12 Pediatric PH

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9.	Usha Raj	*Chicago IL*	*USA*	*usharaj@uic.edu*	
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Recent Advances in the Diagnosis and Medical Management of Children with Chronic Pulmonary Hypertension

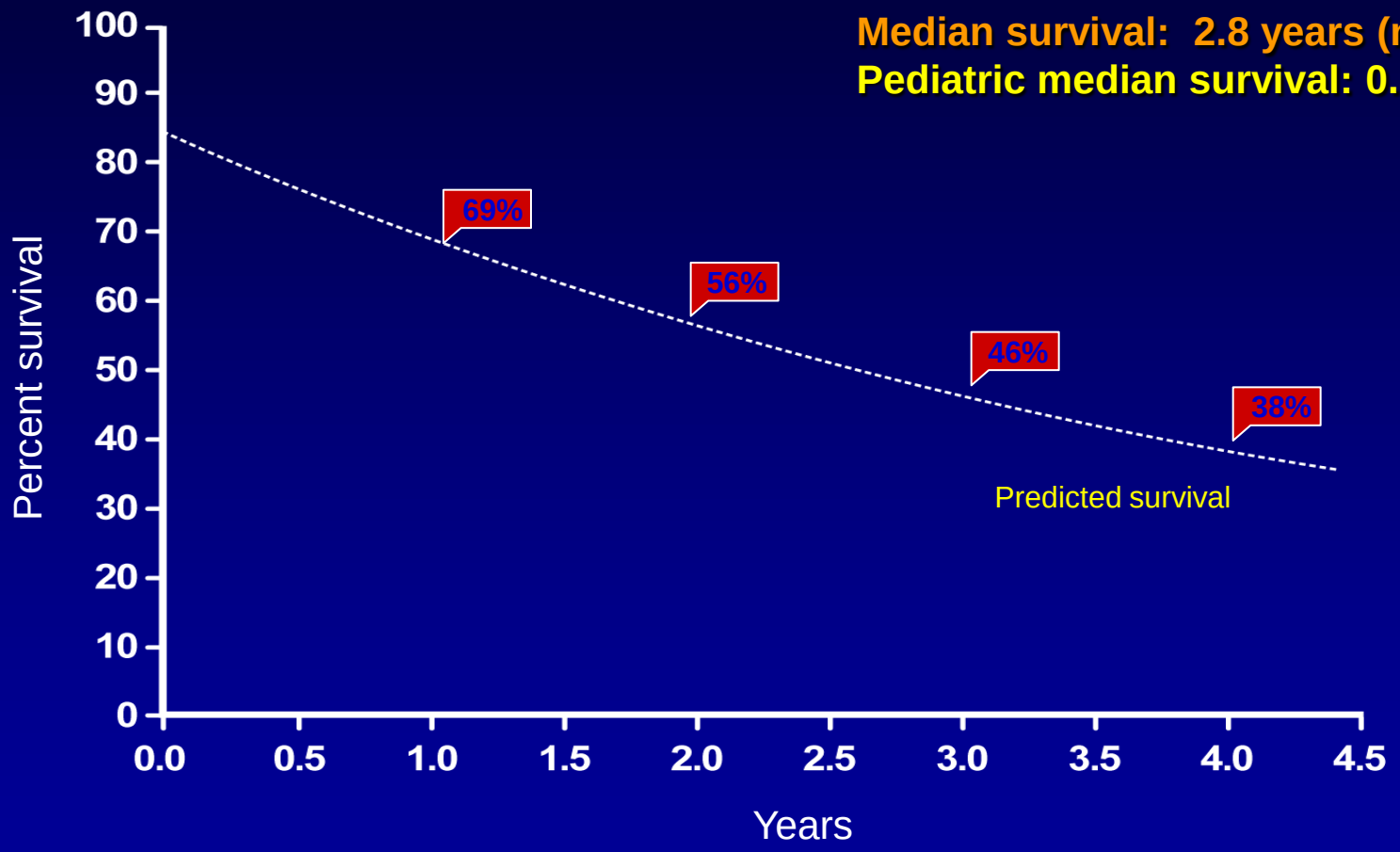
Dunbar Ivy, MD

Children's Hospital Colorado

Disclosures

- The University of Colorado contracts with Actelion, Gilead, Pfizer, United Therapeutics for Dr Ivy to be a consultant
- Investigator Initiated grants: Gilead
- Steering Committee: GSK / Actelion

Natural History of IPAH: NIH Registry[1,2]



NIH = National Institutes of Health.

Predicted survival according to the NIH equation. Predicted survival rates were 69%, 56%, 46%, and 38% at 1, 2, 3, and 4 years, respectively. The numbers of patients at risk were 231, 149, 82, and 10 at 1, 2, 3, and 4 years, respectively. *Patients with primary pulmonary hypertension, now referred to as idiopathic pulmonary hypertension.

Rich et al. *Ann Intern Med*. 1987;107:216-223. **2.** D'Alonzo et al. *Ann Intern Med*. 1991;115:343-349.

Pulmonary Hypertension

Definition and Classification

Pulmonary Arterial Hypertension

- Sustained elevation of mean pulmonary arterial pressure to > 25 mm Hg, with a mean pulmonary capillary and left atrial pressure < 15 mm Hg at rest
  - Pulmonary Vascular resistance > 3 Units X m^2

Simonneau G, et al. *J Am Coll Cardiol* 2009;54:S43-S54

Classification of PH: Dana Point 2008

1.Pulmonary Arterial Hypertension
- **1.1 Idiopathic PAH**
- **1.2 Heritable PAH**
- **1.2.1. BMPR2**
- **1.2.2. ALK-1,endoglin (with or without HHT)**
- **1.2.3 Unknown**
- **1.3 Drugs and toxins induced**
- **1.4 Associated with:**
- **1.4.1. Connective Tissue Diseases**
- **1.4.2 HIV infection**
- **1.4.3 Portal Hypertension**
- **1.4.4 Congenital Heart Diseases**
- **1.4.5 Schistosomiasis**
- **1.4.6 Chronic Haemolytic Anemia**
- **1.5 PPHN**

1' Pulmonary Veno Occlusive Disease and/or Pulmonary Capillary Hemangiomatosis

2. Pulmonary Hypertension Due to Left Heart Disease
- **2.1 Left Ventricular Systolic Dysfunction**
- **2.2 Left Ventricular Diastolic Dysfunction**
- **2.3 Valvular disease**

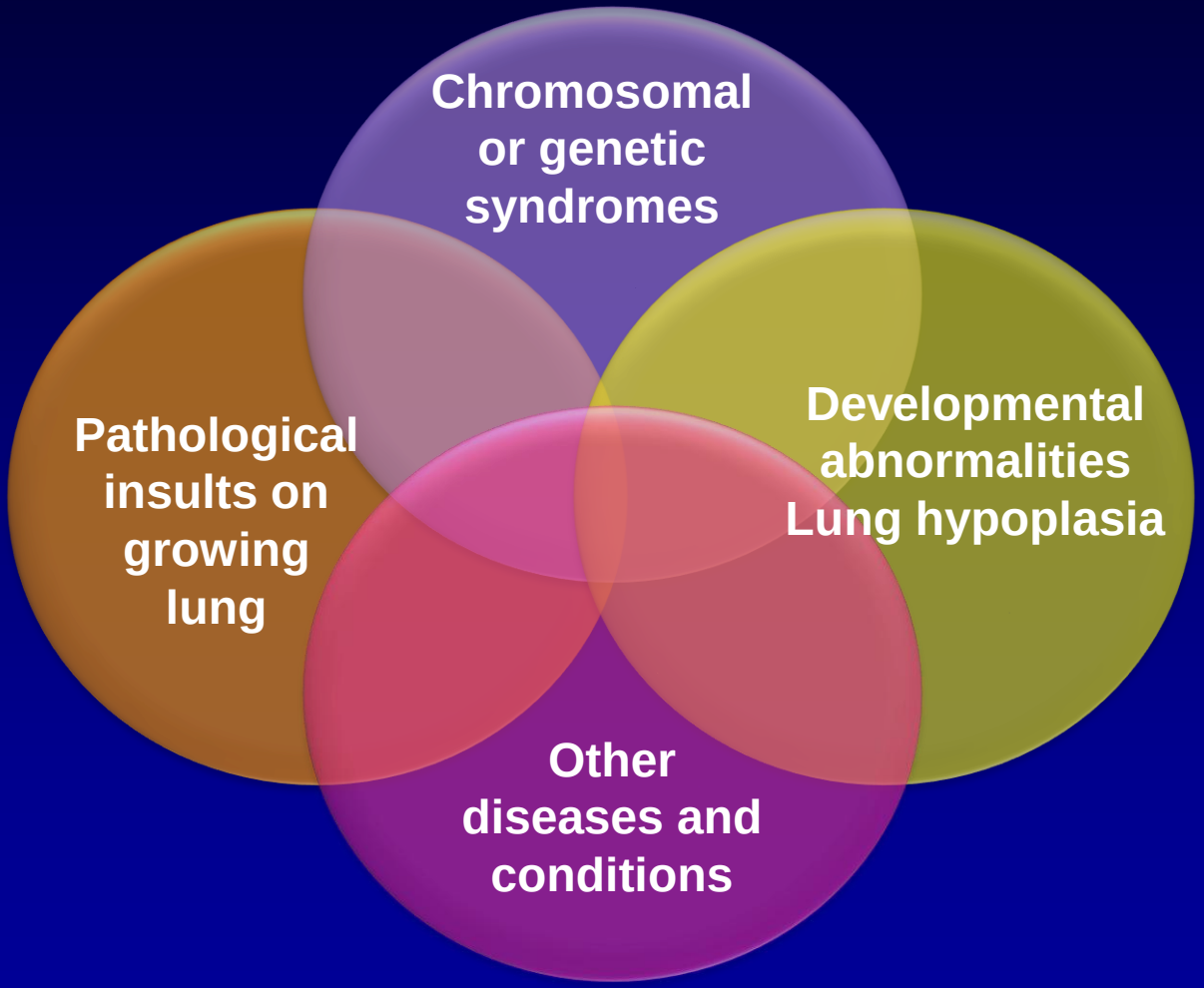
3.Pulmonary Hypertension Due to Lung Diseases and/or Hypoxia
- **3.1 Chronic obstructive pulmonary disease**
- **3.2 Interstitial lung disease**
- **3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern**
- **3.4 Sleep-disordered breathing**
- **3.5 Alveolar hypoventilation disorders**
- **3.6 Chronic exposure to high altitude**
- **3.7 Developmental abnormalities**

4.Chronic Thromboembolic Pulmonary Hypertension

5.Pulmonary Hypertension with Unclear Multifactorial Mechanisms
- **5.1 .Hematologic disorders: Myeloproliferative disorders splenectomy.**
- **5.2 Systemic disorders, Sarcoidosis, pulmonary Langerhans cell histiocytosis, Lymphangioleiomyomatosis, neurofibromatosis, vasculatis**
- **5.3 Metabolic disorders: Glycogen storage disease, Gaucher disease, thyroid disorders**
- **5.4 Others: Tumoral obstruction, fibrosing mediastinitis, chronic renal failure on dialysis**

Simonneau G, et al. *J Am Coll Cardiol* 2009;54:S43-S54

Multifactorial Causes of Pediatric Pulmonary Hypertensive Vascular Disease



Del Cerro, Abman, Diaz, Freudenthal, Harikrishnan, Ivy, Stenmark, Adatia.
***Pulm Circ*. 2011;1:286-298.**

The broad schema of 10 basic categories of Pediatric Pulmonary Hypertensive Vascular Disease

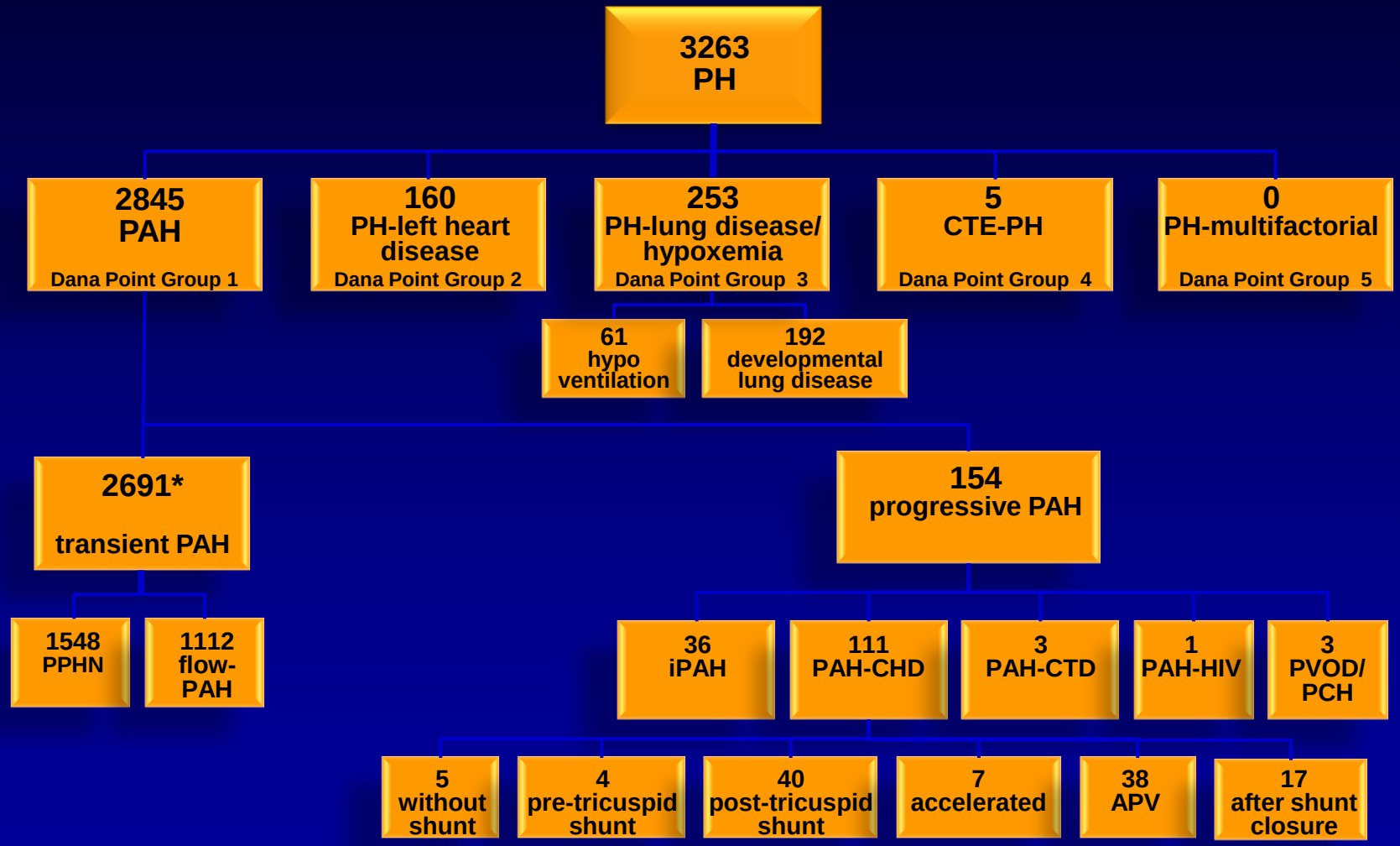
1. Prenatal or developmental pulmonary hypertensive vascular disease
2. Perinatal pulmonary vascular maladaptation
3. Pediatric cardiovascular disease
4. Bronchopulmonary dysplasia
5. Isolated pediatric pulmonary hypertensive vascular disease (isolated pediatric PAH)
6. Multifactorial pulmonary hypertensive vascular disease in congenital malformation syndromes
7. Pediatric lung disease
8. Pediatric thromboembolic disease
9. Pediatric hypobaric hypoxic exposure
10. Pediatric pulmonary vascular disease associated with other system disorders

Del Cerro, Abman, Diaz, Freudenthal, Harikrishnan, Ivy, Stenmark, Adatia.
***Pulm Circ*. 2011;1:286-298.**

Pulmonary Hypertension

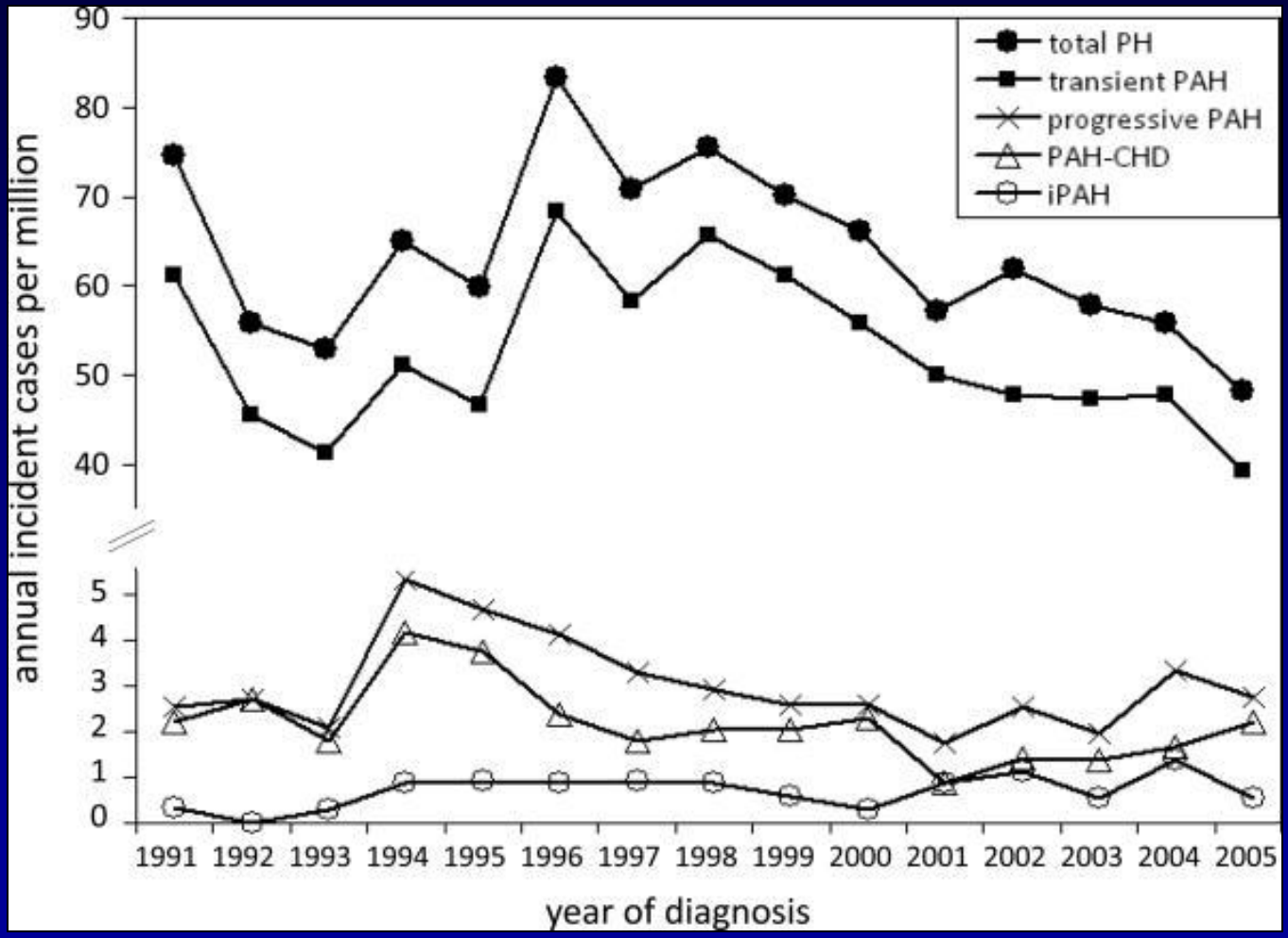
Epidemiology

Classification of Pediatric PH In Combined Netherlands Cohorts: 1991 - 2005



Van Loon et al. *Circulation*. 2011;124:1755-1764.

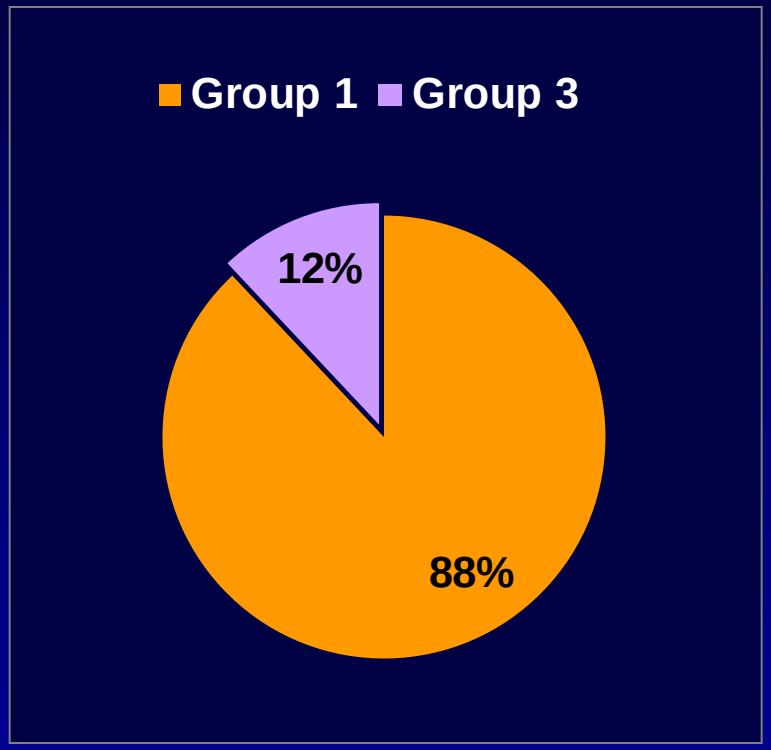
Incidence of Pediatric PH In Combined Netherlands Cohorts: 1991 - 2005



Van Loon et al. *Circulation*. 2011;124:1755-1764.

Global TOPP Registry: Group 3 PH In Pediatric Patients

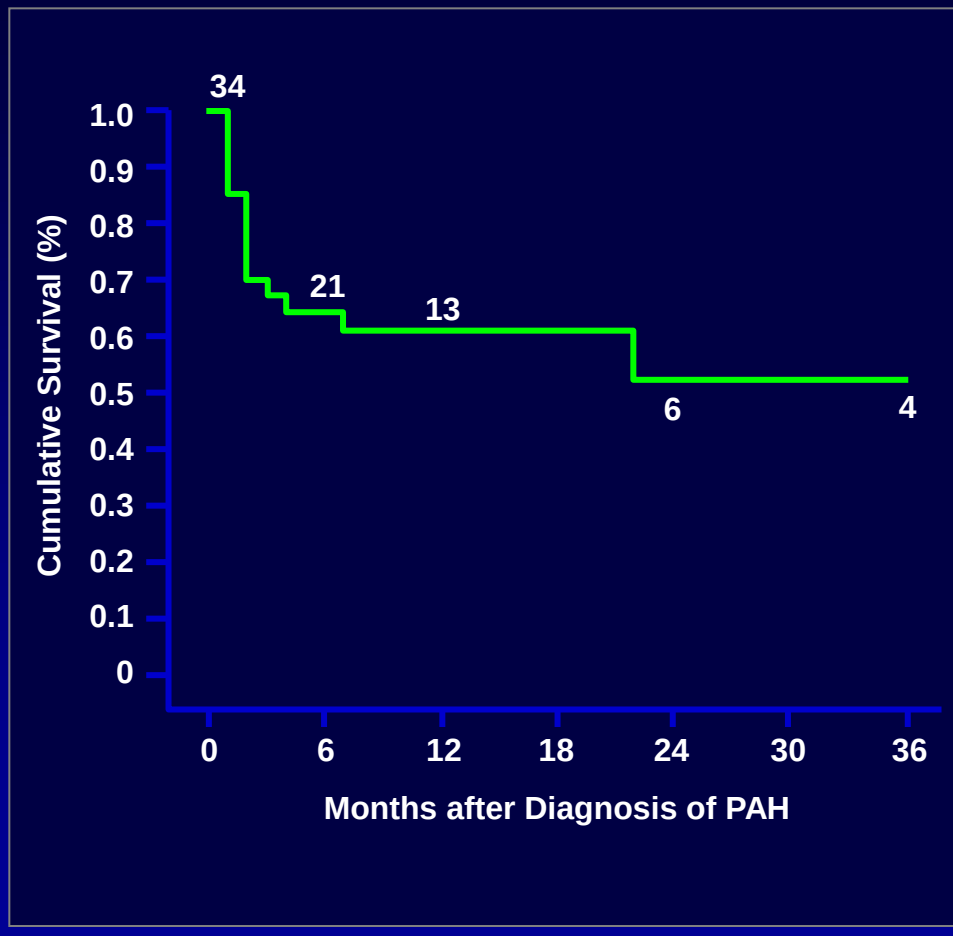
- Most-common Group 3 diagnoses
  - Bronchopulmonary Dysplasia (26%)
  - Interstitial Lung Disease (24%)
- Chromosomal abnormalities, e.g. trisomy 21, reported in 13%

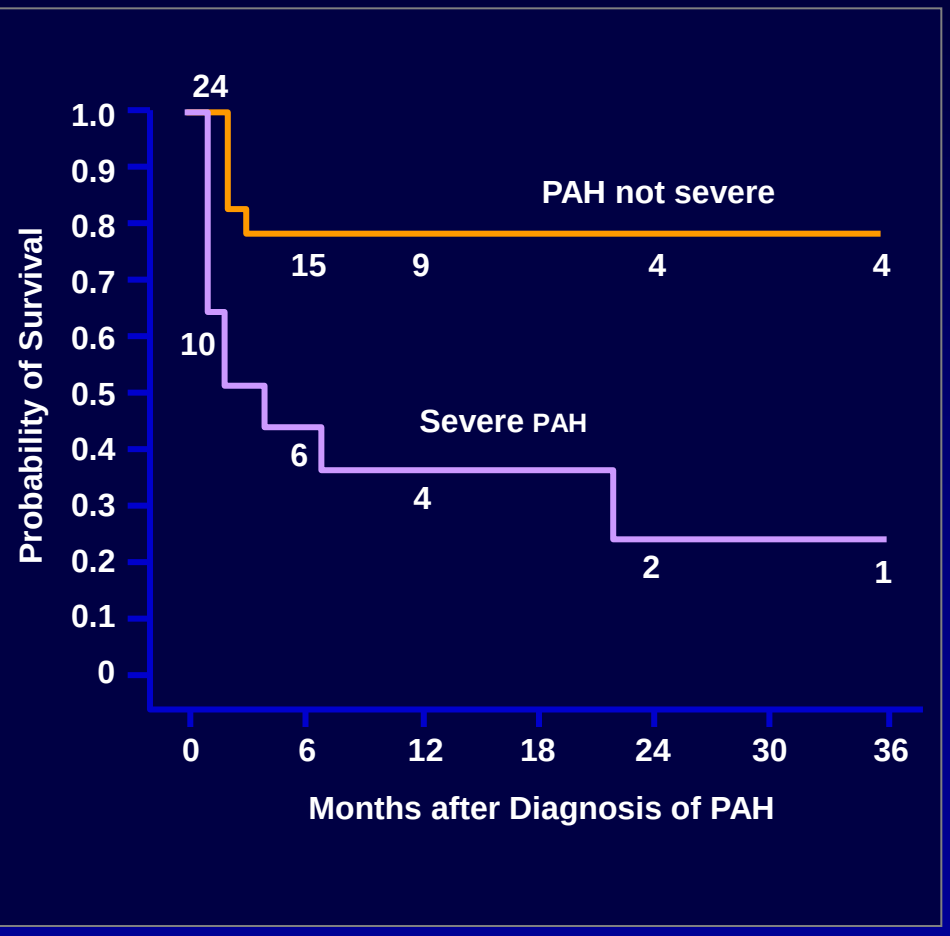


N=456 children with confirmed PH diagnosed between January 2008 and February 2010 from 31 centers in 20 countries.

Berger RM, et al. *Lancet*. 2012; 379: 537–46

Survival in BPD-related PH





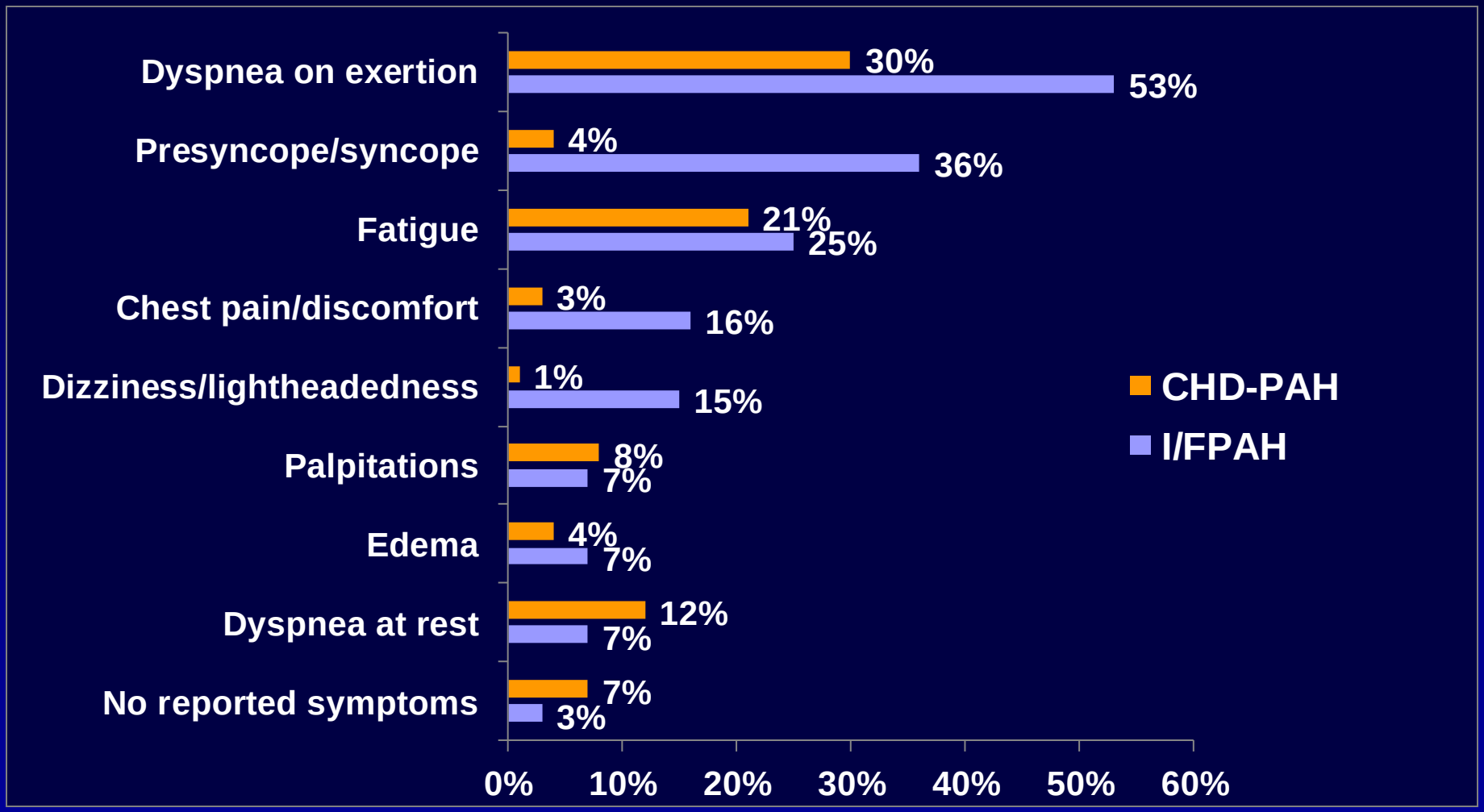
N=42 premature infants with BPD-related PAH

Khemani E, et al. *Pediatrics*. 2007;120;1260-1269.

Pulmonary Arterial Hypertension

Diagnosis

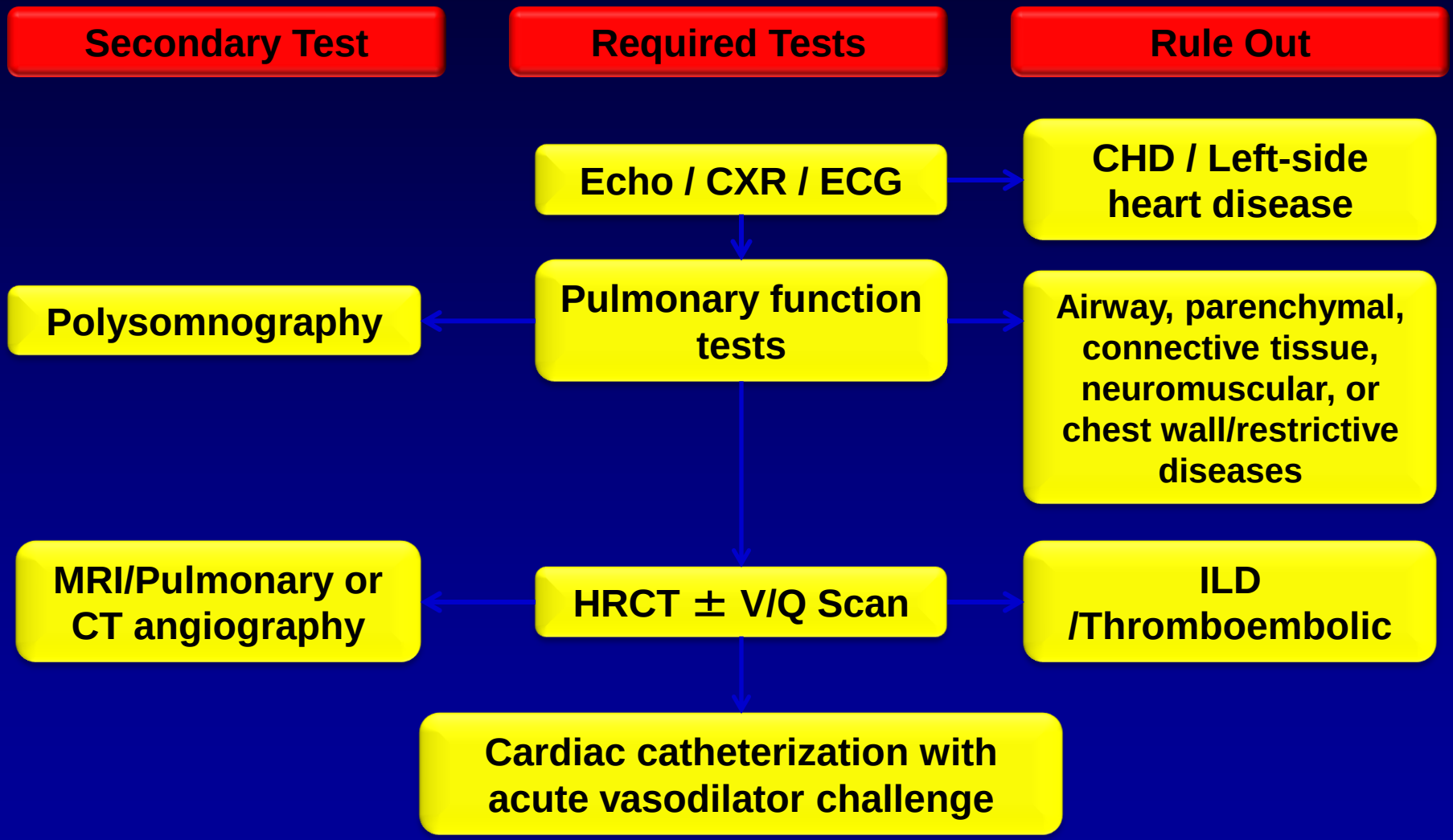
I/FPAH vs APAH-CHD Pediatric PH Presenting Symptoms: REVEAL



N=199.

Barst, McGoon, Elliott, Foreman, Miller, Ivy. *Circulation*. 2012;125:113-122.

Screening/Diagnostic Algorithm For Pediatric PH/PAH



Adapted from Barst RJ, et al. *Eur Respir J*. 2011;37:665-677.

Screening/Diagnostic Algorithm For Pediatric PH/PAH: Associated Tests

Causative or exacerbating associated conditions

- Connective tissue disease
- HIV
- Hypercoagulability
- Liver disease
- Sickle cell disease

Disease severity / Stage

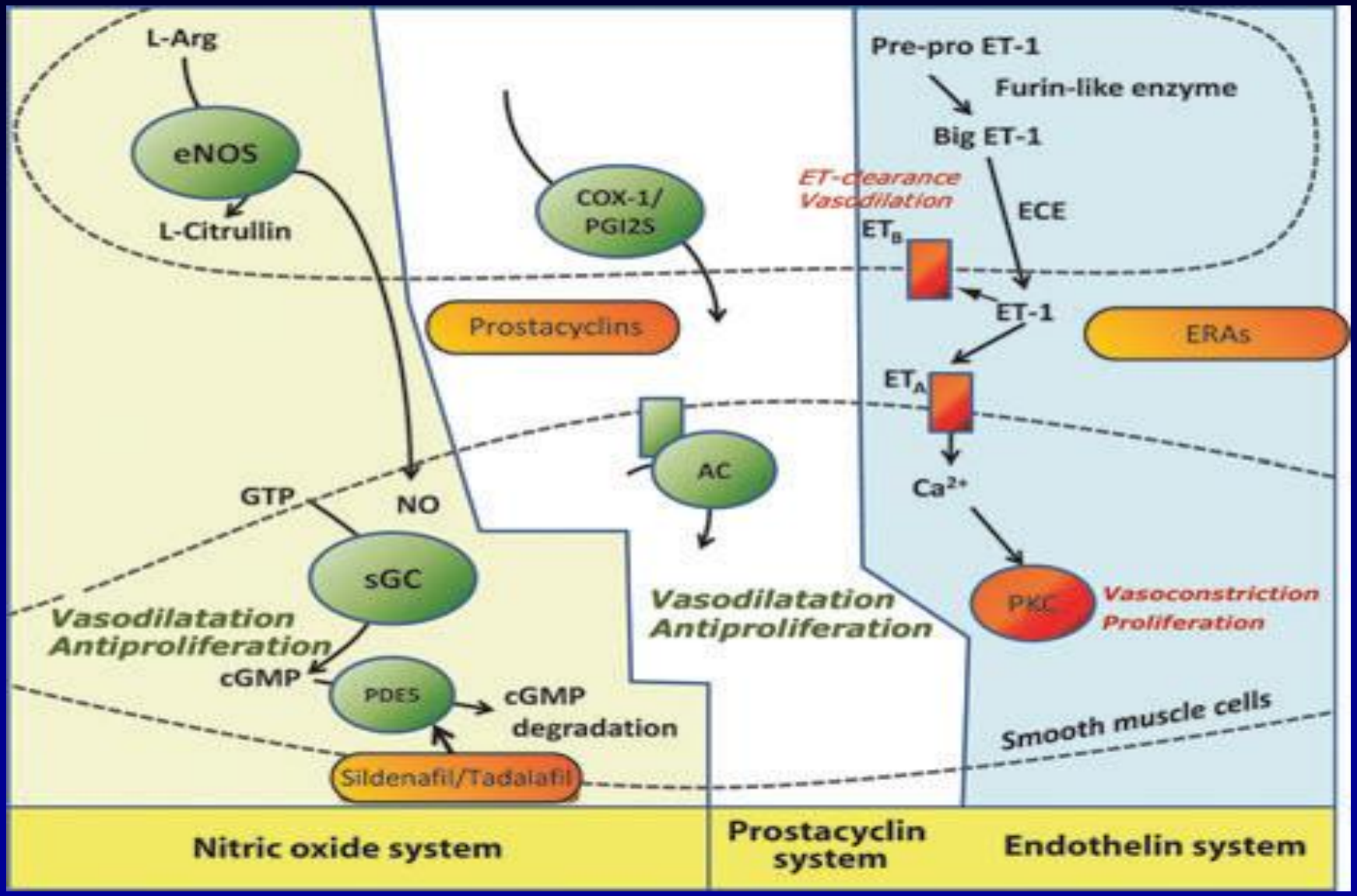
- Six-minute walk test
- Cardiopulmonary exercise testing (CPET)
- Modified NYHA Functional Classification

Adapted from Barst RJ, et al. *Eur Respir J*. 2011;37:665-677.

Pulmonary Arterial Hypertension

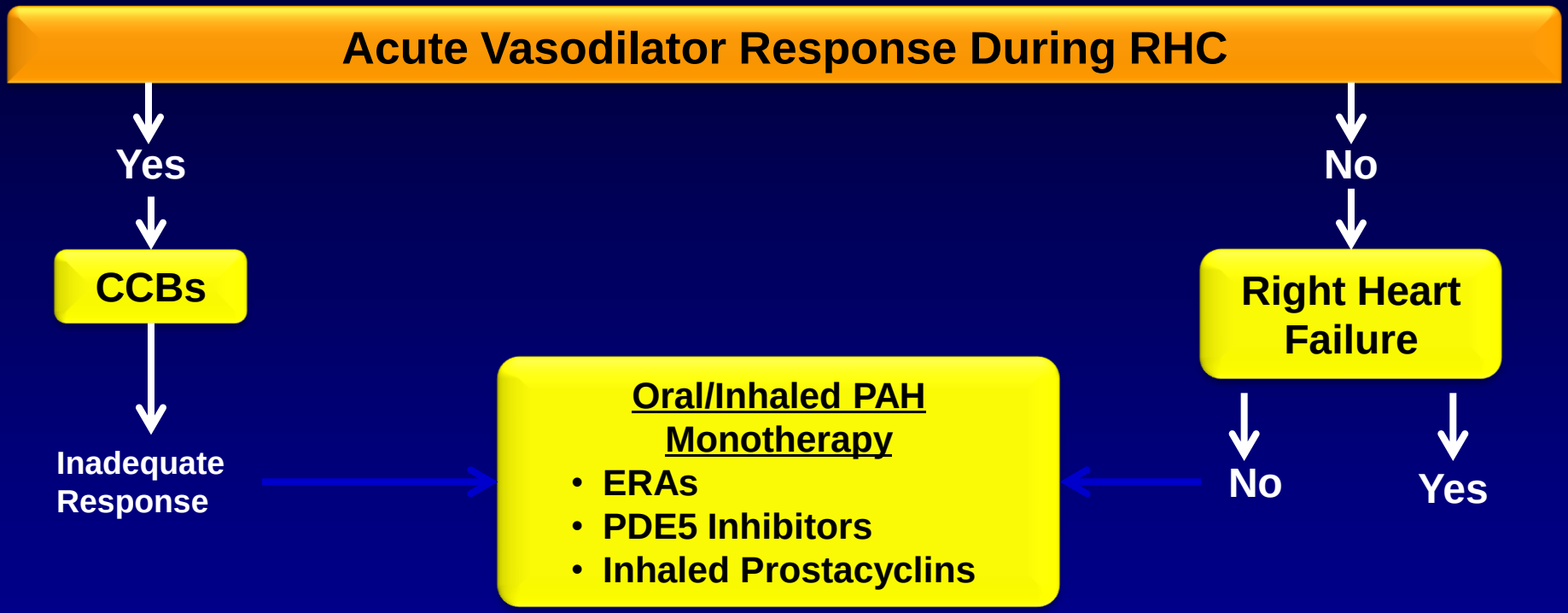
Treatment

PAH Treatment



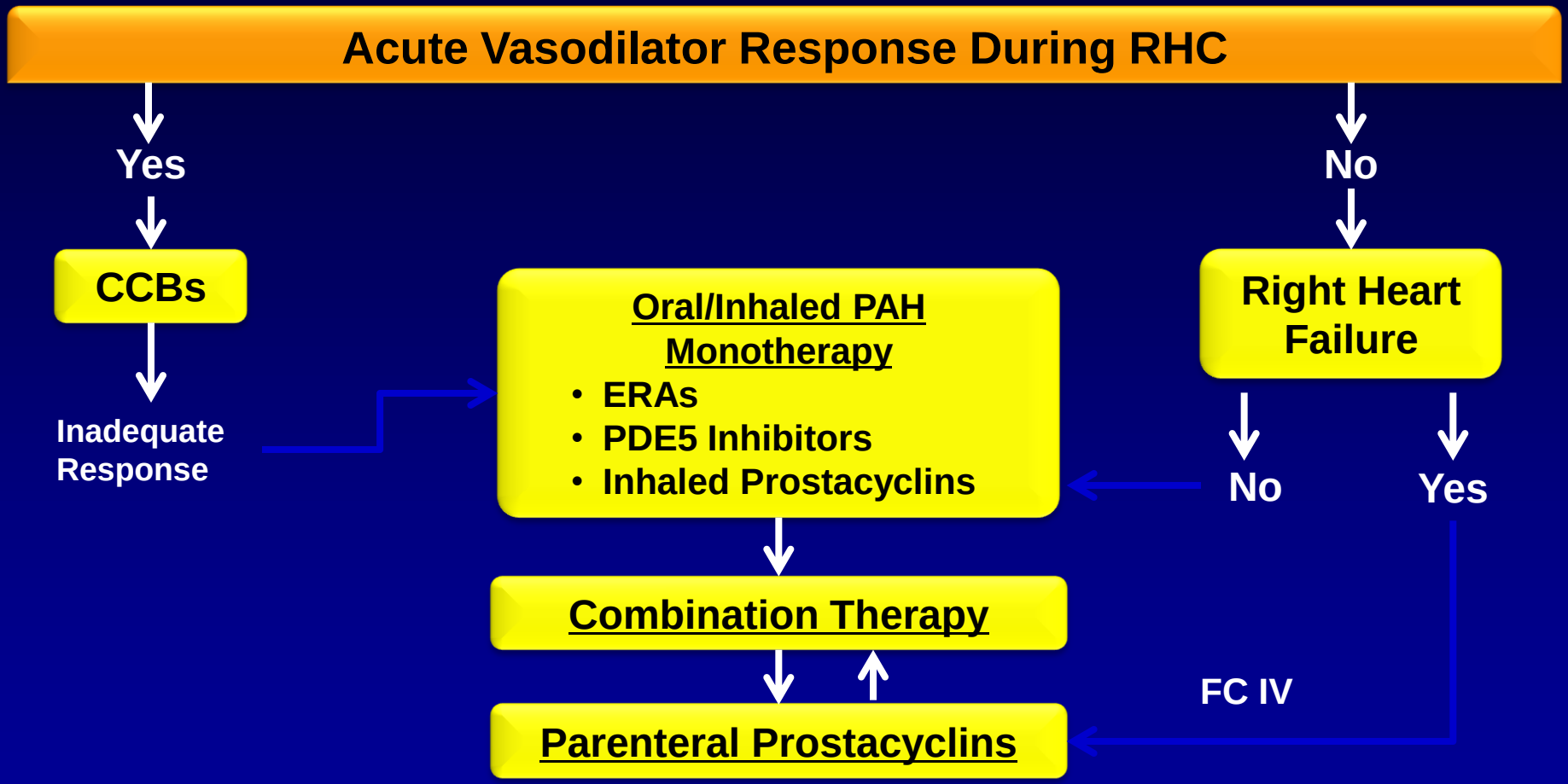
Diller GP, et al. IJCP 2010;64:13-24

Suggested Treatment Algorithm For Pediatric PAH



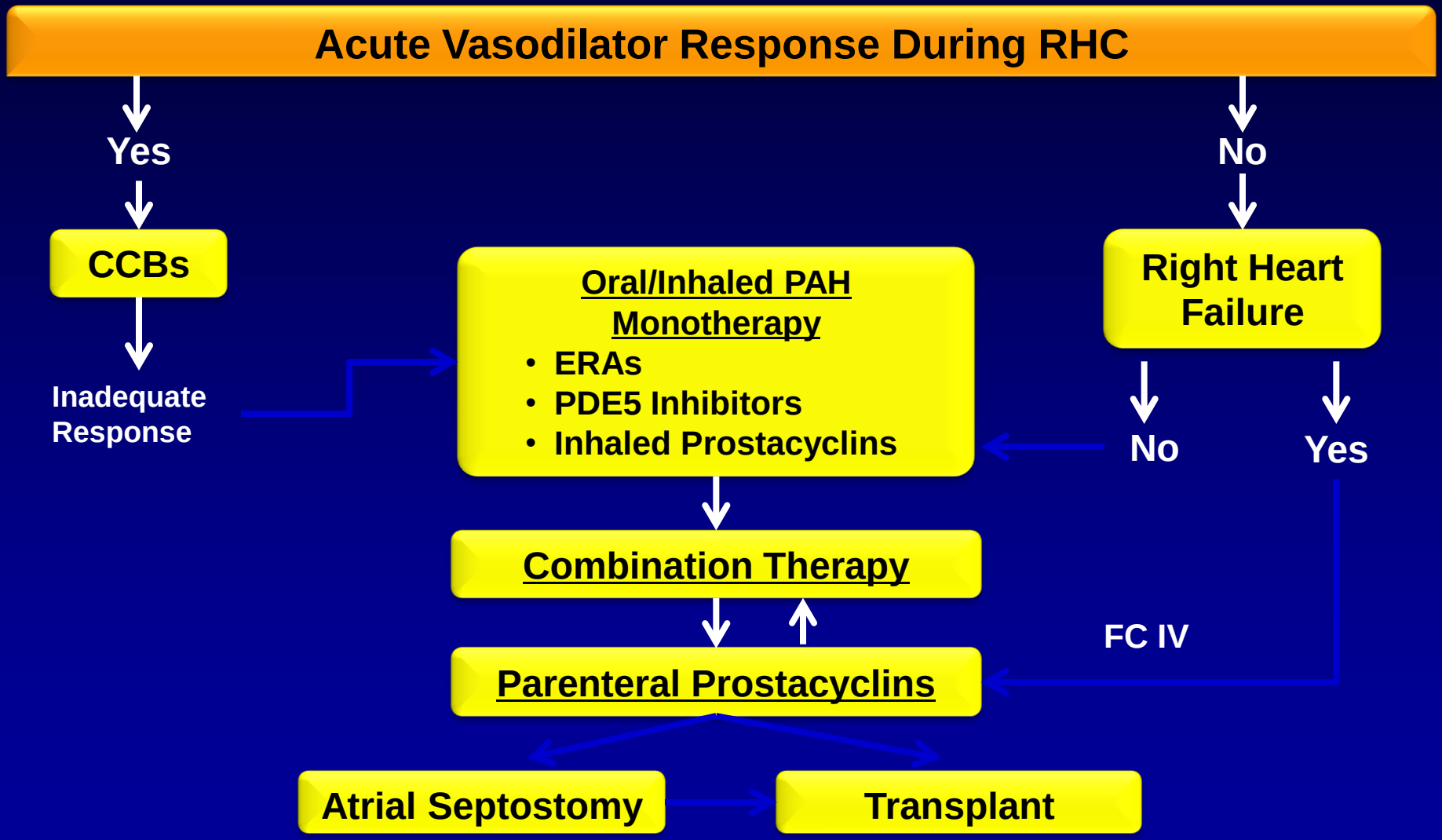
Adapted from Abman SH, Ivy DD. *Curr Opin Pediatr*. 2011;23:298-304.

Suggested Treatment Algorithm For Pediatric PAH



Adapted from Abman SH, Ivy DD. *Curr Opin Pediatr*. 2011;23:298-304.

Suggested Treatment Algorithm For Pediatric PAH

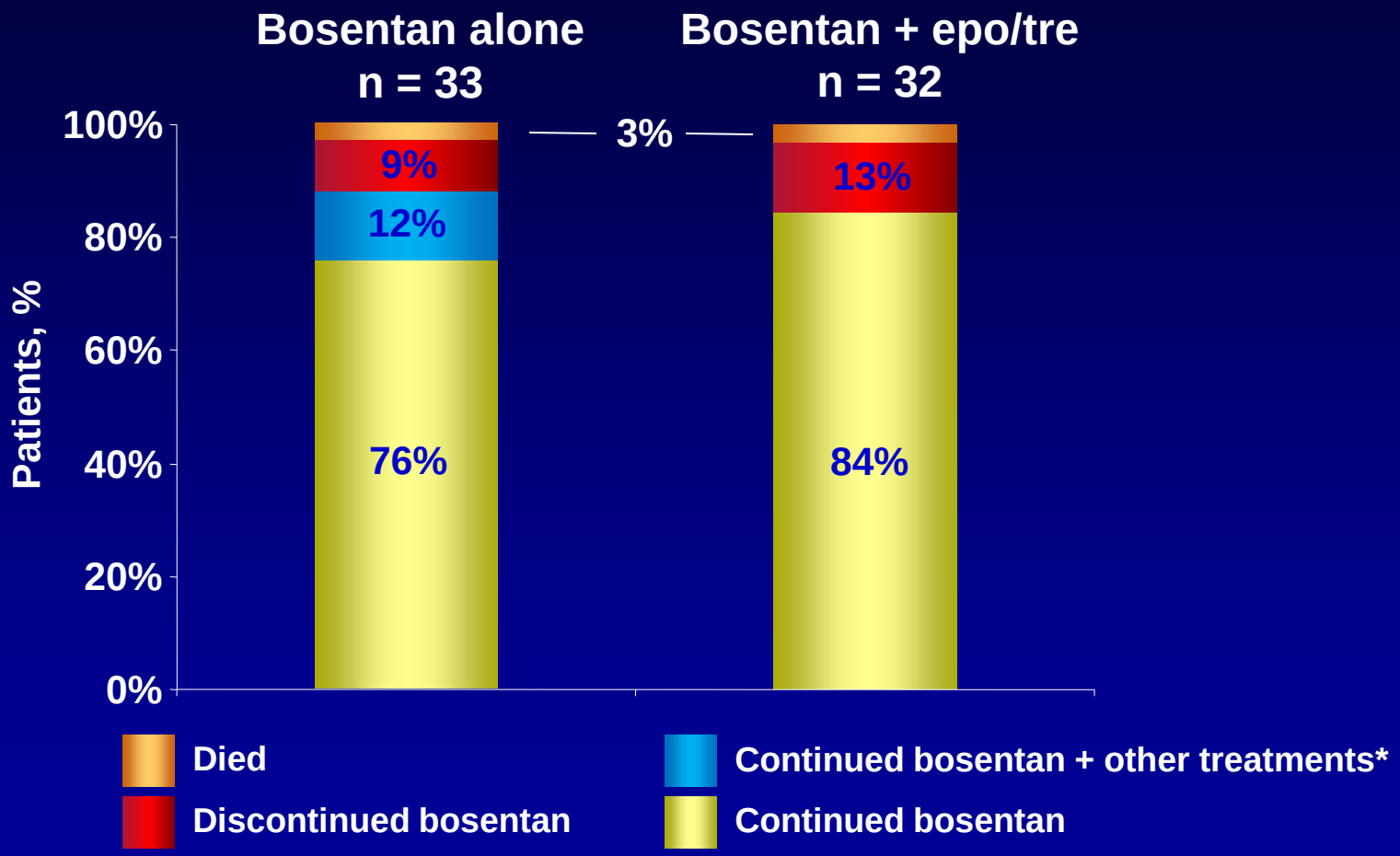


Adapted from Abman SH, Ivy DD. *Curr Opin Pediatr*. 2011;23:298-304.

Endothelin Receptor Antagonists

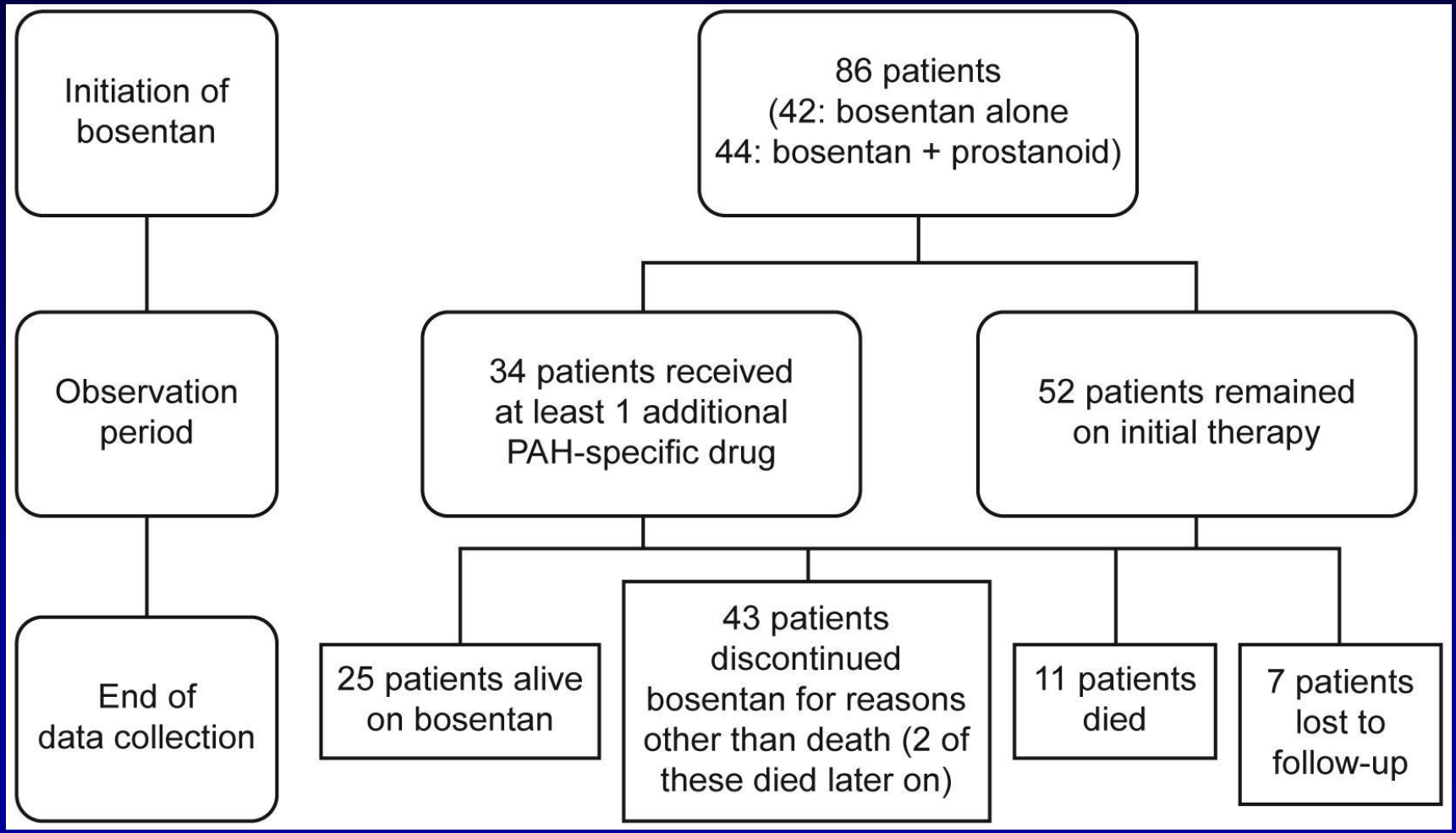
Generic Name	Bosentan	Ambrisentan
Selectivity	ET_A/ET_B	ET_A
Approval	Dec 2001	June 2007
Class	II,III, IV	II, III
Indications (Package Insert)	PAH WHO Group I	PAH WHO Group I
Route	Oral	Oral

Survival At 1 Year with Bosentan



Rosenzweig, Ivy, et al. *J Am Coll Cardiol.* 2005:46:697-504.

Long-term Bosentan in Children with PAH: Patient treatment patterns



Ivy, et al. *AJC* 2010:106:1332-1338

FUTURE 1

An open label, multicentre study to assess the pharmacokinetics, tolerability, and safety of a paediatric formulation of bosentan in children with idiopathic or familial pulmonary arterial hypertension

Ambrisentan in Children: Safety

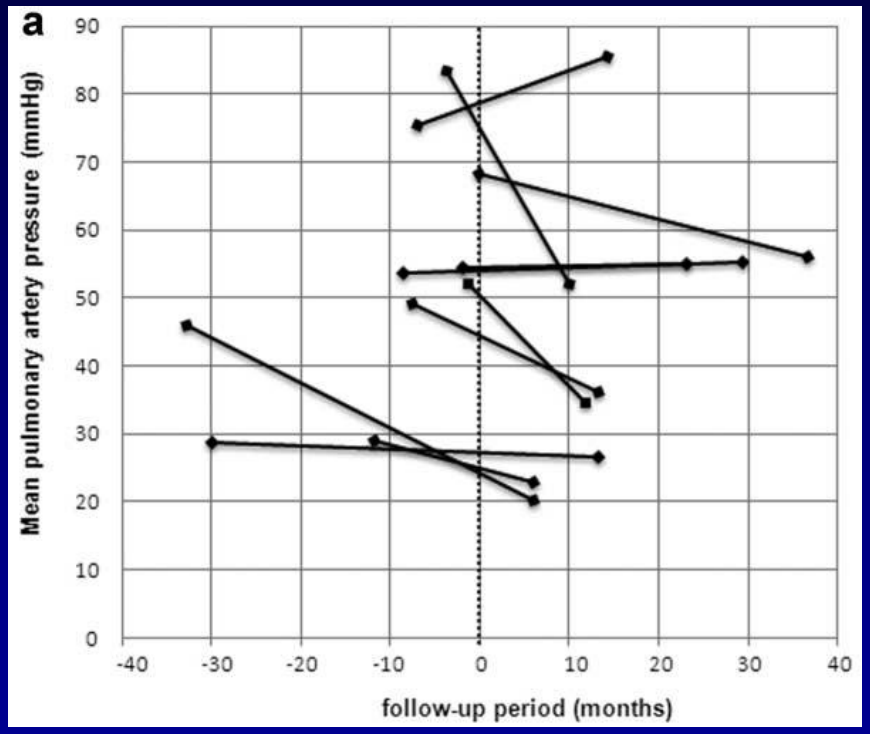
- 0/33 patients had AST/ALT elevations > 2x ULN while on ambrisentan
- 4 patients discontinued ABS due to:

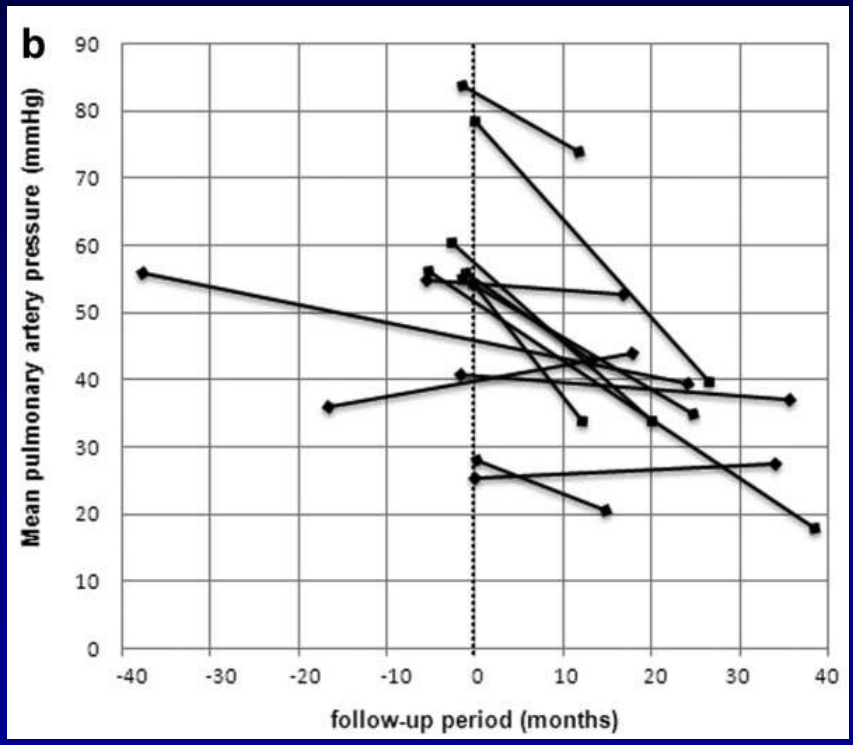
  headache (1), sinusitis (1) or lack of clinical improvement (2)
- Other reported adverse events included: nasal congestion (8), leg edema (2), and

  headaches (2)

Takatsuki , Rosenzweig, Zuckerman, Brady, Calderbank, Ivy. *Pediatr Pulmonology* (in print)

Ambrisentan in Pediatrics





Transition **Add-On**

Takatsuki , Rosenzweig, Zuckerman, Brady, Calderbank, Ivy. *Pediatr Pulmonology* (in print)

PDE5 Inhibitors

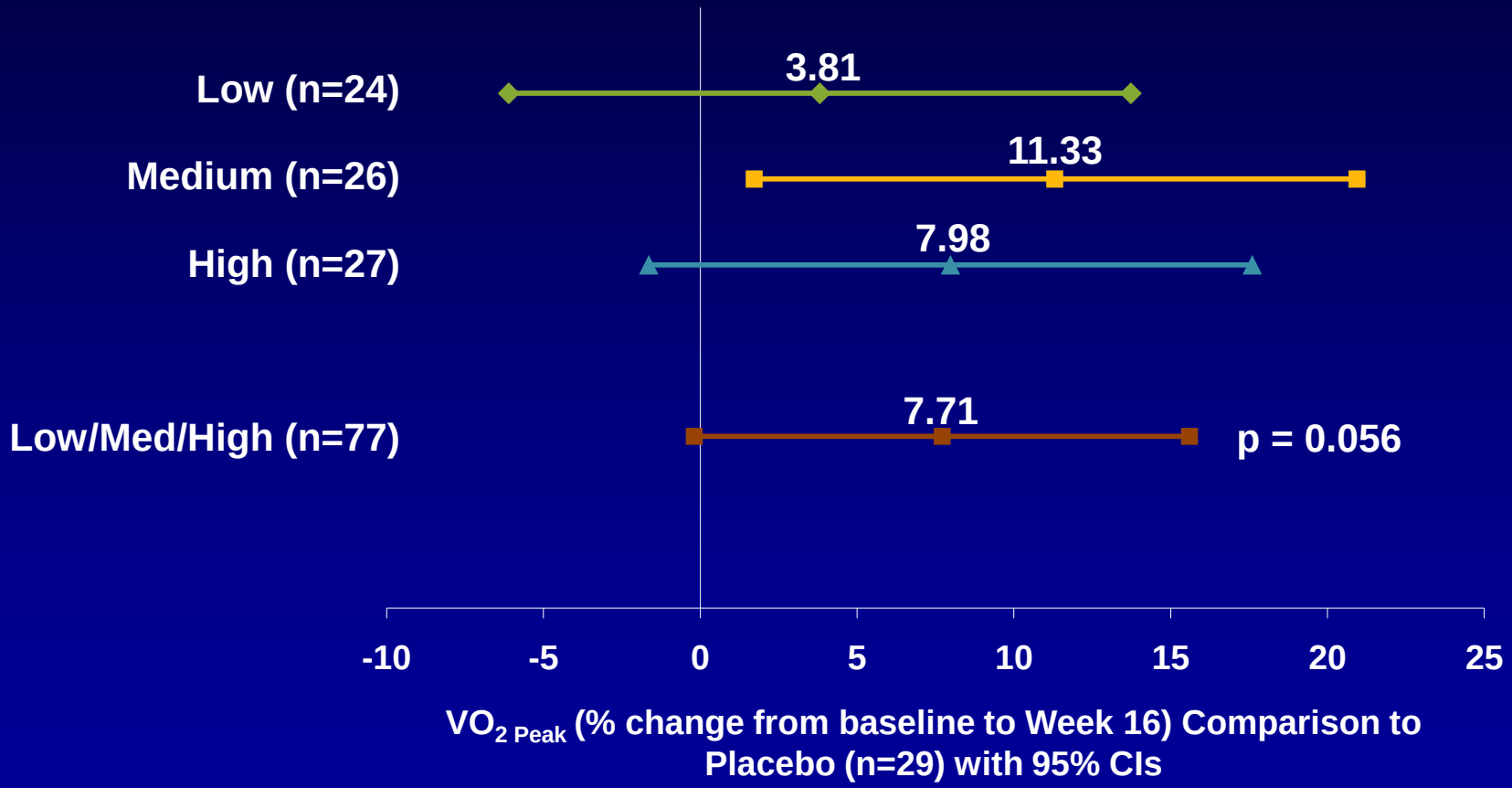
Generic Name	Sildenafil	Tadalafil
Approval	2005	2009
Class	All	All
Indications (Package Insert)	PAH WHO Group I	PAH WHO Group I
Route	oral	oral

STARTS-1 and -2

A randomized, double-blind, placebo controlled, dose ranging, parallel group study of oral sildenafil in the treatment of children, aged 1-17 years, with pulmonary arterial hypertension (PAH)

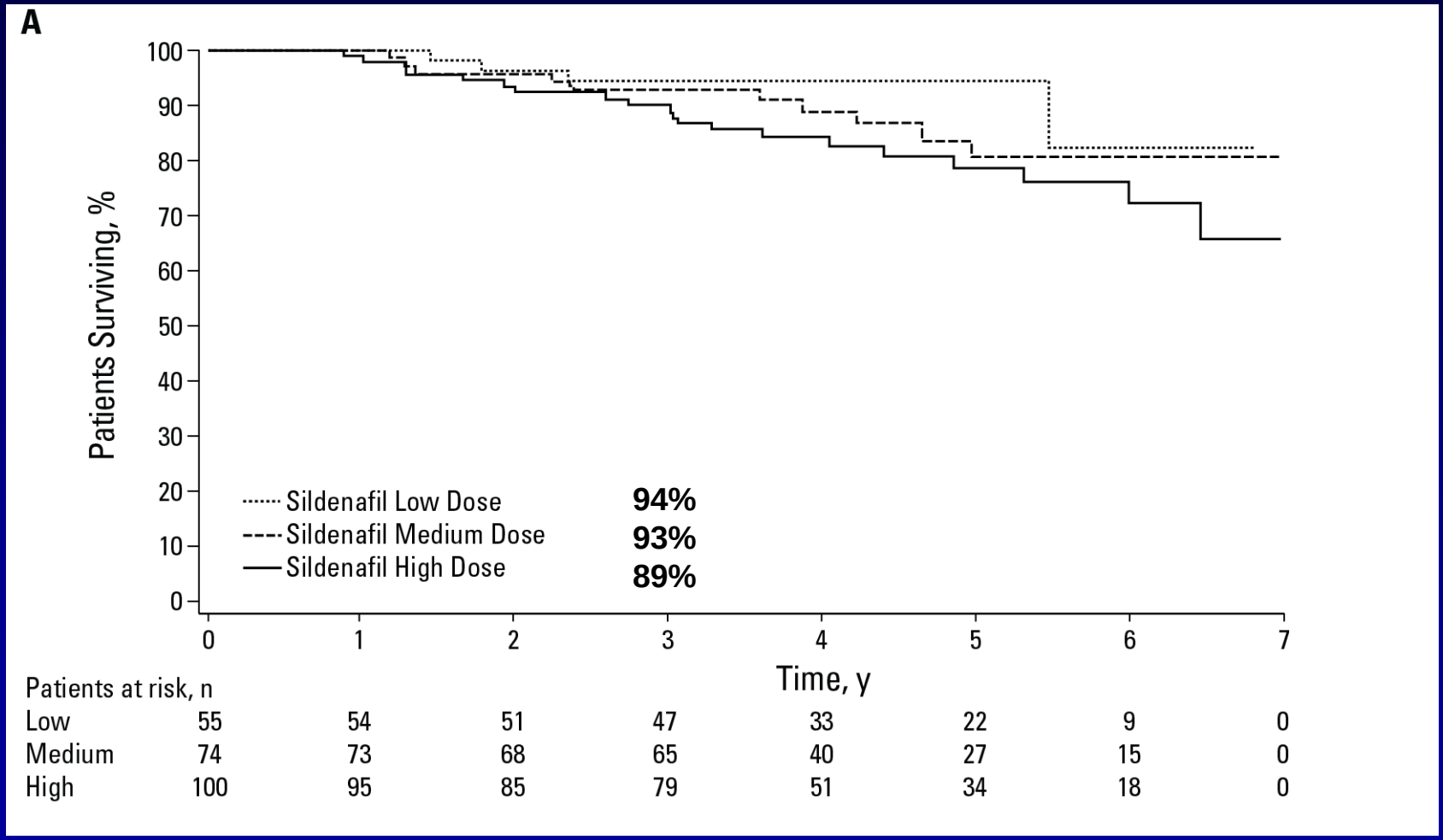
Barst R, Ivy DD, et al. Circulation 2012;125:324-334

Placebo-adjusted Percent Change $VO_{2\ Peak}$



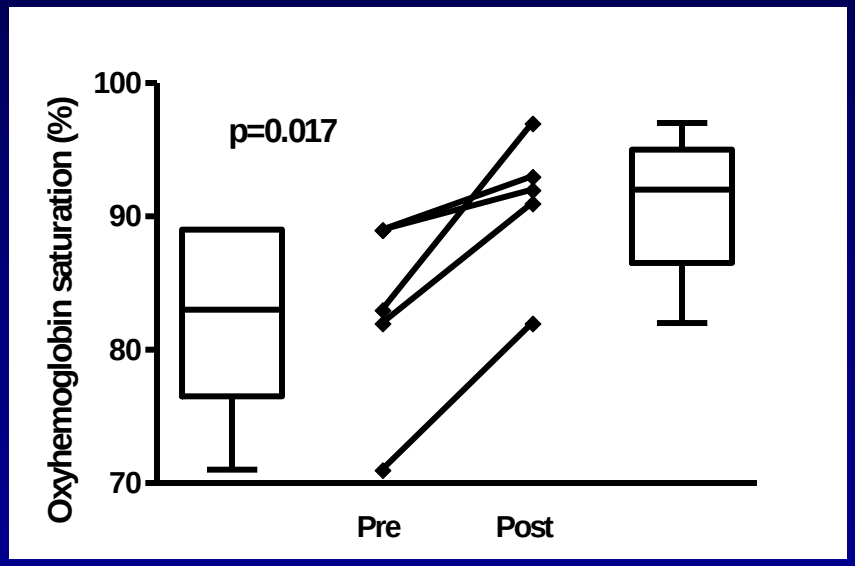
Barst R, Ivy DD, et al. Circulation 2012;125:324-334

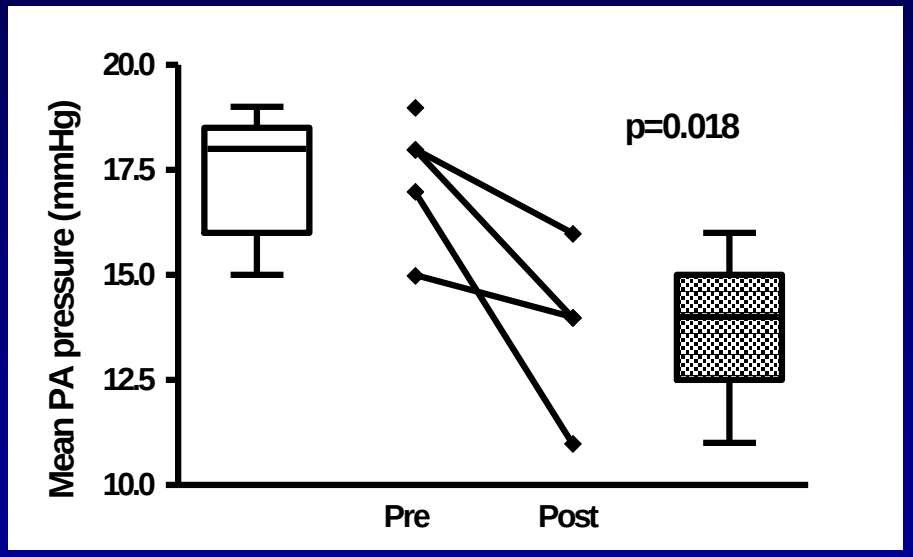
Kaplan-Meier Estimated Survival From Start of Sildenafil Treatment in STARTS-1 and -2



Hazard ratios for mortality were 3.50 (95% CI, 1.29–9.51) H vs L

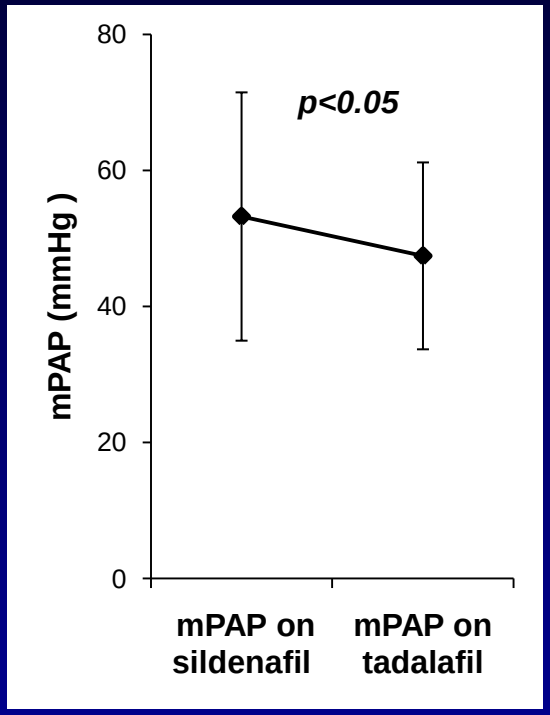
Sildenafil in Failing Fontan Physiology

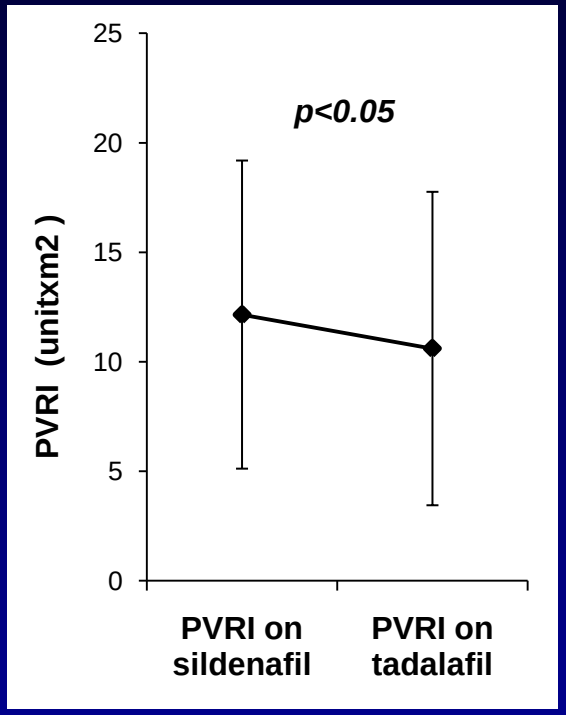


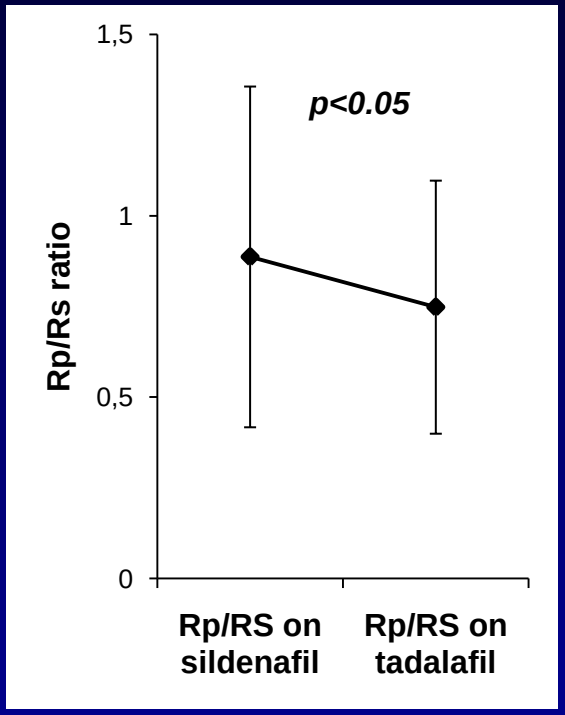


Morchi, Ivy, Duster, et al. Congenit Heart Dis 2009;4:107-111

Tadalafil in Pediatric PAH







N = 33

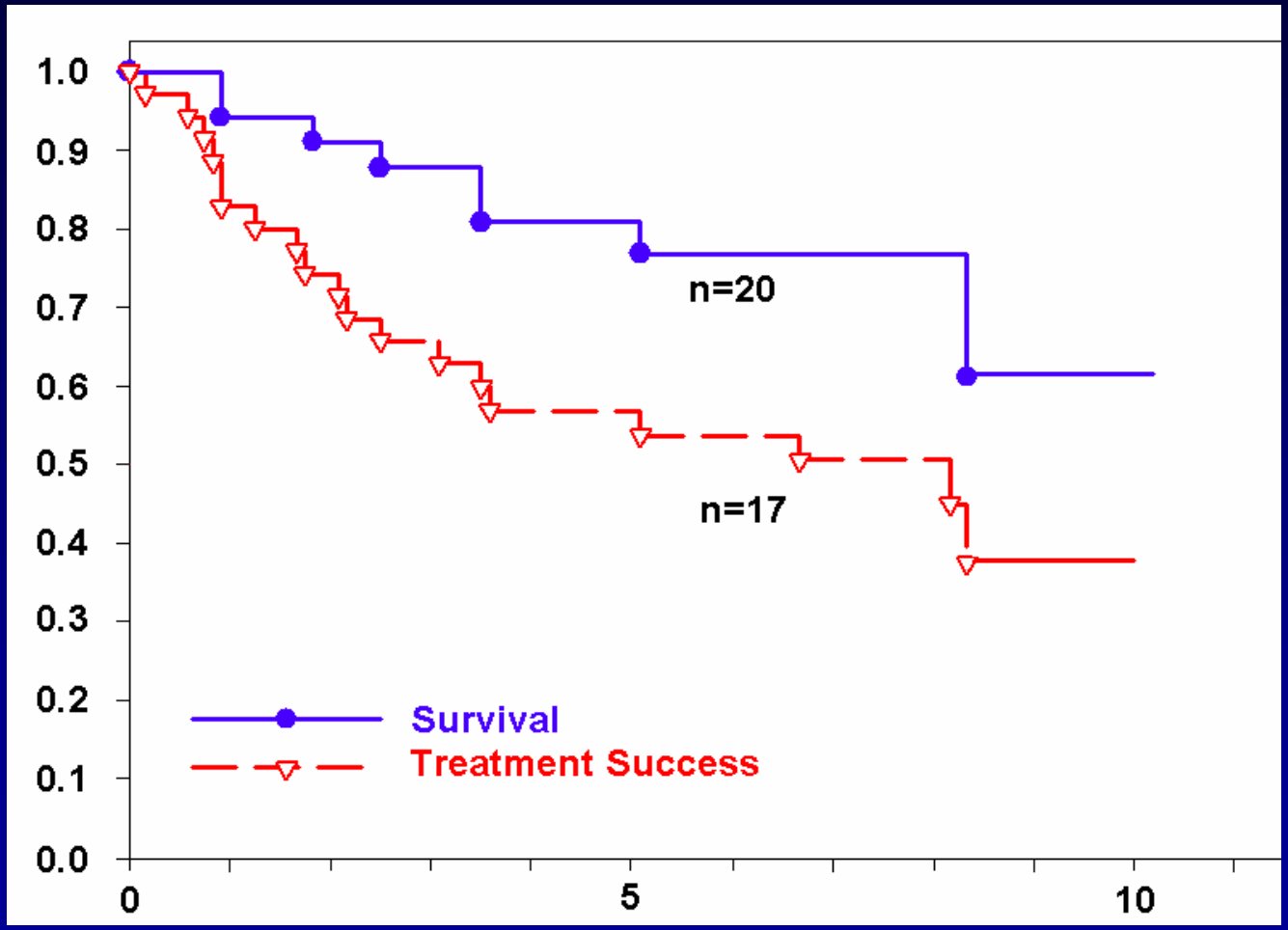
Sildenafil 3.4+/-1.1 mg/kg/day to Tadalafil 1.0+/-0.4 mg/kg/day

Takatsuki, Calderbank, Ivy. Pediatr Cardiology. 2012;33:683–688

Prostanoids

Generic Name	Epoprostenol	Treprostinil	Iloprost	EPO For Injection
Approval	Jan 1996	May 2002(SQ) May 2004 (IV) July 2009 (Inh)	Dec 2004	April 2010
Class	III, IV	All	III, IV	III, IV
Indications (Package Insert)	PPH, SPH due to scleroderma	PAH WHO Group 1	PAH WHO Group 1	PPH, SPH due to scleroderma
Route	Continuous IV	Cont. SQ or IV Inhaled	Inhaled	Continuous IV

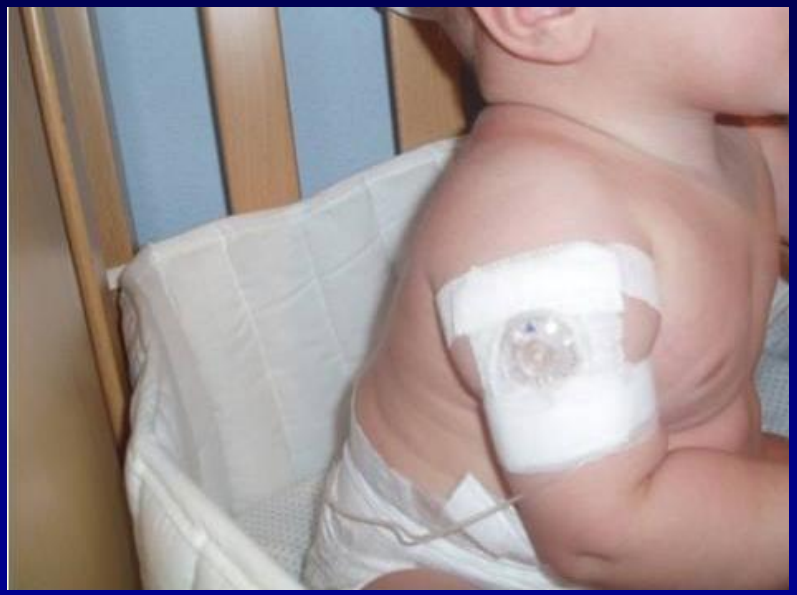
Idiopathic PAH in Children: Survival and Treatment Success with Chronic IV Epoprostenol



Yung D, et al. *Circulation* 2004;110:497-503

Treprostinil Subcutaneous Delivery

- Advantages
  - No central line
  - Smaller infusion pump
  - Longer half life
- Disadvantages
  - Significant site pain
  - Generally not used in pediatrics; however use increasing



Levy, et al. J Pediatr 2011;158:584-588

IV Treprostinil Administration

- Requires higher dose (up to 2.5 times) as compared to Flolan
- Longer half life: 3-4 hours
- Stable at room temp for 48 hrs for IV and 72 hrs for SQ
- No Ice Packs
- Every other day mixing
- Antiplatelet effects and drug stability allow for slow infusions with smaller pumps

Permission given

Ivy, et al. Am J Cardiol. 2007;99:696-698

Iloprost Inhalation System

- Compact, portable, and lightweight inhalation system
- Advanced technology
  - Breath-actuated
  - Patient specific adaptation
  - Consistent and accurate dosing
  - Micro-aerosol for deep pulmonary delivery
  - Treatments 7-9 X / Day

Ivy, et al. *J Am Coll Cardiol*. 2008 15;51:161-169.

Treprostinil Inhalation System

Inhalation device assembled

One inhaled treprostinil ampule

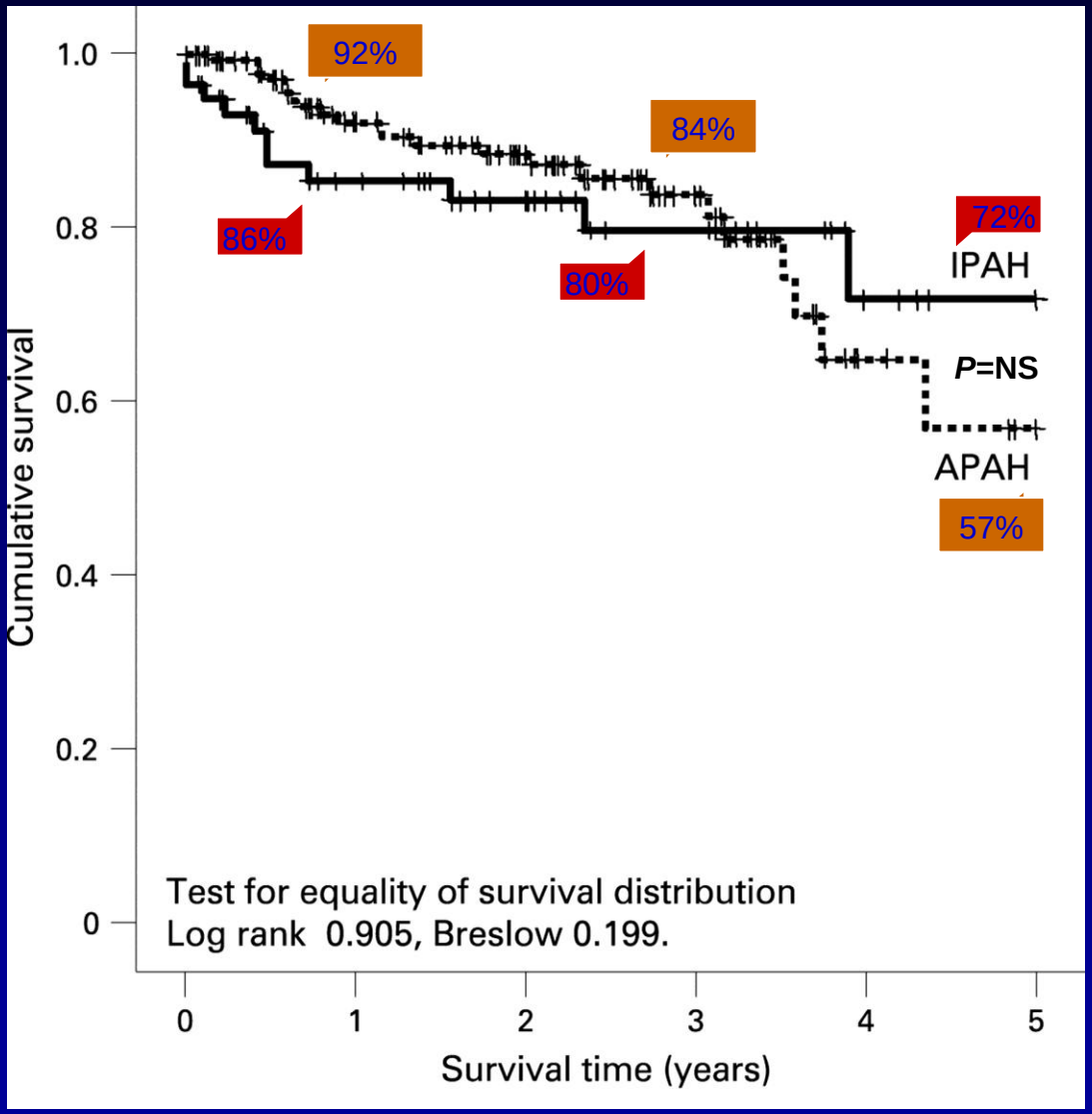
- **4 Treatments per day**
- **6 mcg / breath**
- **3-9 breaths per treatment**
- **Equivalent to less than 15 ng/kg/min IV treprostinil**

Krishnan, et al. *Am J Cardiol (in print)*

Pulmonary Arterial Hypertension

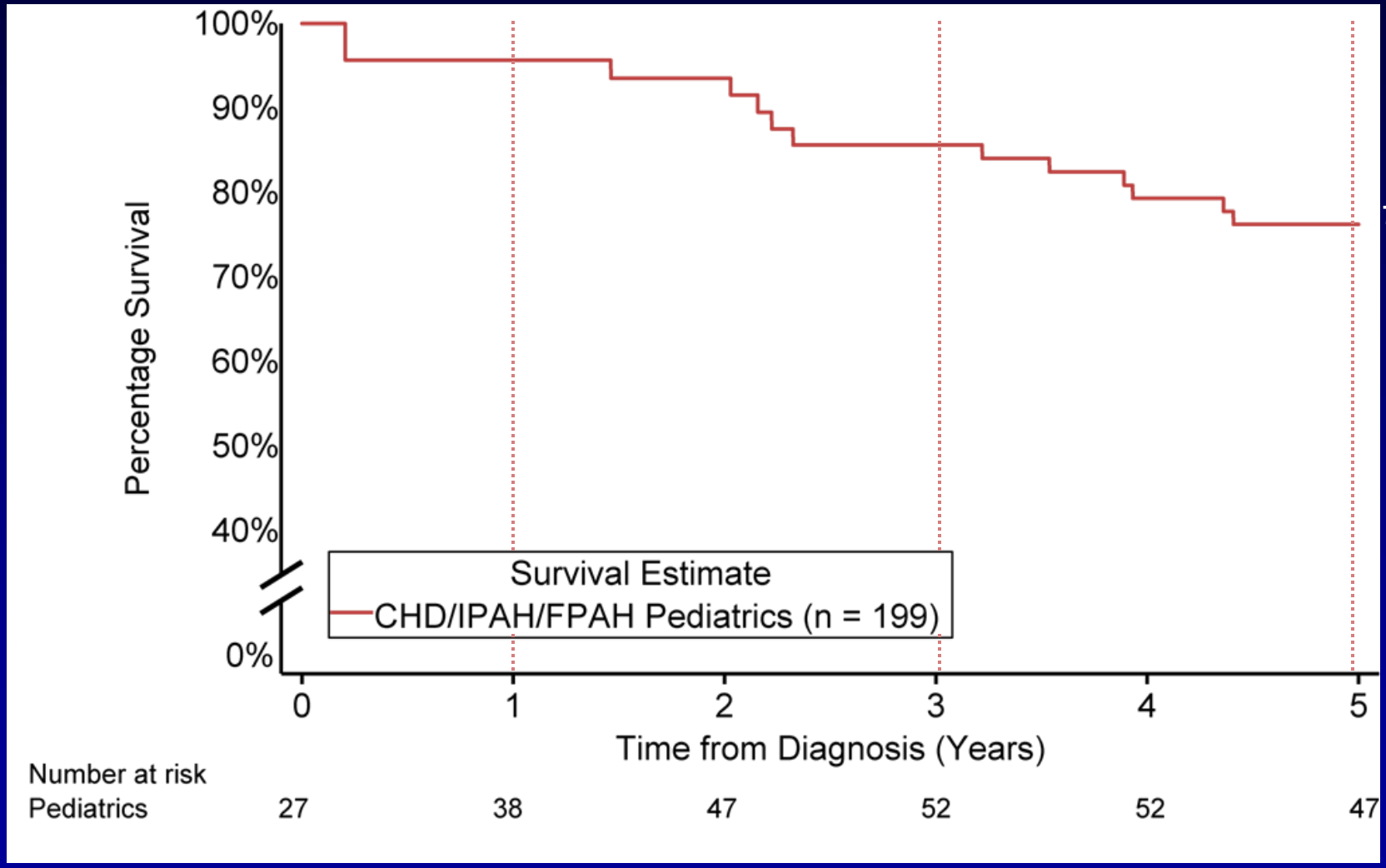
Survival

Survival UK Pulmonary Hypertension Service



Haworth, S G et al. Heart 2009;95:312-317

Pediatric Survival from Diagnosis in At-Risk Population



Barst, McGoon, Elliott, Foreman, Miller, Ivy. *Circulation*. 2012;125:113-122.

Conclusions

- Dyspnea and syncope are common presenting symptoms of pediatric PH
- Accurate diagnosis and treatment of underlying disorders is critical for optimal management of PH
- Novel therapies adapted from adult randomized trials have benefited children
- Although therapy has improved quality of life, there is no cure for many forms of PH in children