Hypertensions pulmonaires de l’enfant

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Centre de Référence Maladies Rares
Maladies Cardiaques Héréditaires- CARDIOGEN

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TASK FORCE 12
Pediatrics

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TENSION

New guidelines since Nice 2013

AHA/ATS Guideline

Pediatric Pulmonary Hypertension

Guidelines From the American Heart Association and American Thoracic Society

Steven H. Abman, MD, Co-Chair; Georg Hansmann, MD, PhD, FAHA, Co-Chair; Stephen L. Archer, MD, FAHA, Co-Chair; D. Dunbar Ivy, MD, FAHA; Ian Adatia, MD; Wendy K. Chung, MD, PhD; Brian D. Hanna, MD; Erika B. Rosenzweig, MD; J. Usha Raj, MD; David Cornfield, MD; Kurt R. Stenmark, MD; Robin Steinhorn, MD, FAHA; Bernard Thébaud, MD, PhD; Jeffrey R. Fineman, MD; Titus Kuehne, MD; Jeffrey A. Feinstein, MD; Mark K. Friedberg, MD; Michael Earing, MD; Robyn J. Barst, MD†; Roberta L. Keller, MD; John P. Kinsella, MD; Mary Mullen, MD, PhD; Robin Deterding, MD; Thomas Kulik, MD; George Mallory, MD; Tilman Humpl, MD; David L. Wessel, MD; on behalf of the American Heart Association Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation; Council on Clinical Cardiology; Council on Cardiovascular Disease in the Young; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Surgery and Anesthesia; and the American Thoracic Society

ORIGINAL ARTICLE

Executive summary. Expert consensus statement on the diagnosis and treatment of paediatric pulmonary hypertension. The European Paediatric Pulmonary Vascular Disease Network, endorsed by ISHLT and DGPK

Georg Hansmann, (Chair)[1] Christian Apitz, (Co-Chair)[2] Hashim Abdul-Khaliq,[3] Tero-Pekka Alastalo,[4,5] Phillip Beerbaum,[1] Damien Bonnet,[6] Karl-Otto Dubowy,[7] Matthias Gorenflo,[8] Alfred Hager,[9] Anne Hilgendorff,[10] Michael Kaestner,[2] Martin Koestenberger,[11] Juha W Koskenvuo,[4,5] Rainer Kozlik-Feldmann,[12] Titus Kuehne,[13] Astrid E Lammers,[14] Heiner Latus,[15] Ina Michel-Behnke,[16] Oliver Miera,[17] Shahin Moledina,[18] Vivek Muthurangu,[19] Joseph Pattathu,[8] Dietmar Schranz,[15] Gregor Warnecke,[20,21] Peter Zartner[22]

Circulation. 2015;132:2037-2099
Heart 2016;102:ii86-ii100.

Specific guidelines for neonatal pulmonary hypertension

MEDICAL PROGRESS www.jpeds.com • THE JOURNAL OF PEDIATRICS

Evaluation and Management of Pulmonary Hypertension in Children with Bronchopulmonary Dysplasia

Usha Krishnan, MD[1,*], Jeffrey A. Feinstein, MD[2,*], Ian Adatia, MBChB[3], Eric D. Austin, MD[4], Mary P. Mullen, MD, PhD[5], Rachel K. Hopper, MD[6], Brian Hanna, MD, PhD[6], Lew Romer, MD[7], Roberta L. Keller, MD[8], Jeffrey Fineman, MD[9], Robin Steinhorn, MD[10], John P. Kinsella, MD[11], D. Dunbar Ivy, MD[12], Erika Berman Rosenzweig, MD[1], Usha Raj, MD[13], Tilman Humpl, MD[14], and Steven H. Abman, MD[15], for the Pediatric Pulmonary Hypertension Network (PPHNet)[†]

COMMENTARY www.jpeds.com • THE JOURNAL OF PEDIATRICS

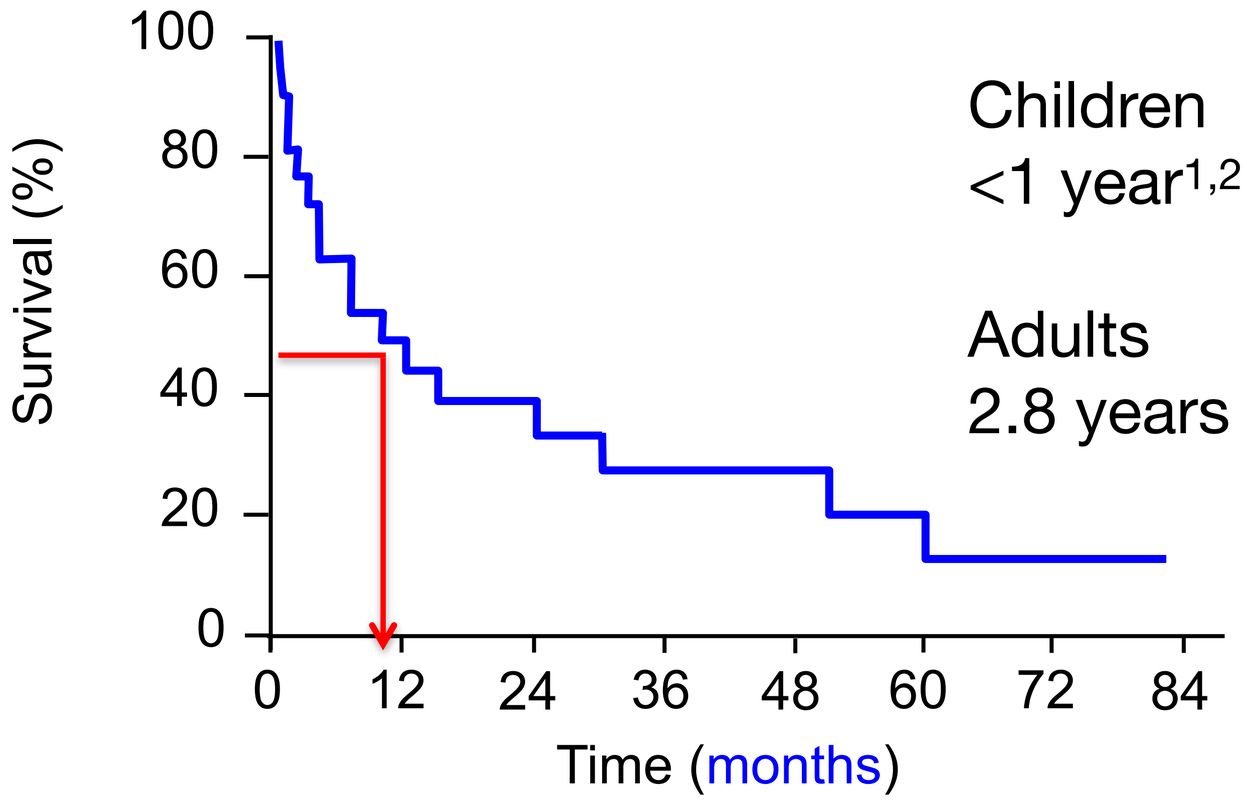
Recommendations for the Use of Inhaled Nitric Oxide Therapy in Premature Newborns with Severe Pulmonary Hypertension

John P. Kinsella, MD[1], Robin H. Steinhorn, MD[2], Usha S. Krishnan, MD[3], Jeffrey A. Feinstein, MD[4], Ian Adatia, MBChB[5], Eric D. Austin, MD[6], Erika B. Rosenzweig, MD[3], Allen D. Everett, MD[7], Jeffrey R. Fineman, MD[8], Brian D. Hanna, MD, PhD[9], Rachel K. Hopper, MD[9], Tilman Humpl, MD[10], D. Dunbar Ivy, MD[11], Roberta L. Keller, MD[12], Mary P. Mullen, MD, PhD[13], J. Usha Raj, MD[14], David L. Wessel, MD[15], and Steven H. Abman, MD[16]

Natural History of IPAH: NIH Registry

Median survival: 2.8 years (n=194)

Pediatric median survival: 0.8 years (n=16)



1. Houde C, *et al. Br Heart J* 1993;70:461-8.
2. Barst, RJ, *et al. Circulation* 1999; 99:1197-208.

Recent landmarks in pediatric PH

- Extension of drug approval in children (n=1) !
- Expansion of use of interventional-surgical approaches for end-stage PAH in children
- Genetic discoveries relevant to pediatric practice
- New insights from pediatric specific registry data

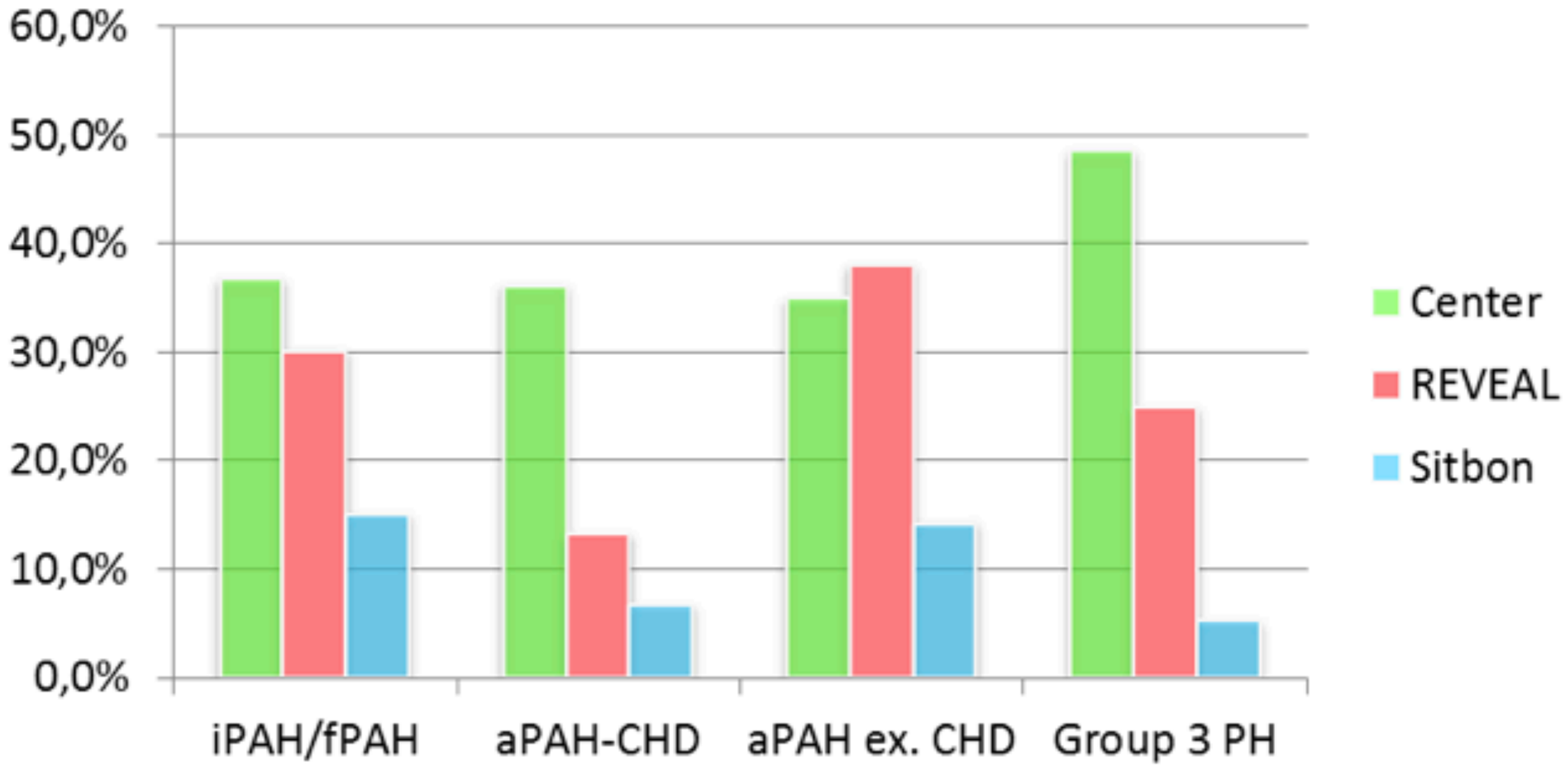
Definition of pediatric PH/PAH

- A mean pulmonary arterial pressure of >25 mmHg with a capillary wedge pressure of <15mmHg and a PVRi >3WU*m2 in children > 3 months of age with two ventricle anatomy.

- Limited data to extend the definition to children with mean PAP 21-24 mmHg.

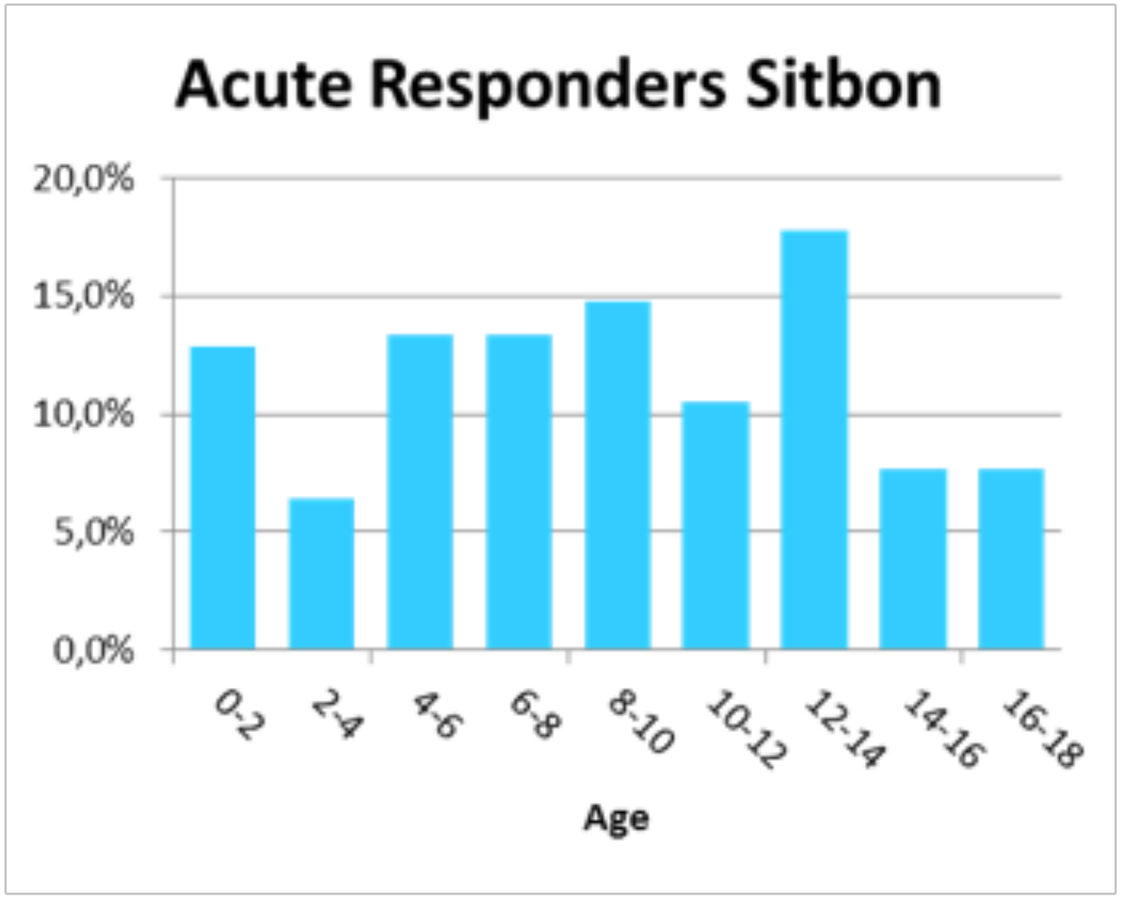
- Age is a pending problem:
  - Definition of PH in children less than 3 months of age
  - No RHC measure of pulmonary pressure in neonates with PPHN or PH associated with developmental lung disease

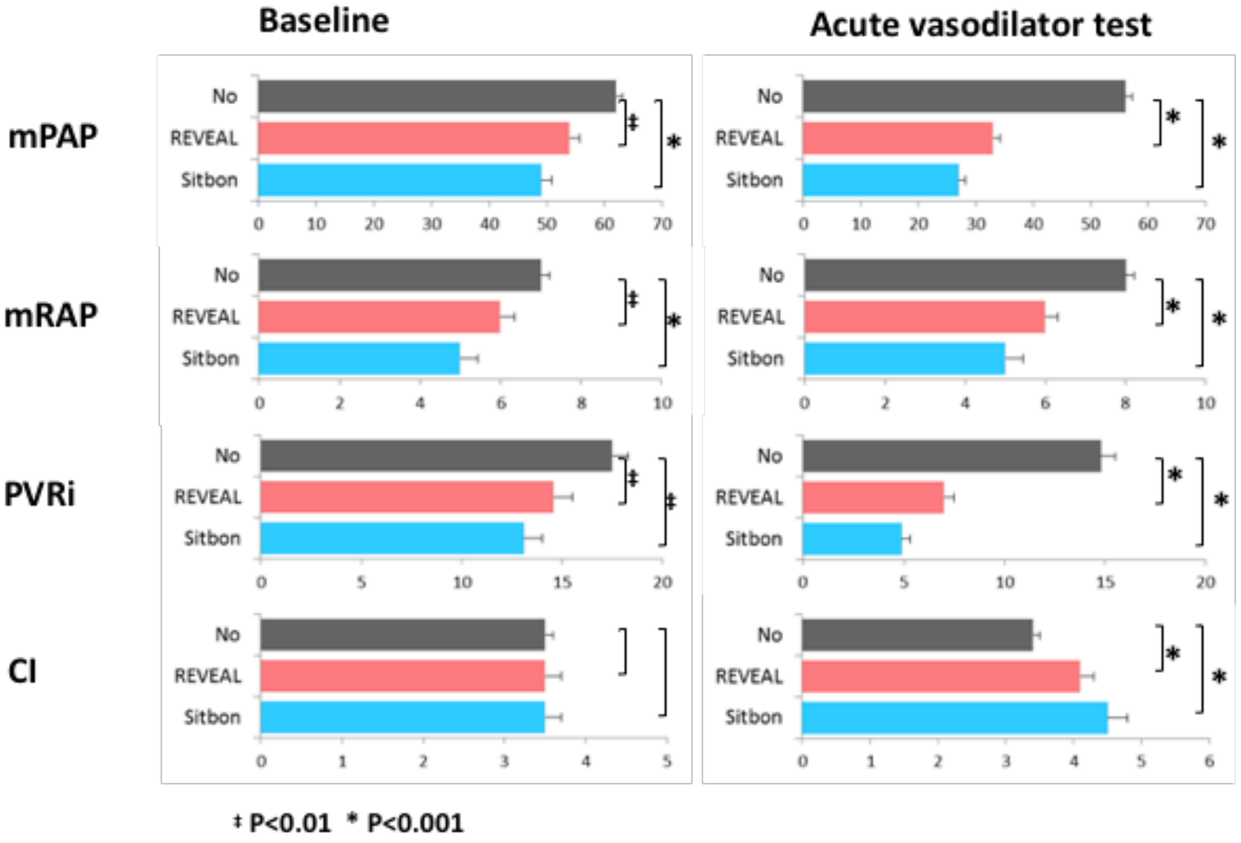
Definition of vasoreactivity in children



Douwes M et al. JACC 2016

Definition of vasoreactivity in children





Douwes M et al. JACC 2016

Heritable PAH in pediatrics

- Known mutations: BMPR2, ALK1, ENG, CAV1, KCNK3, EIF2AK4, TBX4, SOX17
- TBX4 – described potential role in pediatric PAH and small patella syndrome and lung development [1]
- SOX17 - role in PAH and cardiac development

1-Kerstjens-Frederikse WS, J Clin Genet 2013
2-Levy M, ERJ, 2016

Heritable PAH in pediatrics

- Genetic screening for PAH genes mutations should be performed in children
  – in expert centers with a genetic counseling group in all children diagnosed with IPAH and HPAH

- Genetic screening for PAH/lung-cardiac development should be done in APAH-CHD ?
  – TBX4 and SOX17 genes mutations

- Genetic screening for neonatal pulmonary hypertension is potentially recommended
  – FOXF1 in alveolo-capillary dysplasia
  – TBX4 in neonatal respiratory distress and PPHN

- Sharing exception may hold key to future understanding of PH in children

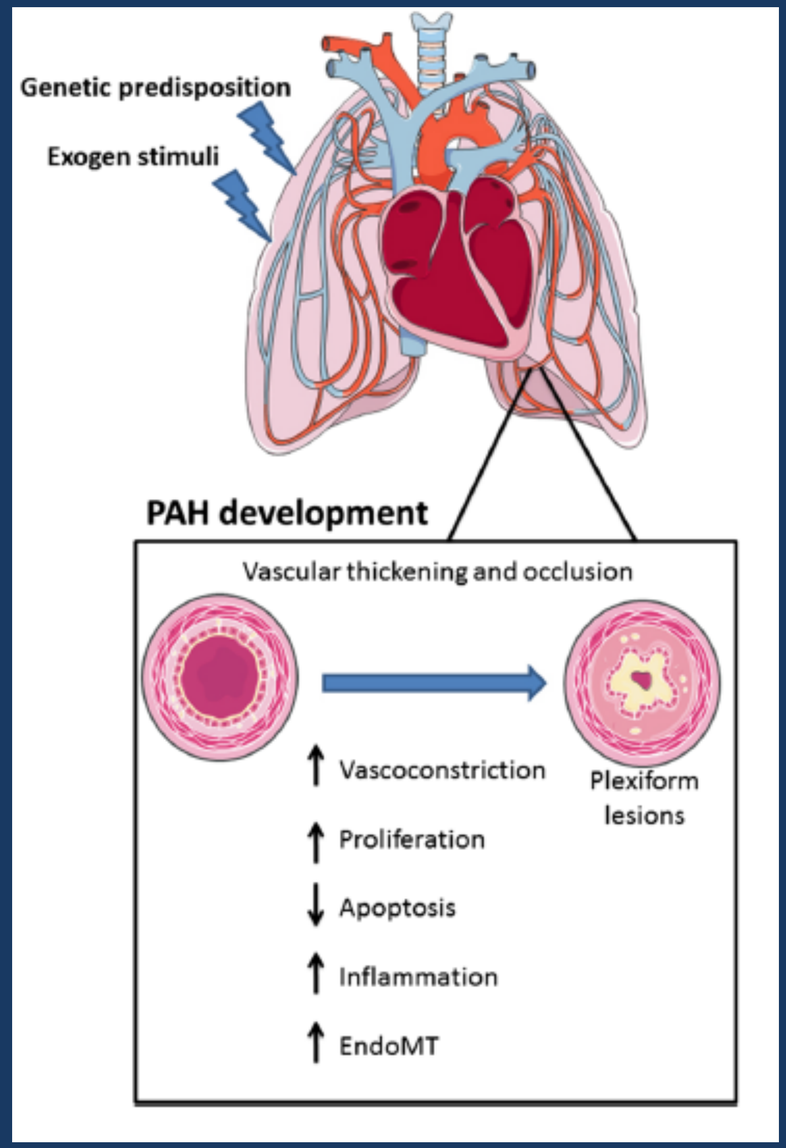
Gräf S et al. Nature Communication 2017

Identification of PAH genes mutations in a pediatric population
Results

- No mutations in children with group 3 and type 4 APAH-CHD.
- **8 mutations were found in 36 children with iPAH (22%)**
  - 3 in *BMPR2,*
  - 3 in *ALK1*,
  - 2 in *TBX4*.
  - No mutations were identified in *ENG, SMAD9* or *KCNK3.*
- **4 mutations were found in the 8 fPAH families (50%)**
  - *2* in *BMPR2,* 1 in *ALK1*, 1 in *TBX4*.
  - only one sibling of an index case with a *TBX4* mutation was alive with PAH, and had the same mutation. In the three remaining families, the first-degree relatives who had PAH were all dead at inclusion of the index case into our study with no material available for genetic testing.
- **2 mutation in *EIF2AK4* in the two patients with clinical, hemodynamic and CT features of PVOD**.

Lévy M et al. ERJ 2016

Low prevalence of known genes for PAH
PAH genes variants and risk of PVD



Gender and PAH

Ethnicity

Genetic predisposition in CHD

• Down syndrome:
-comorbid condition in pediatric PAH 13%[1]

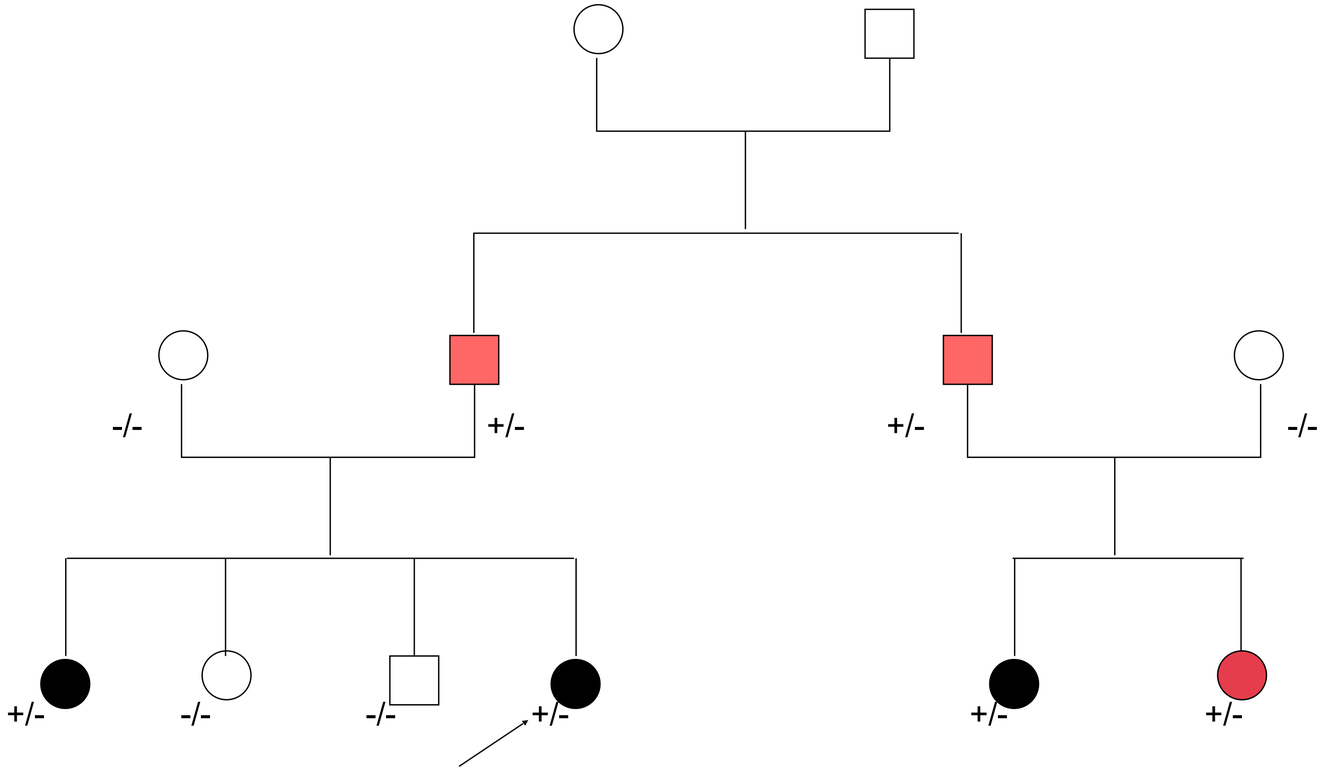
•Noonan syndrome

•*BMPR2* mutations in CHD[2]

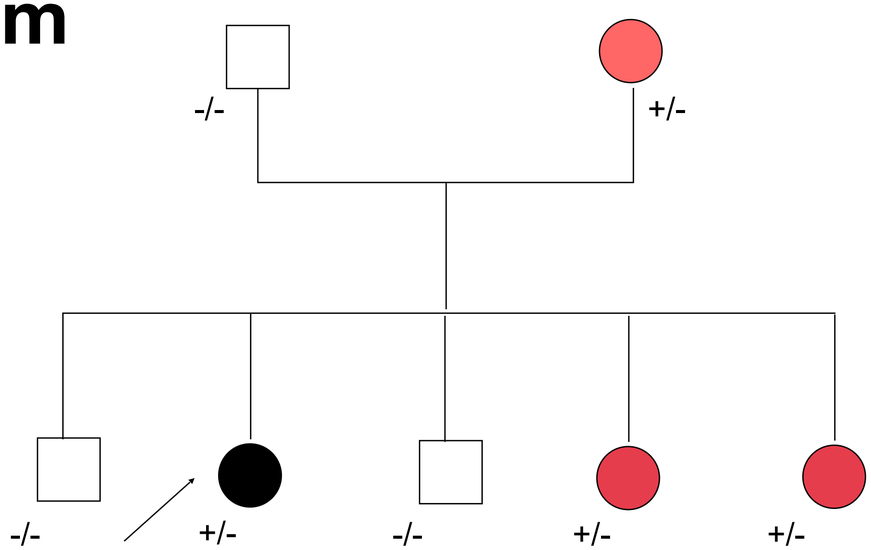
24 mutations were identified, accounting for 22 of the 294 patients with CHD-PVD (7.5%) and 2 of the 161 CHD patients without PVD (1.2%, P=0.004)

Liu et al. Pulm Circ 2017
Liu D et al. Int J Cardio 2016

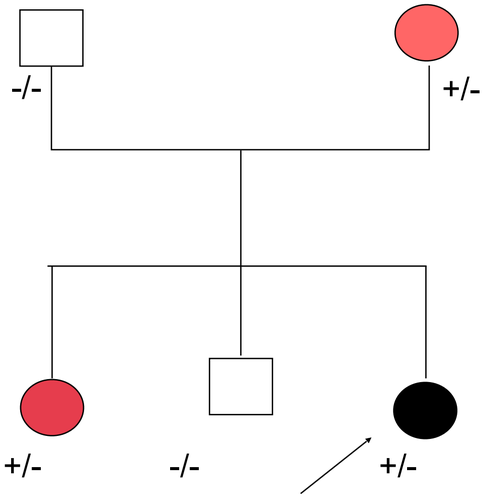
Genetic counseling : the penetrance problem



TBX4 c.1119C>G, p.Tyr373*



TBX4 c.231G>A, p.Trp77*



TBX4 c.781C>T, p.Arg261*

PAH+mutation

No PAH + mutation

Classification of pediatric PH

3 Main topics

1-Neonatal pulmonary hypertension

2-Developmental lung disorders and PH

3-Congenital heart diseases and PH/PAH

Pathogenesis of PPHN

PRENATAL FACTORS

- Maternal NSAID, SSRI use;
- Premature closure of the DA
- C-section delivery
- Post-term (> 41 weeks)
- Large for gestational age
- Abnormal placenta
- Altered lung development
- Cardiovascular abnormaliities

POSTNATAL FACTORS

- Hyperoxia/oxidative stress
- Ventilator Induced Injury
- Asphyxia
- Inflammation/Infection

Injury to the Developing Lung Circulation

Impaired Vasoreactivity

Decreased Angiogenesis

Altered Vascular Structure

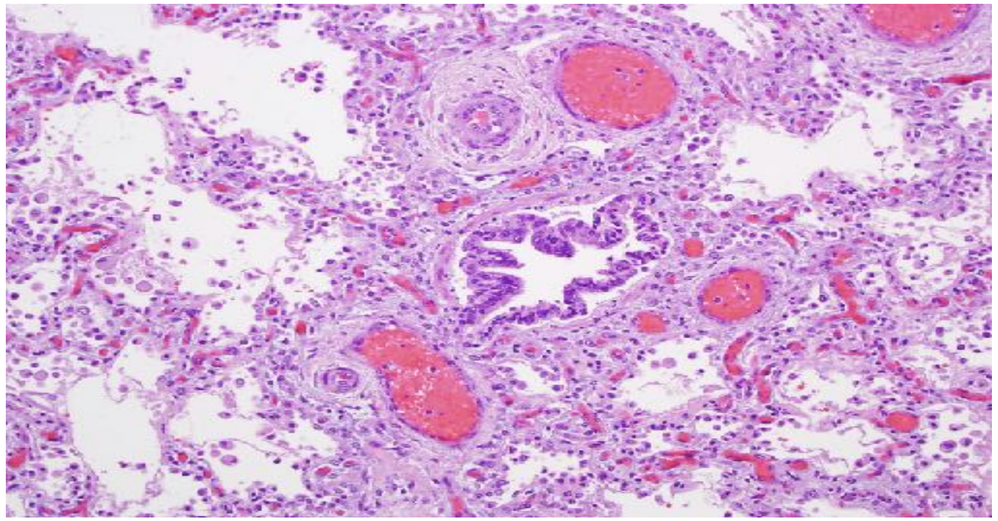
↓

<u>Persistent Pulmonary Hypertension of the Newborn</u>

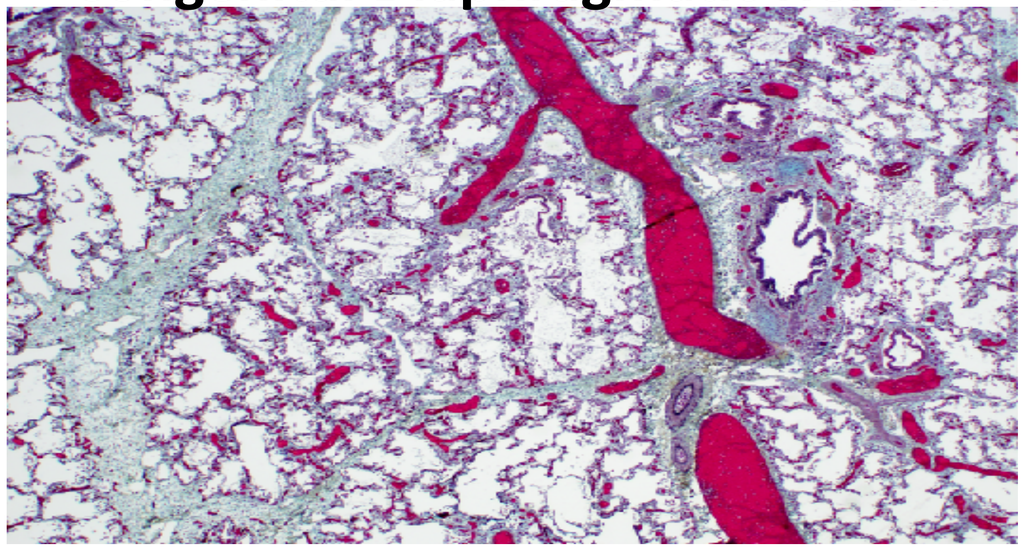
- Failure to decrease PVR at birth
- Extra-pulmonary shunting across DA, PFO
- Severe hypoxemia, Respiratory Failure

Pulmonary Vascular Disease in Developmental Lung Disorders

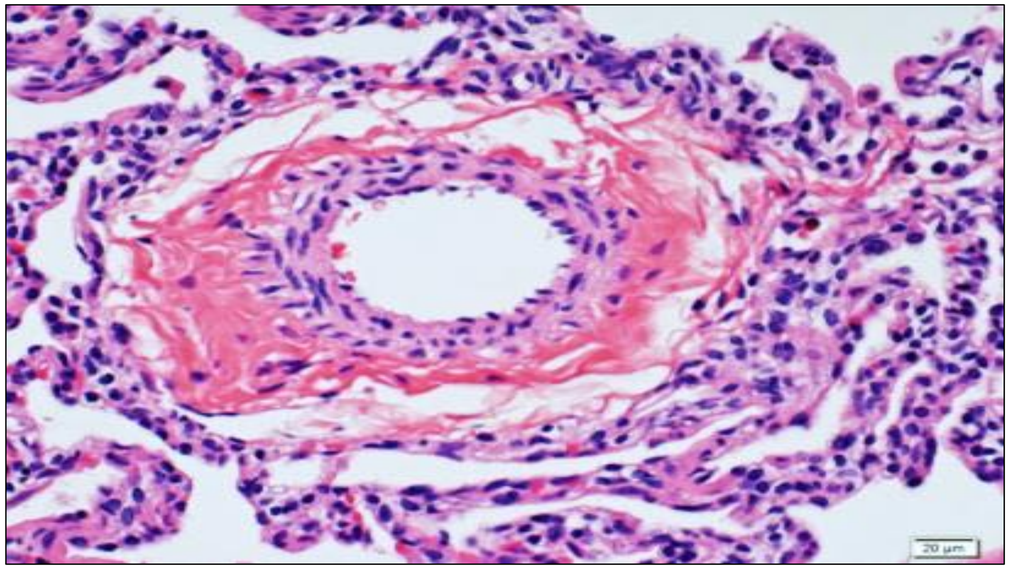
Alveolar Capillary Dysplasia



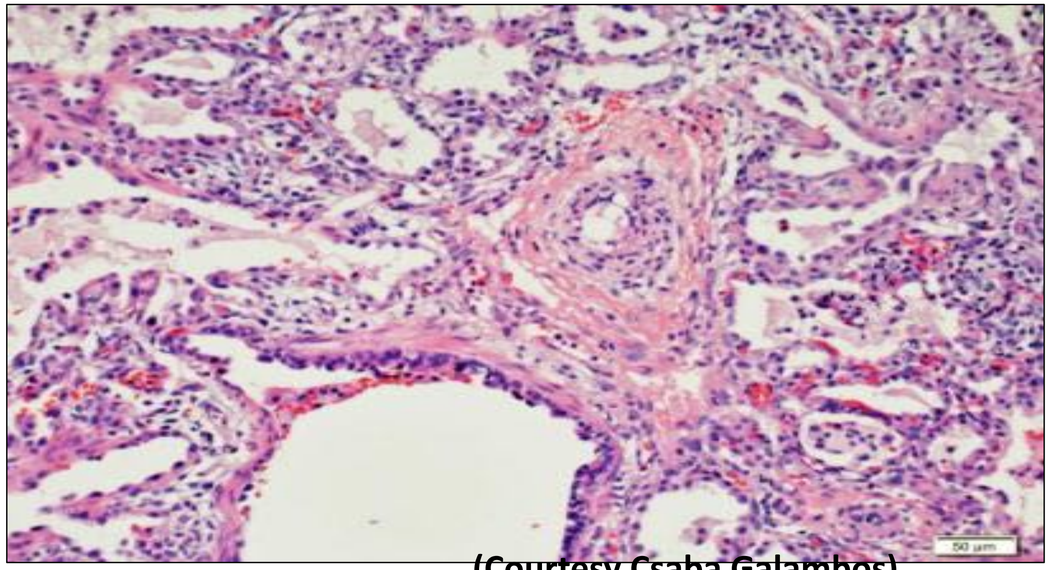
Congenital Diaphragmatic Hernia



Pulmonary Interstitial Glycogenosis

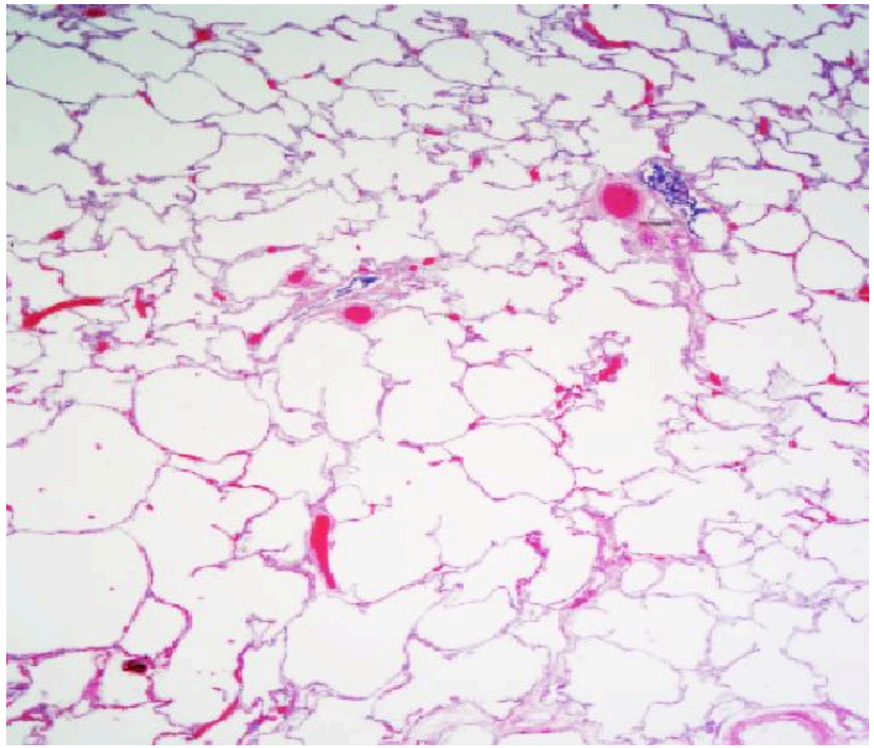


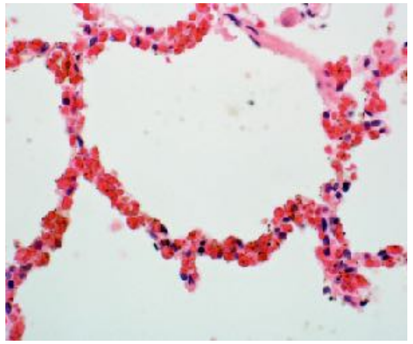
Surfactant Protein B Deficiency

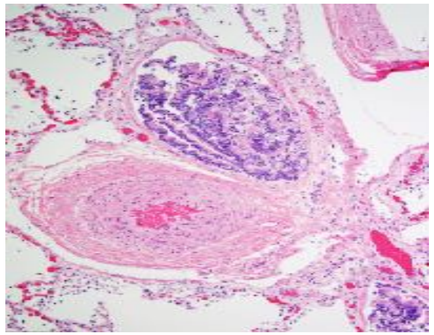


(Courtesy Csaba Galambos)

PH in Down syndrome/trisomy 21 is a developmental lung disorder







- PPHN more frequent in Down syndrome
- APAH-CHD has an earlier onset in DS

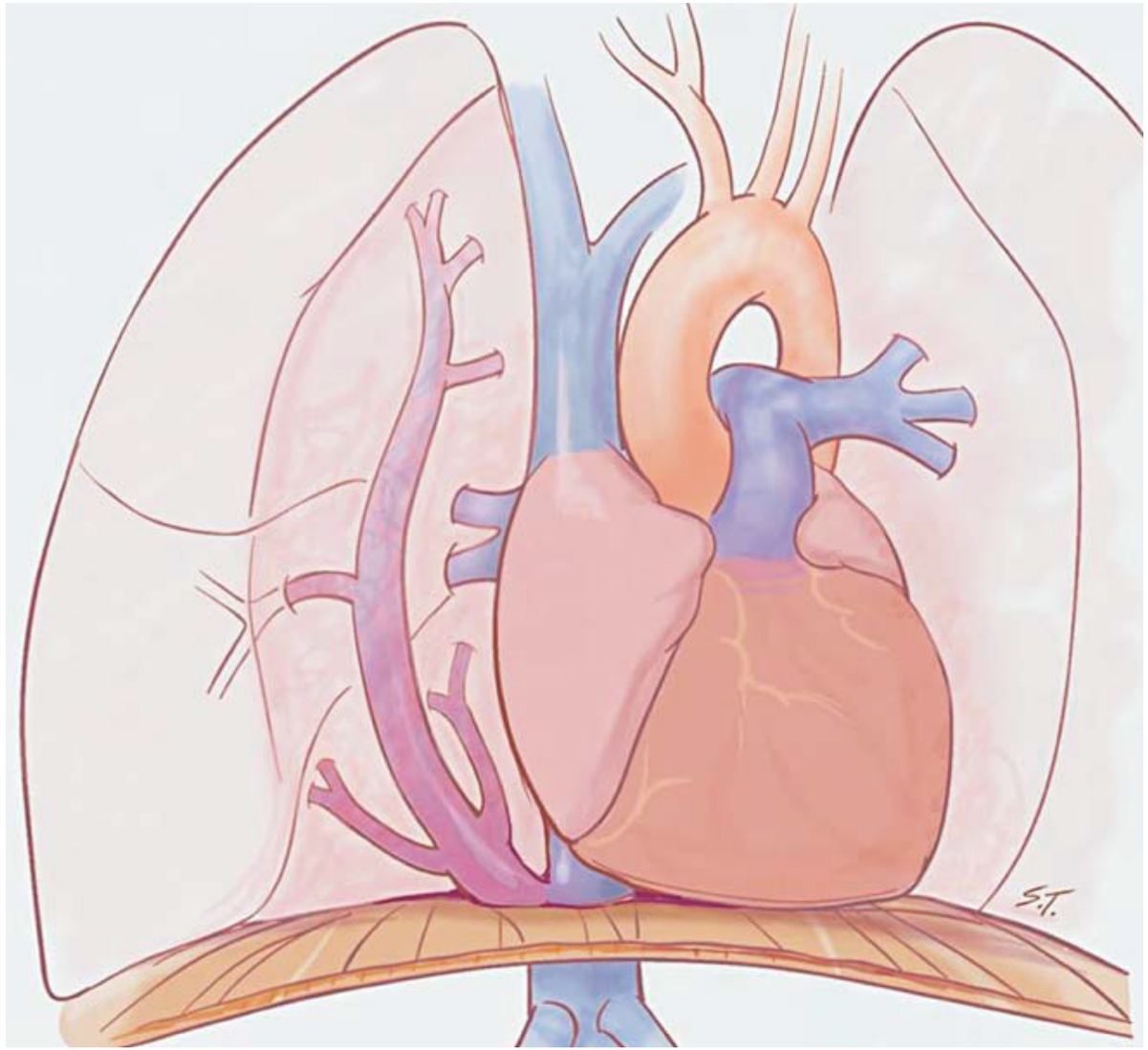
Bush D et al. J Pediatr 2017

Multifactorial pulmonary hypertension in children

Lung disease

Post-capillary PH

Systemic supply to the lung

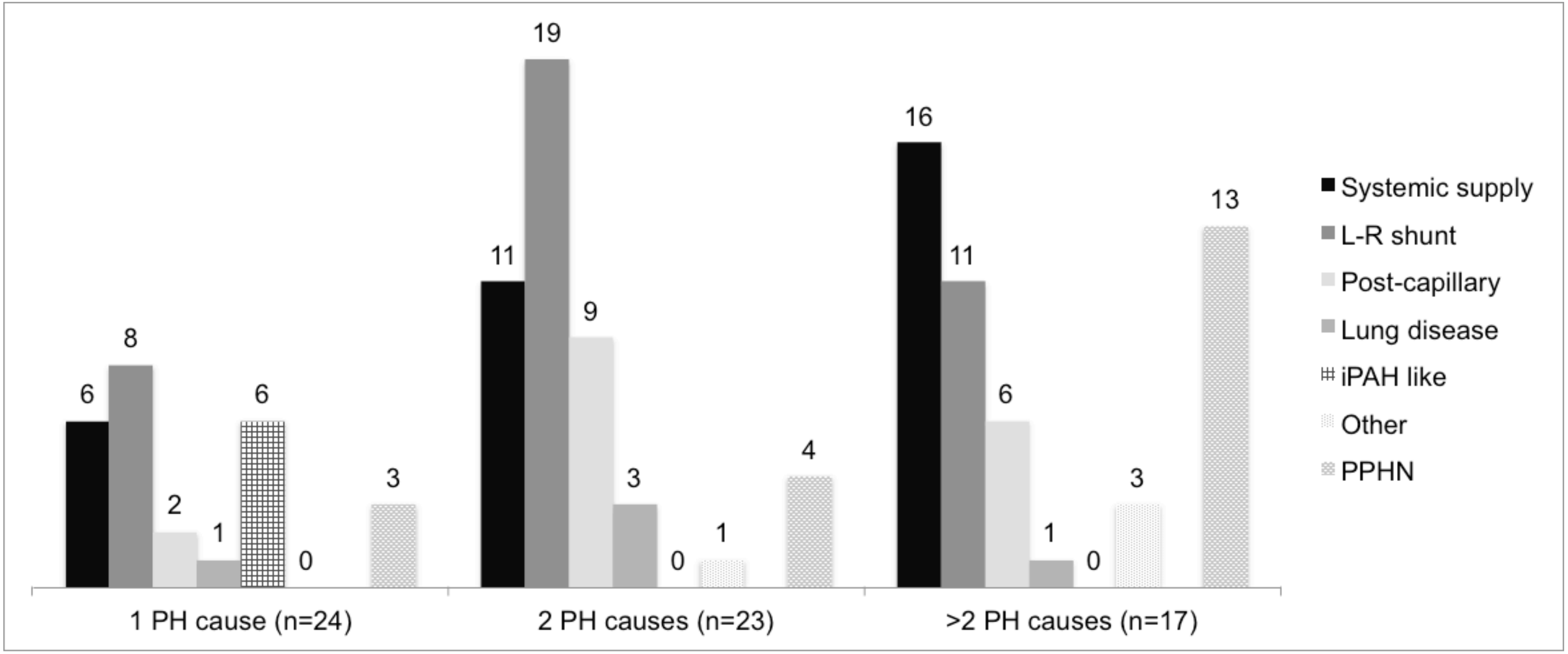


Pulmonary vascular disease /maladaptation

Left-to right shunt /CHD

Scimitar syndrome

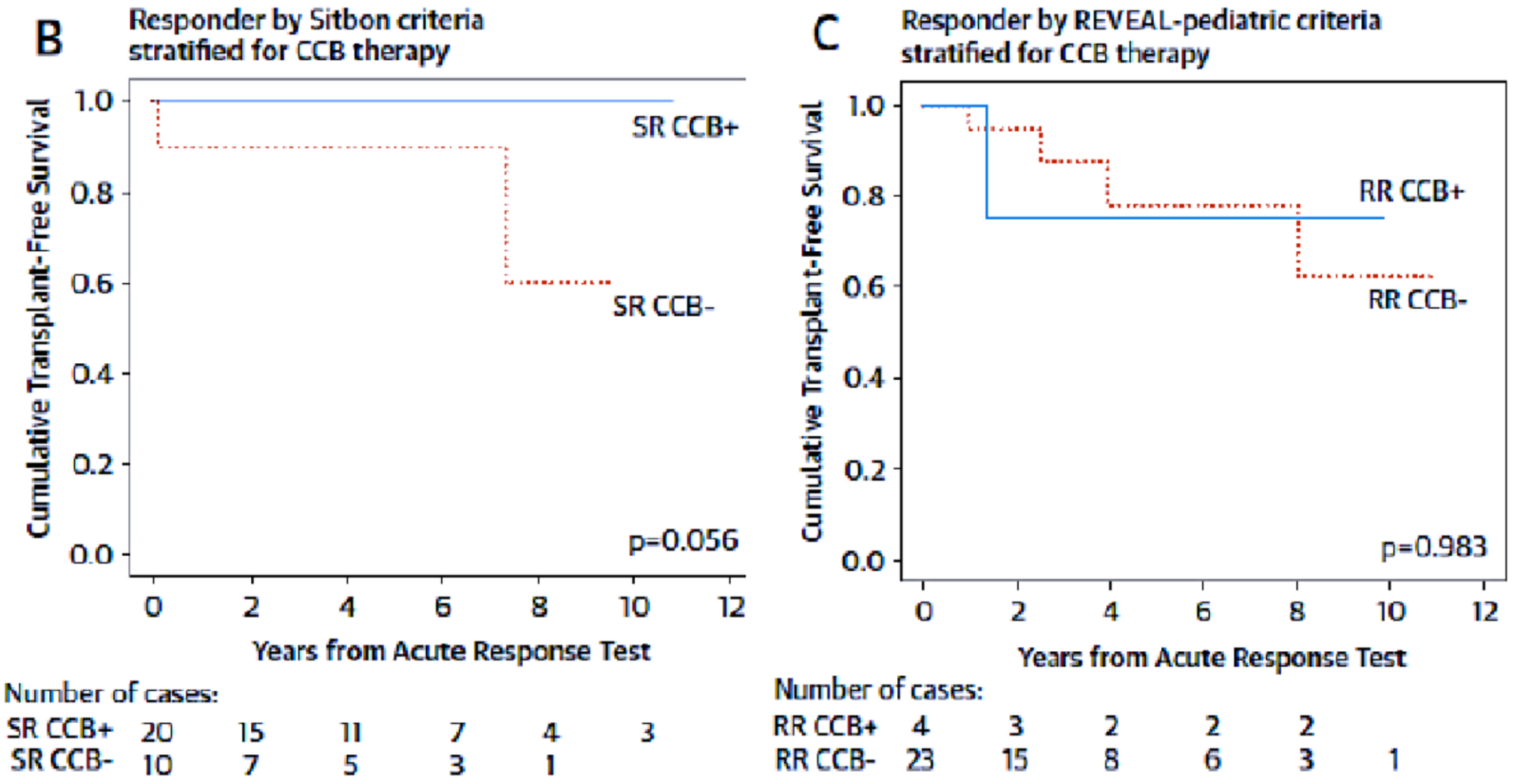
Multifactorial pulmonary hypertension in scimitar syndrome



Bonnet D et al. 2019

Treatment of pediatric PAH/PH and current challenges

1. AVT responders should receive Calcium channel blockers

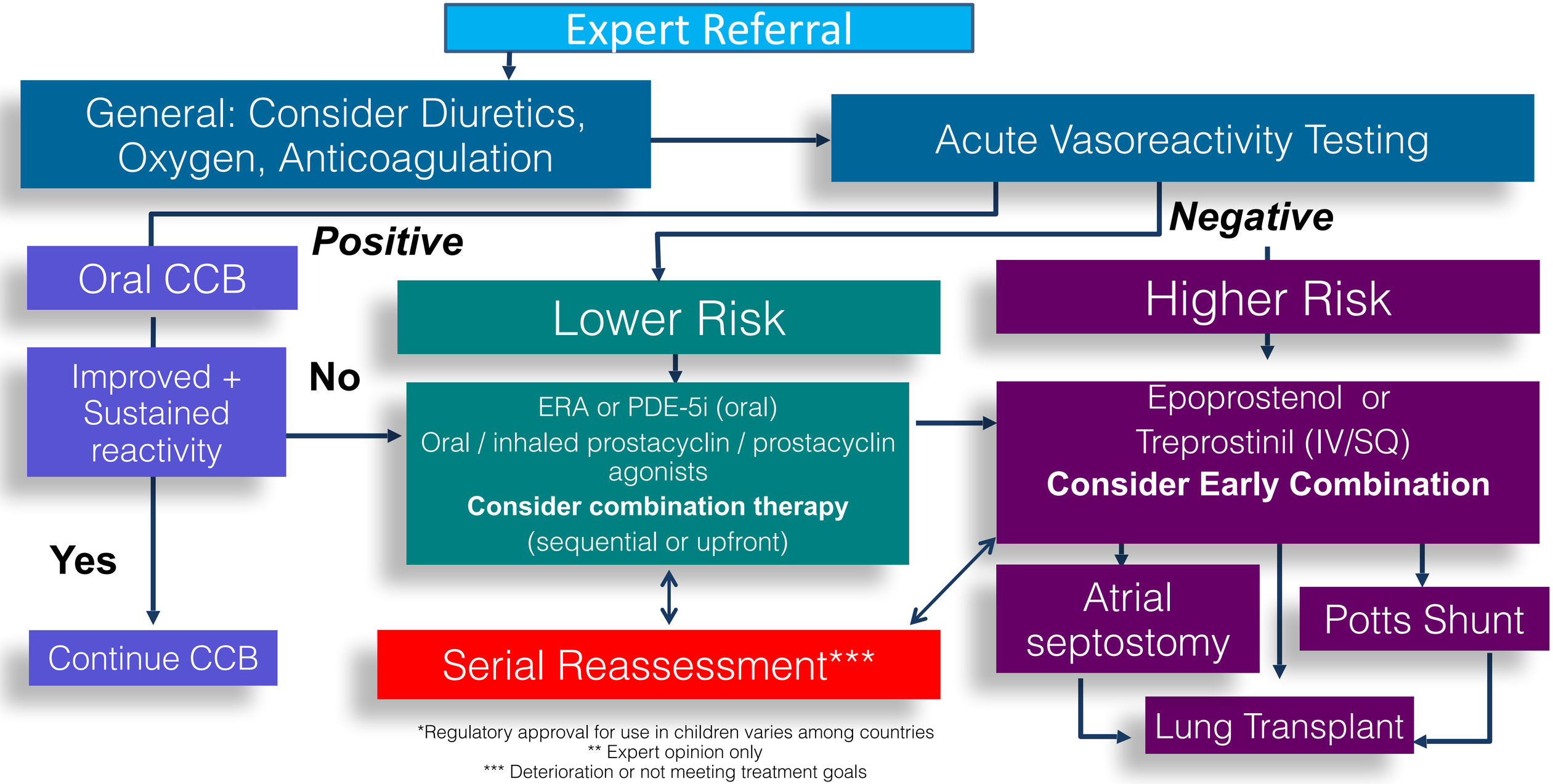


Douwes M et al. JACC 2016

Low and high risk pediatric patients with PAH

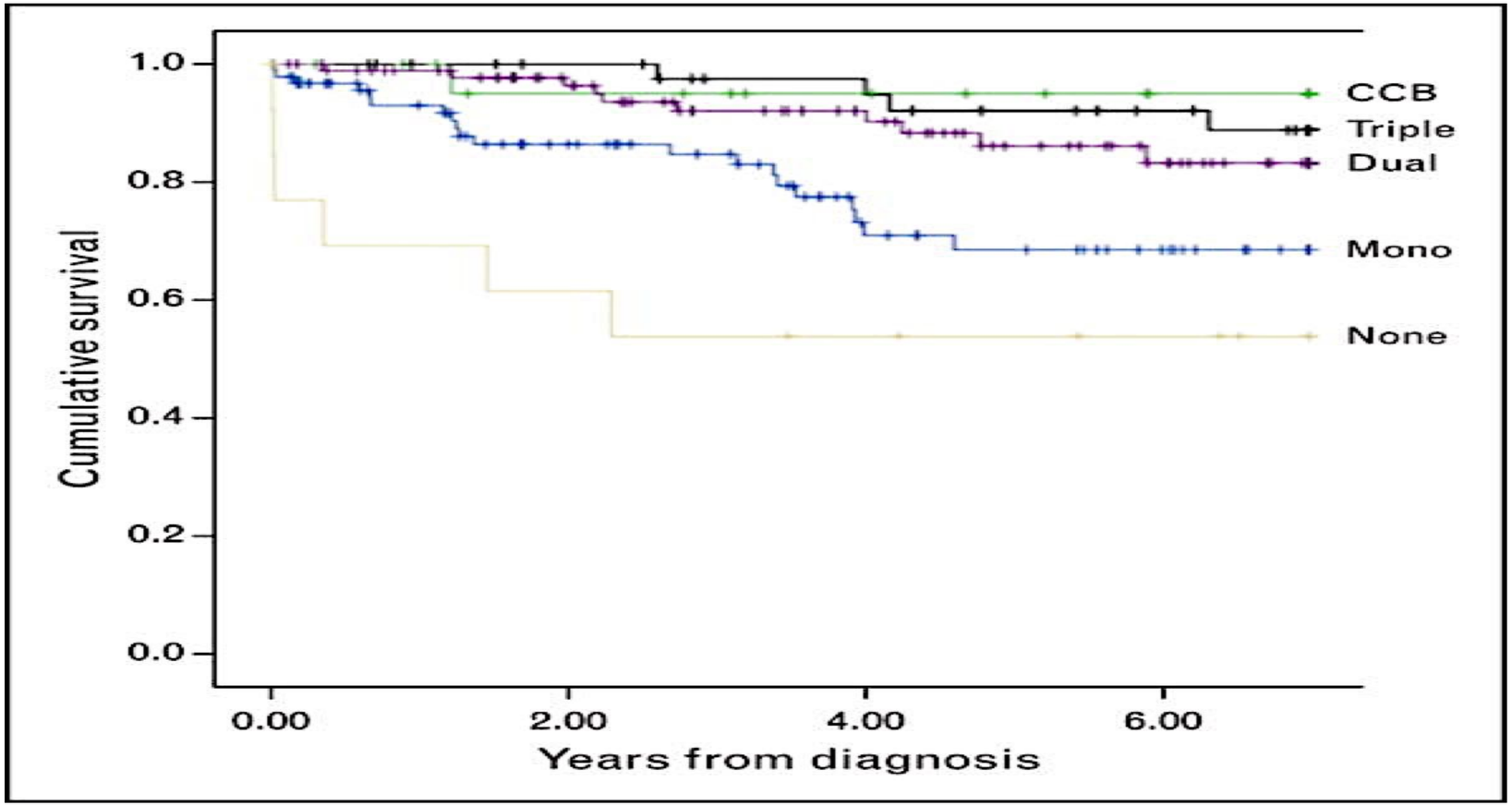
LOWER RISK	DETERMINANTS OF RISK	HIGHER RISK
No	Clinical evidence of RV failure	Yes
No	Progression of Symptoms	Yes
> 350 meters	6MWT (>7 yrs old)	< 350 meters
	Growth	Failure to thrive
I,II	WHO Functional Class	III,IV
Minimally elevated	BNP / NTproBNP	Significantly elevated Rising level
	Echocardiography	RA / RV Enlargement Reduced LV size Increased RV/LV Ratio Reduced TAPSE Low RV FAC Pericardial Effusion
Systemic CI > 3.0 L/min/m^2 Systemic venous saturation >65% + Acute Vasoreactivity	Hemodynamics	Systemic CI < 2.5 L/min/m^2 RAP > 10mmHg PVRI > 20 WU*m^2 Systemic venous saturation < 60% PACi <0.85

Pediatric IPAH/HPAH Treatment algorithm WSPH 2018



*Regulatory approval for use in children varies among countries
** Expert opinion only
*** Deterioration or not meeting treatment goals

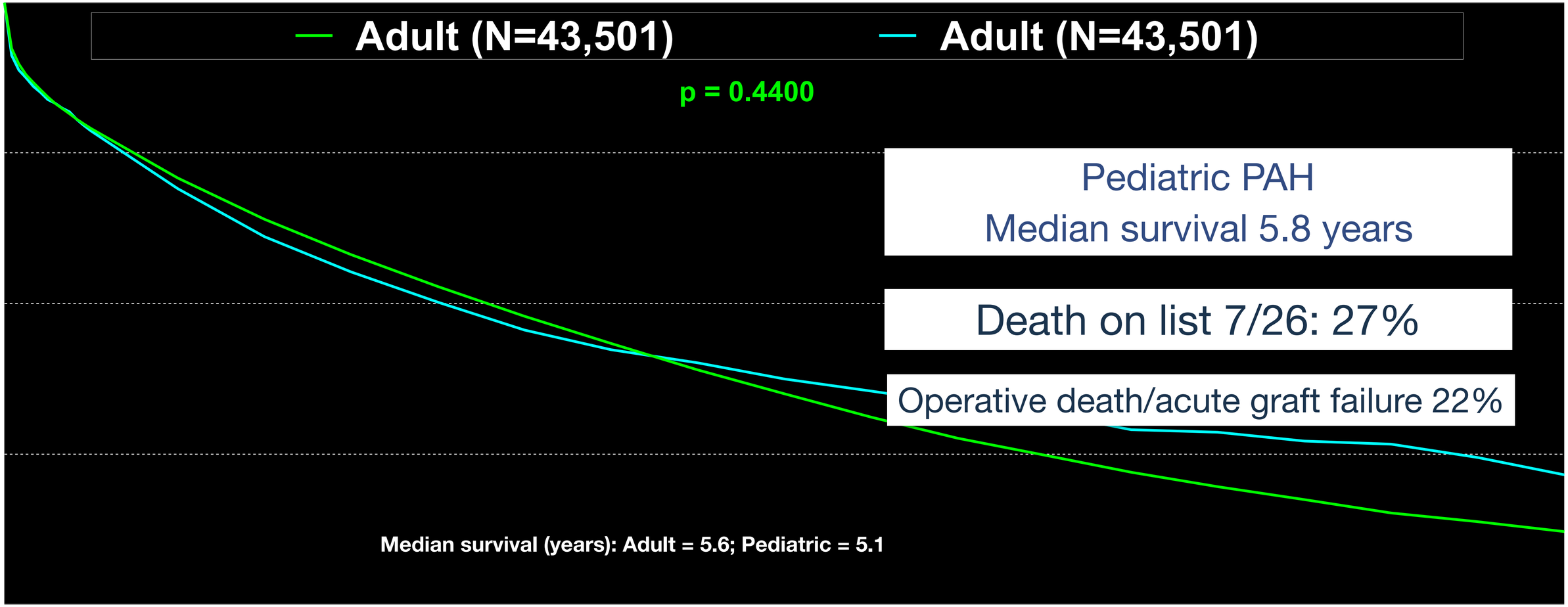
Limited evidence in RCT for this algorithm but convincing registries data



Zijlstra WMH, et al. JACC 2014

Lung transplantation in children

(Lung Transplantations: january 1990 – june 2012)



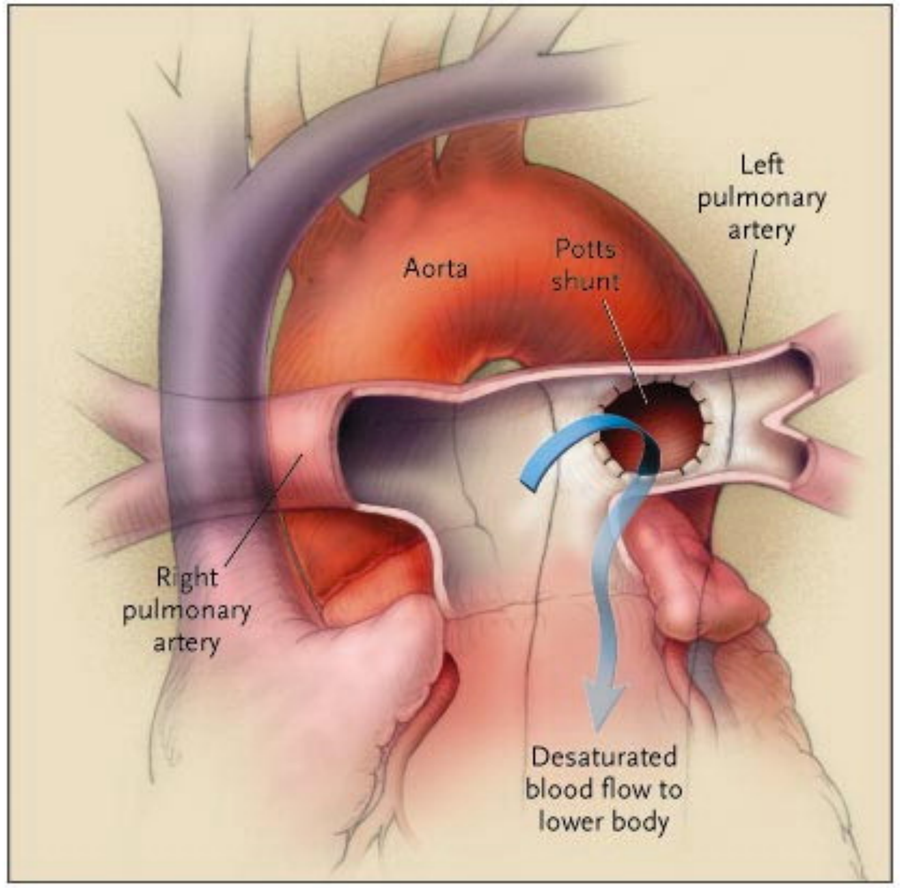
ISHLT • INTERNATIONAL SOCIETY FOR HEART AND LUNG TRANSPLANTATION

2014

JHLT. 2014 Oct; 33(10): 1025-1033

Goldstein BS et al. J Heart Lung Transplant 2011

Potts shunt in pediatric PAH



- Good long term responders
- Still high risk procedure
- Need to further define indications/ contraindications
- Registry data from PePH association

Blanc J, Vouhe P, Bonnet D. N Engl J Med. 2004 Feb 5;350(6):623

Predictor of outcome

1-is measured at baseline
2-its initial value predicts « hard » outcomes (death, transplantation)

Therapeutic target

1-baseline values correlate with outcome
2-is in the pathway of the disease
3-treatment induces changes in the surrogate value
4-changes in the surrogate value modifies outcome

Therapeutic trial endpoint

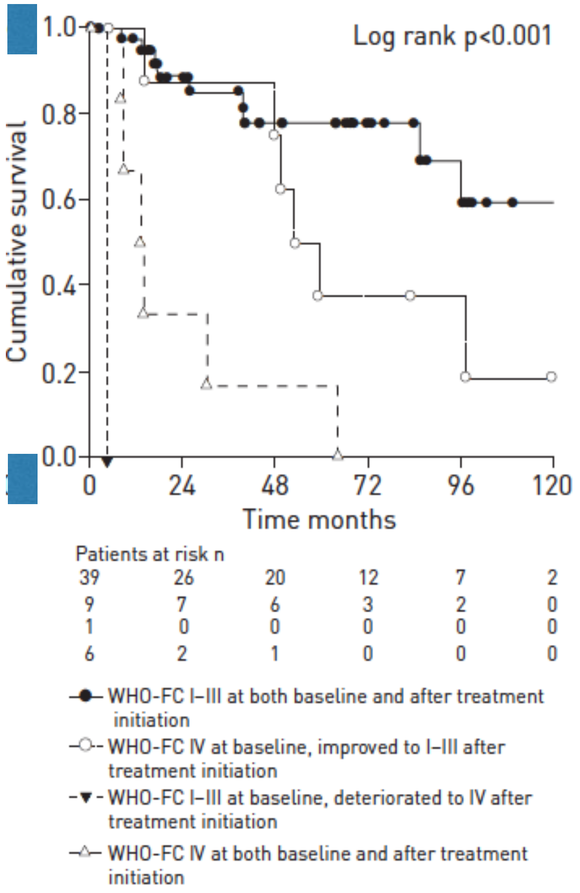
1-Measure of how the patient behaves, feels, survives
2-Measuring the endpoint should do no/limited harm

What is the path to demonstrate efficacy of a new compound in pediatric PAH ?

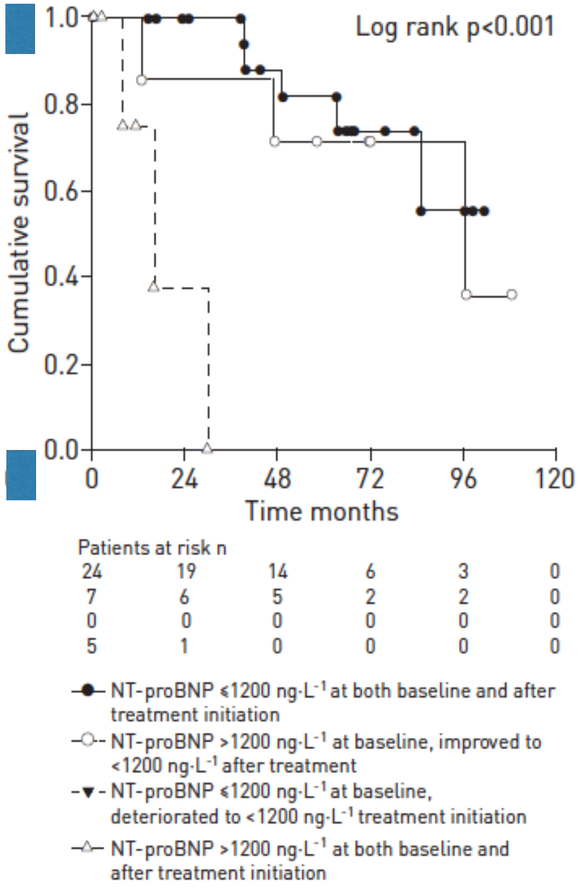


Treatment Goals in Pediatric PAH

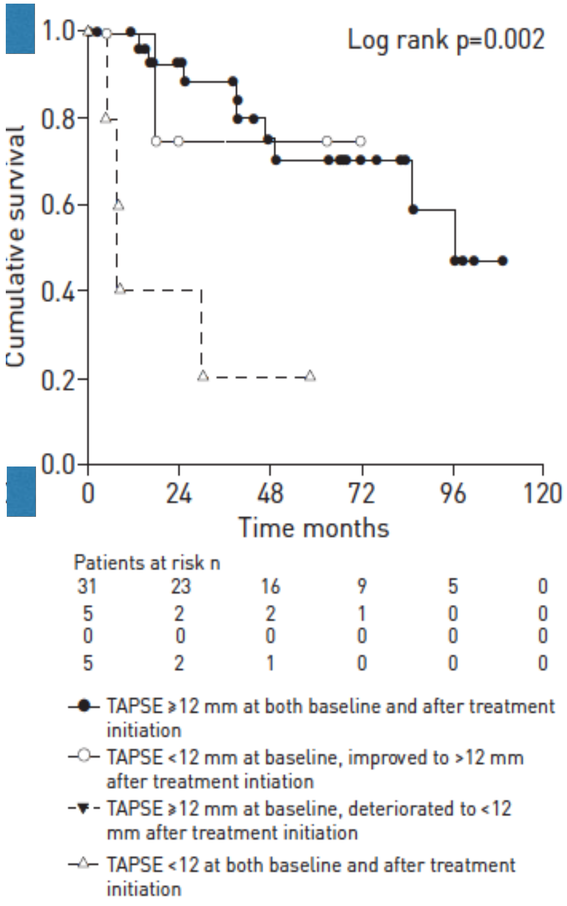
WHO-FC



NT-pro-BNP

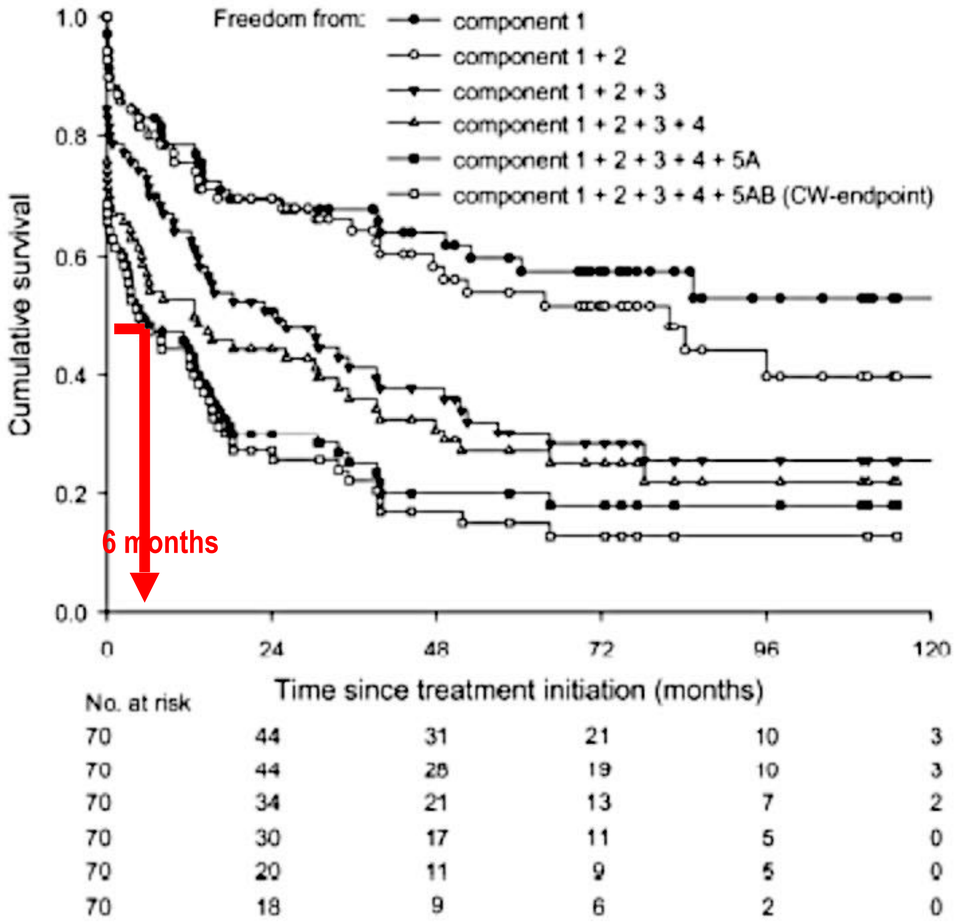


TAPSE



Ploegstra MJ et al. Eur Resp J 2015

Clinical worsening as composite study endpoint in pediatric PAH



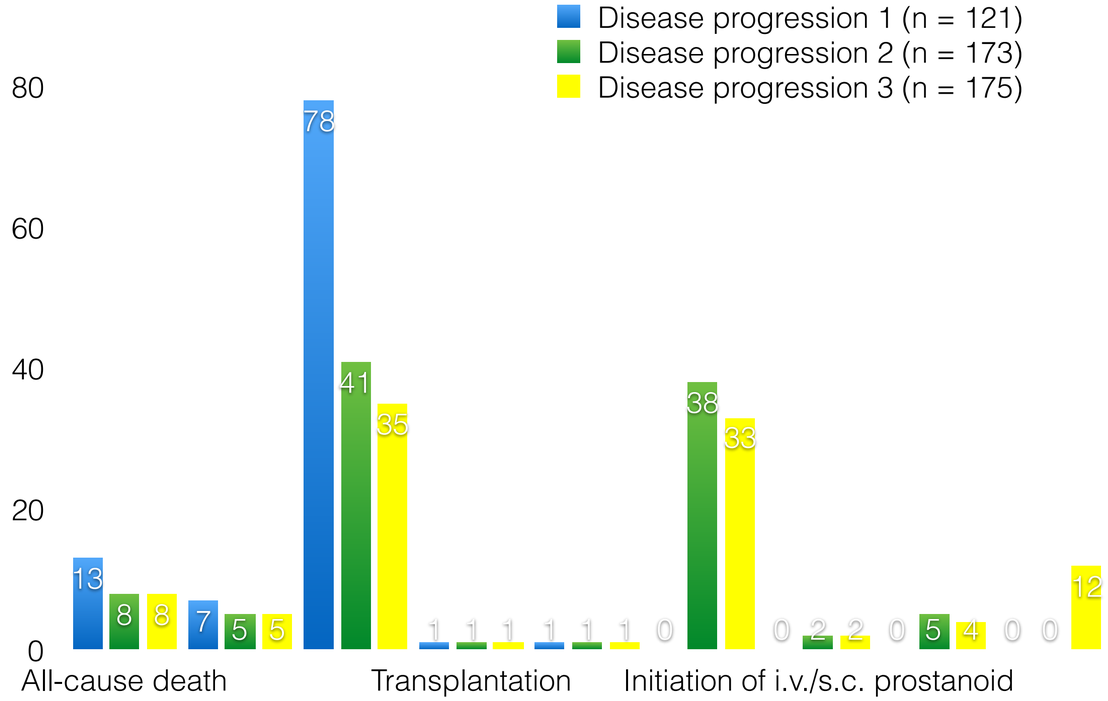
Event-free survival of 6 endpoint combinations
Only the first occurrence of endpoint components are incorporated as events

Component 1 = death
Component 2 = lung-transplantation
Component 3 = non-elective PAH-related hospitalization
Component 4 = initiation of intravenous prostanoid
Component 5A = functional deterioration (defined as worsening of WHO-FC only)
Component 5AB = functional deterioration (defined as worsening of WHO FC
and/or ≥ 15 % decrease in 6-MWD)
CW-endpoint = Full composite clinical worsening endpoint consisting of death, lung-transplantation, non-elective PAH related hospitalization, initiation of intravenous prostanoids and functional deterioration.

Ploegstra MJ et al. Eur Respir J 2015.

Disease progression composite outcomes and the first occurring events within these outcomes

	Disease progression 1	Disease progression 2 (*n*	Disease progression 3
Number of	121	173	175
Person–years	524.7	396.5	377.6
Rate (95% CI)	23.1 (19.3, 27.6)	43.6 (37.6, 50.6)	46.3 (40.0, 53.7)
	Death (all-cause)	Death (all-cause)	Death (all-cause)
	PAH related	PAH related	PAH related
	Lung transplantation	Lung transplantation	Lung transplantation
	Atrial septostomy	Atrial septostomy	Atrial septostomy
		WHO FC deterioration†	WHO FC deterioration†
		Initiation of i.v. / s.c. prostanoids	Initiation of i.v. / s.c. prostanoids
		Syncope	Syncope
			PAH worsening



Association for Paediatric pulmonary hypertension
*Increased right heart failure, haemoptysis; †Increase ≥1 WHO FC

Beghetti M, *et al.* Int J Cardiol 2019

Designing RCT in pediatrics

- Common approach among regulators (requirements for approval)
- Consensus on acceptable clinical endpoints (physicians/regulators)
- Use of targeted PAH therapy that does not have established benefit should not cause lack of equipose
- Extrapolation opportunities: adult PAH -> pediatric PAH
- Novel trial design / analysis: composite with ranked analysis
- Potential clinically meaningful endpoints: TTCW, PROs, Functional Activity measurements (WHO-FC, 6MWD, Accelerometry)
- Potential surrogates : NT-pro-BNP; Not invasive hemodynamics (risk); Imaging biomarkers

Conclusions

- Approval and development of PAH treatment in children : drugs, strategies
- Identification of a genetic profile slightly different from that of adults
- Registry data have grown substantially and inform for future trial design
- Pediatric specific trials are ongoing but new concepts should be developed to succeed
- A growing number of children transition to adult centers and this should be anticipated