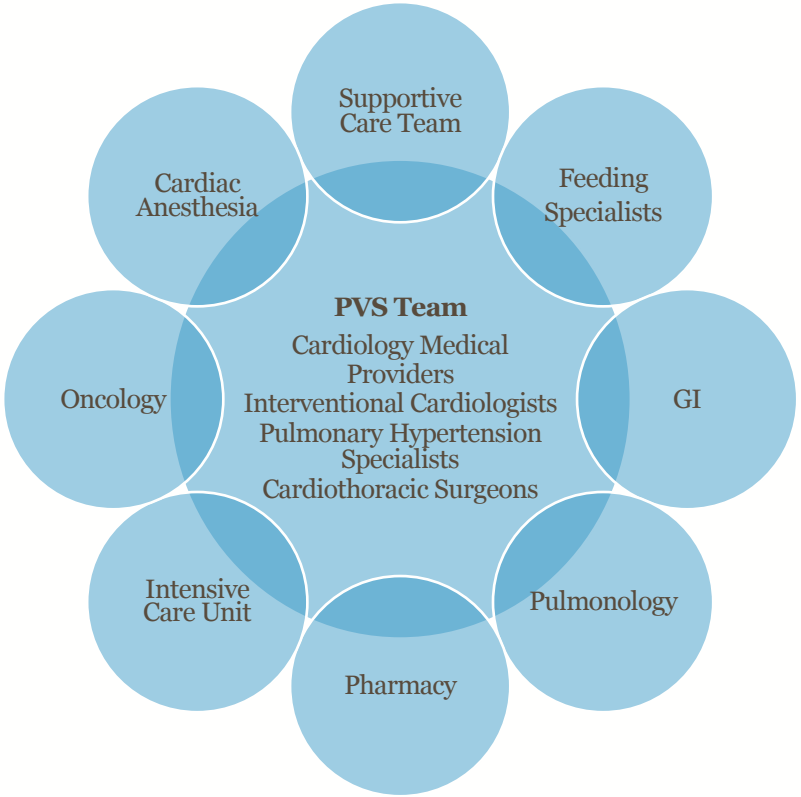
ESTABLISH A PROGRAM/PROTOCOL



1. • Understand the mechanism of obstruction
   • Determine the overall disease burden
2. • Family education/counseling
3. • Intervene: Individual vein approach
   • Goal: Achieve laminar flow
4. • Optimize nutrition
   • Identify and remove PVS stimulus
5. • Initiate targeted anti-proliferative medical therapy
6. • Manage symptoms/comorbidities
   • Active surveillance
7. • Understand the mechanism of restenosis
   • Evaluate need to modify or escalate therapy

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TREATING PVS STIMULI

Table V. Associations between patient characteristics and outcomes at 72 weeks

Patient characteristic	Survival			Progression			Stabilization		
	Alive (n = 37)	Dead (n = 11)	*P* value	Yes (n = 6)	No (n = 42)	*P* value	Yes (n = 16)	No (n = 32)	*P* value
Prematurity	14 (38)	4 (36)	.99	3 (50)	15 (36)	.66	6 (38)	12 (38)	.99
Age, diagnosis (mo)			.35			.91			.77
<3	10 (27)	6 (55)		3 (50)	13 (31)		5 (31)	11 (34)	
3 to <6	18 (49)	3 (27)		2 (33)	19 (45)		6 (38)	15 (47)	
6 to <12	6 (16)	1 (9)		1 (17)	6 (14)		3 (19)	4 (13)	
≥12	3 (8)	1 (9)		0 (0)	4 (10)		2 (12)	2 (6)	
Isolated PVS	2 (5)	3 (27)	.07	1 (17)	4 (10)	.50	2 (12)	3 (9)	.99
Lung Disease	15 (41)	2 (18)	.28	2 (33)	15 (36)	.99	2 (12)	15 (47)	.03
CHD	31 (84)	7 (64)	.21	5 (83)	33 (79)	.99	14 (88)	24 (75)	.46
If CHD, anomalous veins	13 (42)	4 (57)	.68	1 (20)	16 (48)	.36	7 (50)	10 (42)	.74
Bilateral disease	29 (78)	10 (91)	.66	6 (100)	33 (79)	.58	12 (75)	27 (84)	.46
No. of veins involved at start of treatment			.99			.70			.23
2	7 (19)	2 (18)		1 (17)	8 (19)		4 (25)	5 (16)	
3	13 (35)	4 (36)		2 (33)	15 (36)		3 (19)	14 (44)	
4	15 (41)	4 (36)		2 (33)	17 (40)		7 (44)	12 (38)	
5	2 (5)	1 (9)		1 (17)	2 (5)		2 (12)	1 (3)	
Age, initiation of treatment (mo)			.15			.87			.55
<6	11 (30)	7 (64)		3 (50)	15 (36)		5 (31)	13 (41)	
6 to <12	15 (40)	2 (18)		2 (33)	15 (36)		5 (31)	12 (38)	
≥12	11 (30)	2 (18)		1 (17)	12 (28)		6 (38)	7 (22)	
Percentage of eligible doses received	0.87 (0.54-0.99)	0.77 (0.55-0.93)	.09	0.83 (0.72-0.99)	0.86 (0.54-0.99)	.82	0.90 (0.54-0.99)	0.83 (0.55-0.99)	.03
Treated per protocol	29 (78)	7 (64)	.43	3 (50)	33 (79)	.16	13 (81)	23 (72)	.73

Callahan R, Kieran MW, Baird CW, Colan SD, Gauvreau K, Ireland CM, Marshall AC, Sena LM, Vargas SO, Jenkins KJ. Adjunct Targeted Biologic Inhibition Agents to Treat Aggressive Multi-Vessel Intraluminal Pediatric Pulmonary Vein Stenosis. J Pediatr. 2018 Jul;198:29-35.e5.

TREATING PVS STIMULI

- N = 69 patients with multi-vessel PVS receiving medical and interventional therapy
- Poor treatment response = death, lung transplant, addition of Avastin due to disease progression, cath interval < 3 months after 1 year of therapy

Table 3b: Multivariable Model

	Odds Ratio	95% Confidence Interval	p value
Clinically Significant Aspiration	4.85	(1.37, 17.2)	0.014*
Age at Start of Treatment (years)	1.39	(0.50, 3.92)	0.53
Male Sex	3.67	(1.04, 12.9)	0.043*
Bilateral Disease at Diagnosis	1.48	(0.23, 9.50)	0.68
Lung Disease	1.84	(0.47, 7.26)	0.38

Lung hyperinflation/fibrosis --> stretch/traction on pulmonary veins --> increase wall shear stress --> myofibroblast proliferation --> pulmonary vein obstruction.

Niccum M, Callahan R, Gauvreau K, Jenkins KJ. Aspiration is associated with poor treatment response in pediatric pulmonary vein stenosis. Children. 2021; 8, 783.

TREATING PVS STIMULI

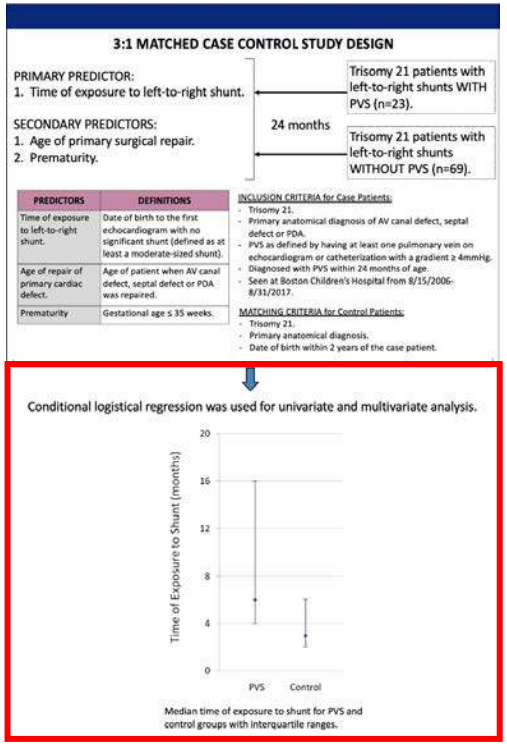

Table 2. Univariate and Multivariate Analyses of Primary and Secondary Predictors.

Analysis	PVS (n = 23)	No PVS (n = 69)	p-Value
Univariate			
Time of exposure to shunt (months)	6 (4, 16)	3 (2, 6)	0.002
Age at primary repair (≥4 months)	17 (81%)	29 (42%)	0.003
Premature (birth ≤ 35 weeks GA)	11 (48%)	9 (13%)	0.003
Multivariate	Odds Ratio	95% CI	
Risk of PVS per month of exposure to shunt	1.21	(1.06, 1.39)	0.007
Premature (birth ≤ 35 weeks GA)	4.77	(1.36, 16.8)	0.015

All data is presented at numbers (percentages) or median (interquartile range) for the univariate analysis and odds ratio with 95% confidence intervals for the multivariate analysis. GA: gestational age, CI: confidence interval.

Choi C, Gauvreau K, Levy P, Callahan R, Jenkins KJ, Chen M. Longer Exposure to Left-to-Right Shunts Is a Risk Factor for Pulmonary Vein Stenosis in Patients with Trisomy 21. Children 2021, 8, 19.

ACTIVE SURVEILLANCE

- Regular clinical assessments and PVS imaging
  - Echocardiogram paired with lung perfusion scan
  - CTA
  - Less commonly CMR
- Diagnosis restenosis prior to vein atresia
  - Aggressive or undertreated PVS can recur in less than 4 weeks
- Waiting for overt symptoms increases risk of…

Table 3. Multivariable Analysis of Serious Adverse Events

	Odds Ratio	95% CI	P Value
Age at intervention			
<6 months	2.05	1.11, 3.81	0.023
6-11.9 months	1.30	0.77, 2.22	0.33
≥1 year	1.00	--	--
Systemic arterial saturation <95% BiV, <78% SV	1.52	1.02, 2.27	0.041
Mean PA pressure ≥45 mm Hg BiV, ≥17 mm Hg SV	1.74	1.16, 2.63	0.008

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Barreto JA, Gauvreau K, Porras D, Esch JJ, Maschietto N, Quinn B, Bergersen L, Stein M, Callahan R. Predictors of Serious Adverse Events and High-Level Cardiorespiratory Support in Patients Undergoing Transcatheter Pulmonary Vein Interventions. Pediatric Cardiology. 2023. *In press.*

Table 5. Multivariate Analyses of Perioperative Factors and Postoperative ICU Admission and Mechanical Ventilation

	ICU Admission		Mechanical Ventilation	
	Adjusted OR (95% CI)	p	Adjusted OR (95% CI)	p
Male gender	3.93 (1.64-9.41)	0.002	2.89 (1.26-6.66)	0.013
Body weight,per 1 kg increment	0.80 (0.68-0.92)	0.003	0.79 (0.68-0.92)	0.002
Preoperative O_2 supplement	4.01 (1.69-9.53)	0.002	3.67 (1.55-8.68)	0.003
PVS severity score, per 1 unit increment	1.15 (1.02-1.30)	0.028	1.11 (0.98-1.24)	0.10
Hypotension requiring inotrope	4.03 (1.38-11.77)	0.011	2.89 (1.08-7.77)	0.035
Red blood cell transfusion	3.25 (1.18-8.94)	0.023	4.09 (1.53-10.93)	0.005
Preintervention PaO_2/F_IO_2 ratio, per 100 units increment	0.63 (0.45-0.89)	0.009	0.59 (0.42-0.83)	0.002
Preintervention RVSP, per 10 mmHg increment	1.39 (1.11-1.75)	0.004	1.27 (1.03-1.57)	0.023

Maisat W, Yuki K. Predictive Factors for Postoperative Intensive Care Unit Admission and Mechanical Ventilation After Cardiac Catheterization for Pediatric Pulmonary Vein Stenosis. J Cardiothorac Vasc Anesth. 2022 Aug;36(8 Pt A):2500-2508.

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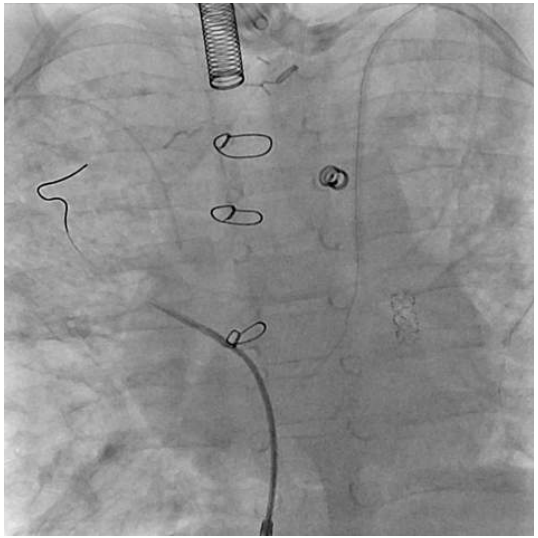
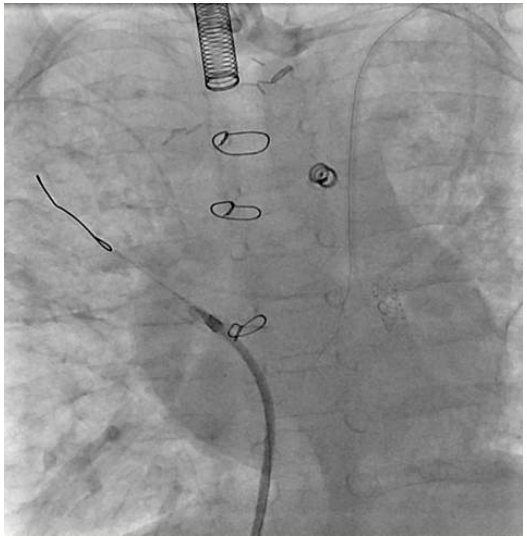
WHAT WAS ONCE LOST…

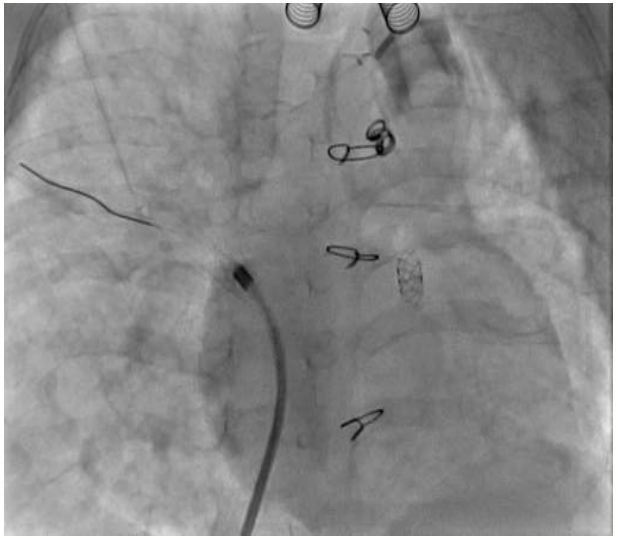
Pre-Intervention



Post-Intervention

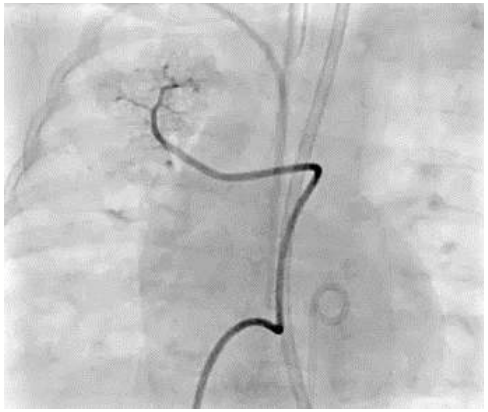


Follow-up

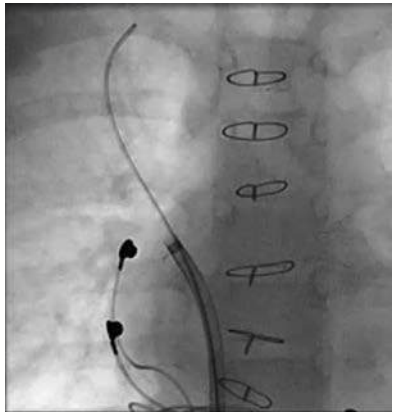


WHAT WAS ONCE LOST…

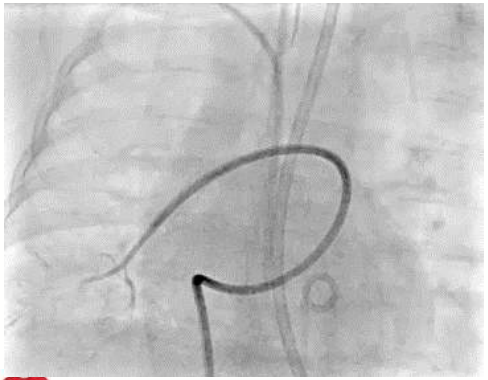
2 months old



Right Upper Pulm Vein



3 years old



Right Lower Pulm Vein

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WHAT WAS ONCE LOST

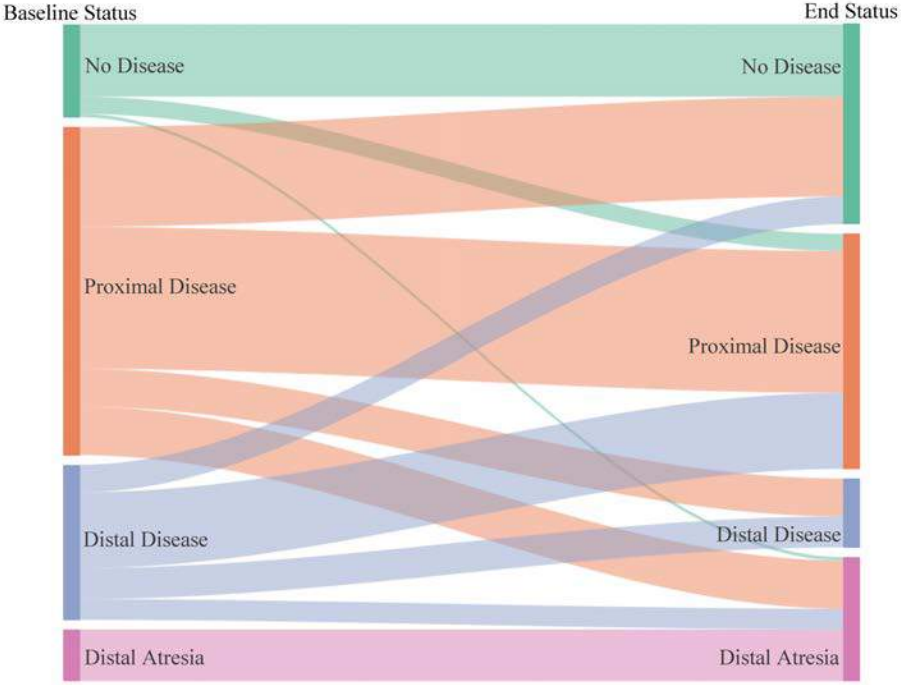

Figure 1. Change in disease status of all pulmonary veins, baseline to study endpoint. **(n = 182 pulmonary veins)**

Callahan R, Gauvreau K, Marshall AC, et al. Outcomes in Establishing Individual Vessel Patency for Pediatric Pulmonary Vein Stenosis. *Child (Basel, Switzerland).* 2021;8(3).

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SUMMARY

- PVS outcomes are improving with standardized management protocols and evolving therapies
- Still work to be done on non-responders

- Let's go!

THANK YOU

PVS at CHOP

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