Paediatric Pulmonary Arterial Hypertension

Current Treatment, Needs and Challenges

London, June 12 2017

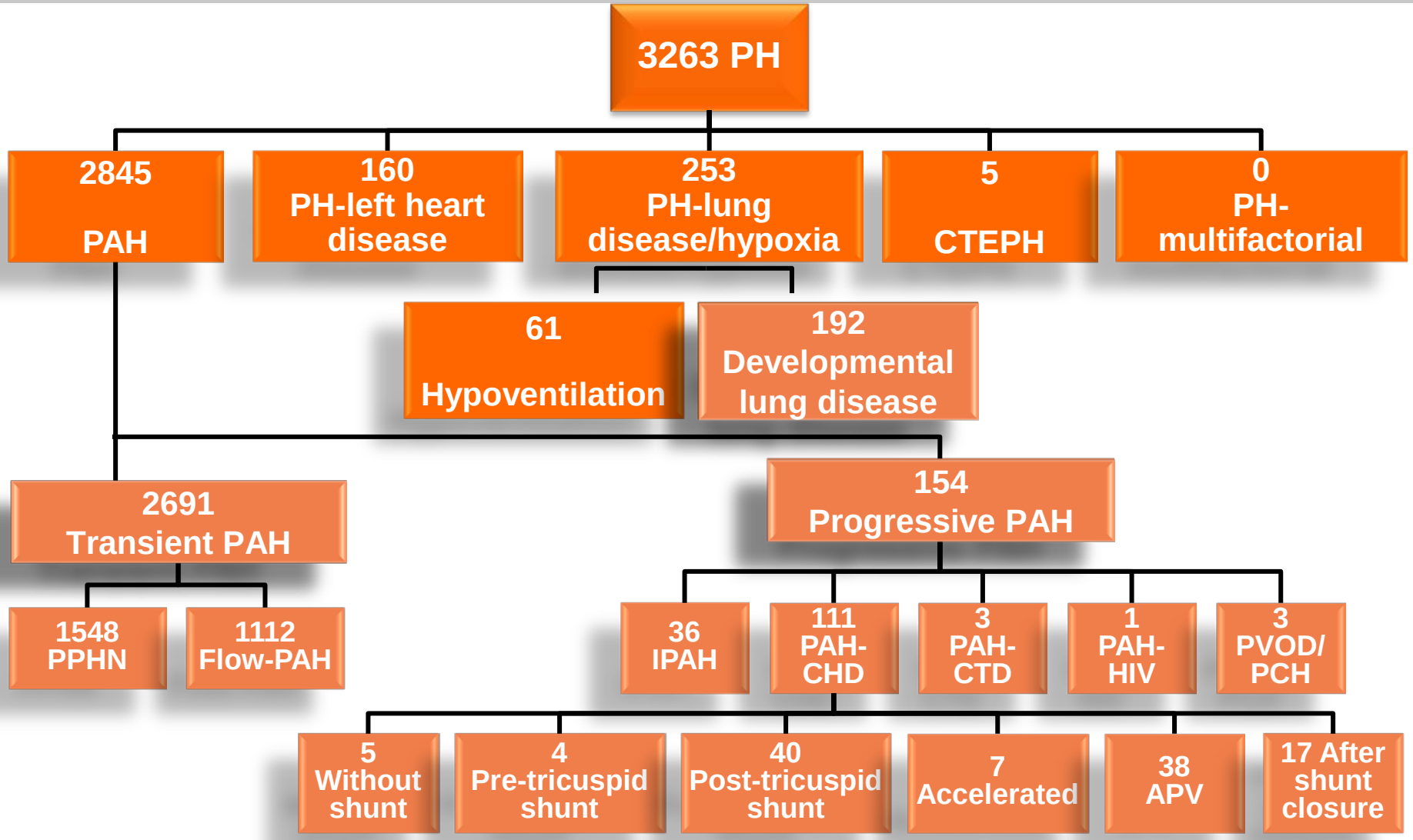
Rolf M.F. Berger

National Referral Center for Pulmonary Hypertension in Childhood

University Medical Center Groningen

The Netherlands

Classification of Paediatric PH in Dutch National cohort: 1991-2005



Van Loon R, *et al*. *Circulation*. 2011

Epidemiology Pediatric PAH
data from large registries

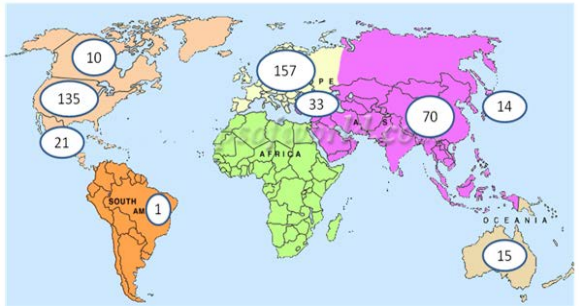
	TOPP [1]	*Reveal-children* [2]	*Reveal-Adults*[3]
Patients, *n*	362	216	2525
Age at Dx (yrs), median	7.5	7	53
Female, %	59	64	80
Group 1: PAH	317 (88)	216 (100)	2525 (100)
IPAH/HPAH	212 (53)	122 (56)	1166 (46)
CHD	160 (40)	23 (36)	215 (10)
CTD	9 (3)	10 (5)	639 (25)
Portopulmonary	2 (1)	3 (1)	136 (5)
Other	14 (4)	4 (2)	255 (10)
Group 3: Lung disease	42 (12)	NE	NE
Other	3 (1)	NE	NE

Values given are *n* (%) unless otherwise indicated

1. Berger et al. *Lancet* 2012.
2. Barst et al. *Circulation* 2012.
3. Badesch et al. Chest 2010.

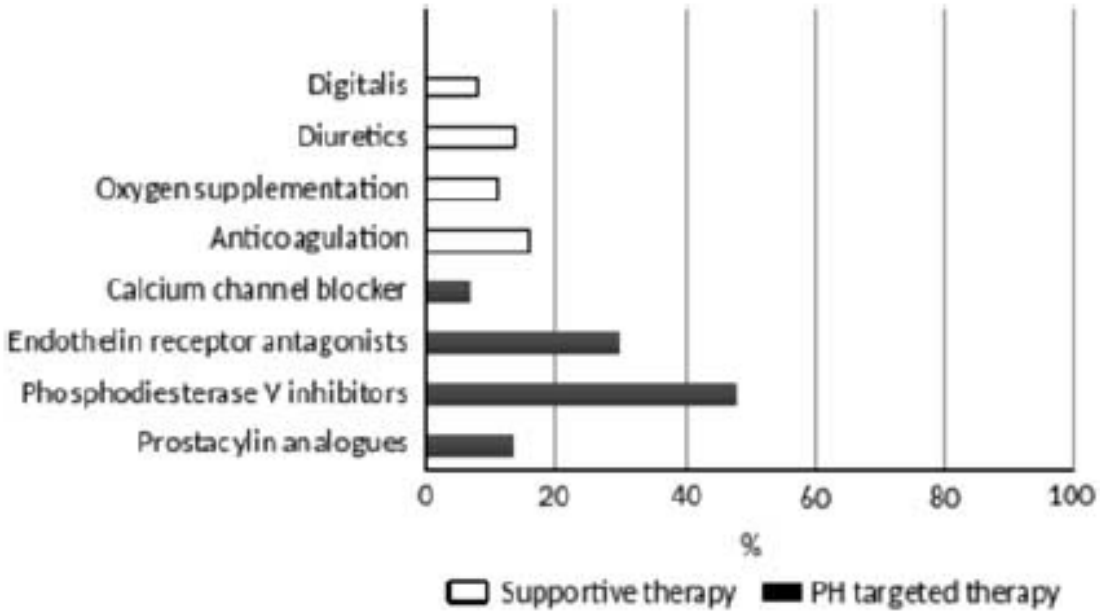
Current Treatment Practice
Global TOPP-1 registry

TOPP
Tracking Outcomes and Practice in Pediatric Pulmonary Hypertension



244 incident patients

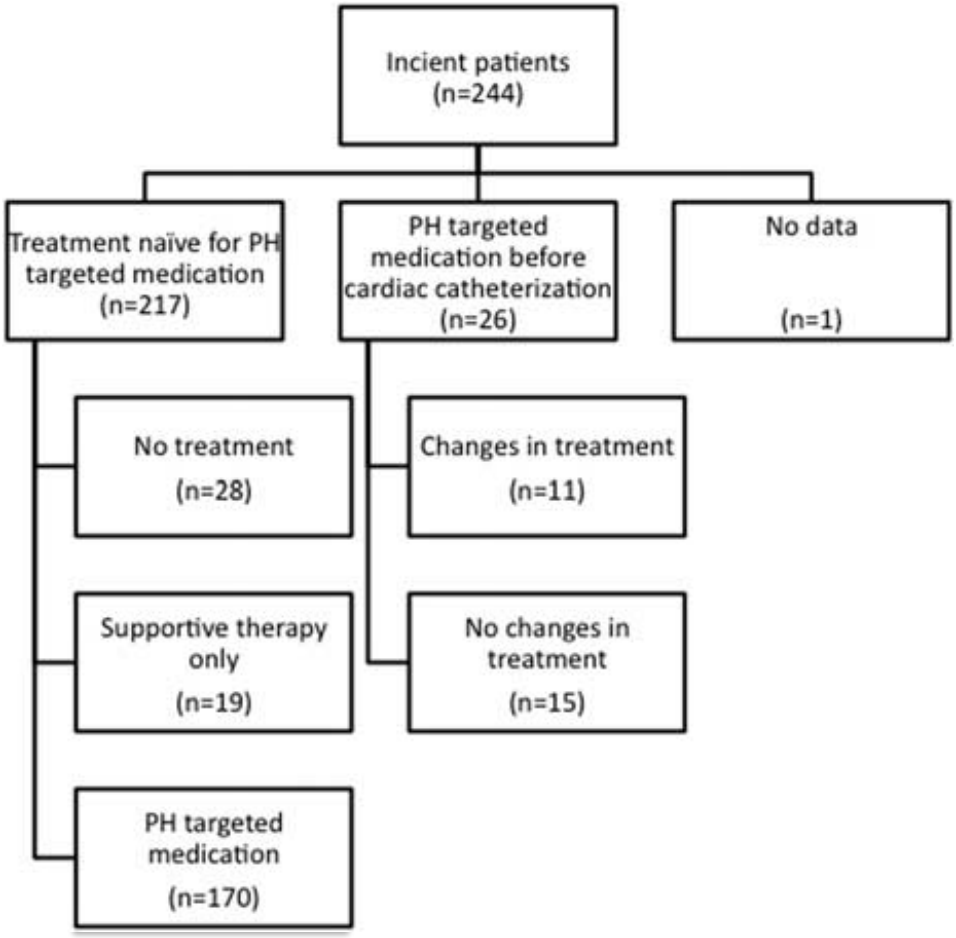
- Age at Dx 6yrs
  (3 months – 17 yrs)
- Female 58%
- Time Dx –Enr. < 3mo
- WHO-FC
  - I 30 (12%)
  - II 104 (42%)
  - III 89 (36%)
  - IV 21 (10%)



Humpl et al, Cardiol Young 2016

Current Treatment Practice: treatment initiation

Global TOPP-1 registry



- 80% of children were initiated on PAH-treatment
- **“standard of care”**
- placebo-controls pose ethical issues for study design
- legal issues for paediatric study designs

Current treatment practice
stratified by by age groups

TOPP
Tracking Outcomes and Practice in Pediatric Pulmonary Hypertension

Table 7. Targeted and supportive therapy by age.

	> 3 months to <2 years	2 to <6 years	6 to <12 years	12 to <18 years	P het*	P trend**
n	50	64	38	65		
PH-targeted therapy	31 (62.0%)	48 (75.0%)	28 (73.7%)	48 (73.8%)	0.43	0.18
Prostacyclin analogue	10 (20.0%)	9 (14.1%)	3 (7.9%)	8 (12.3%)	0.45	0.32
Endothelin receptor antagonist	8 (16.0%)	25 (39.1%)	14 (36.8%)	18 (27.7%)	0.04	0.30
PDE V inhibitor	23 (46.0%)	30 (46.9%)	18 (47.4%)	33 (50.8%)	0.96	0.60
CCB (high dose for PH)	1 (2.0%)	6 (9.4%)	1 (2.6%)	7 (10.8%)	0.18	0.17
Supportive therapy						
Anticoagulation	5 (10.0%)	6 (9.4%)	9 (23.7%)	14 (21.5%)	0.08	0.03
Oxygen	3 (6.0%)	5 (7.8%)	7 (18.4%)	8 (12.3%)	0.25	0.15
Diuretics	7 (14.0%)	12 (18.8%)	3 (7.9%)	8 (12.3%)	0.49	0.46
Digitalis	4 (8.0%)	5 (7.8%)	4 (10.5%)	5 (7.7%)	0.96	0.96

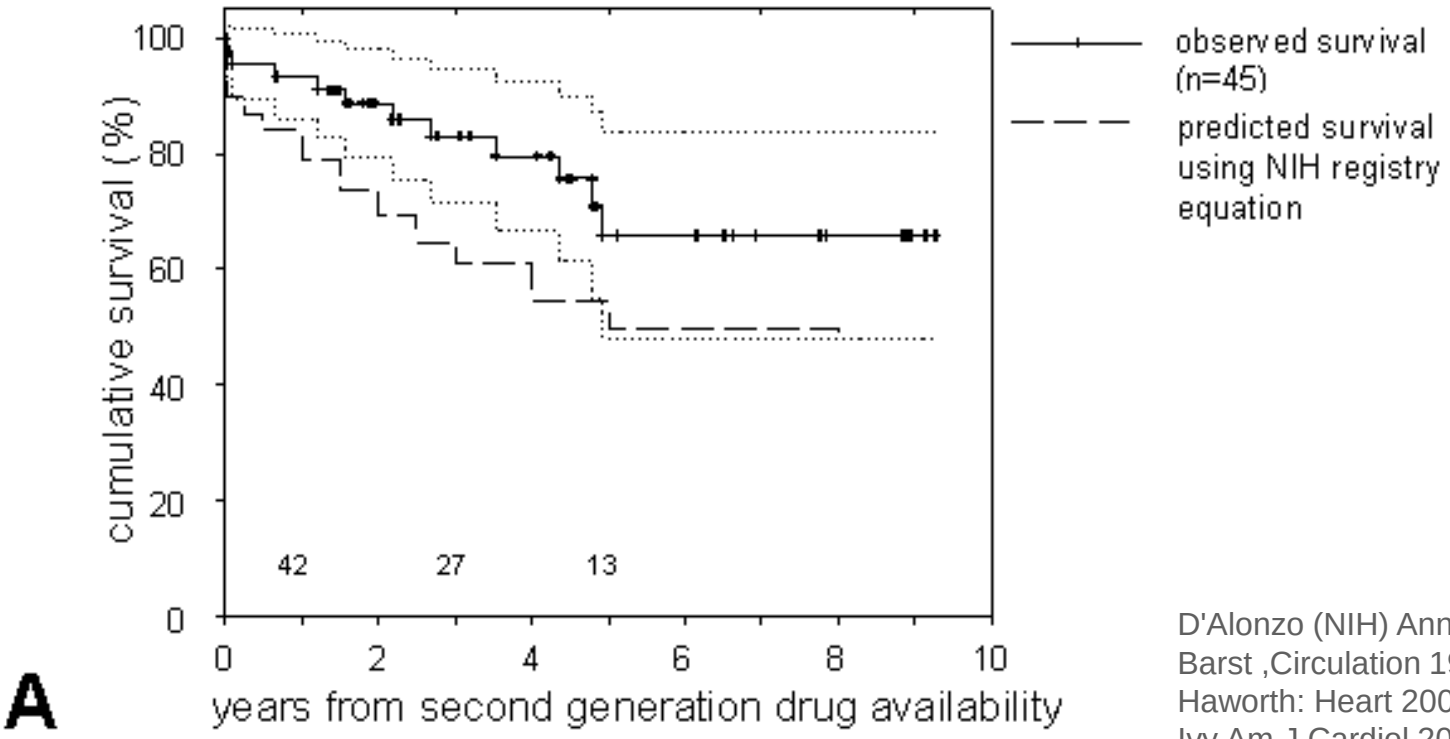
CCB = calcium channel blockers; PDE = phosphodiesterase; PH = pulmonary hypertension
*P-value from Fisher's exact test for heterogeneity
**P-value from χ^2 trend test

Humpl et al, Cardiol Young 2016

Survival

Dutch National Registry for Pediatric PAH

In the era of PAH-targeted drugs vs. predicted (NIH)



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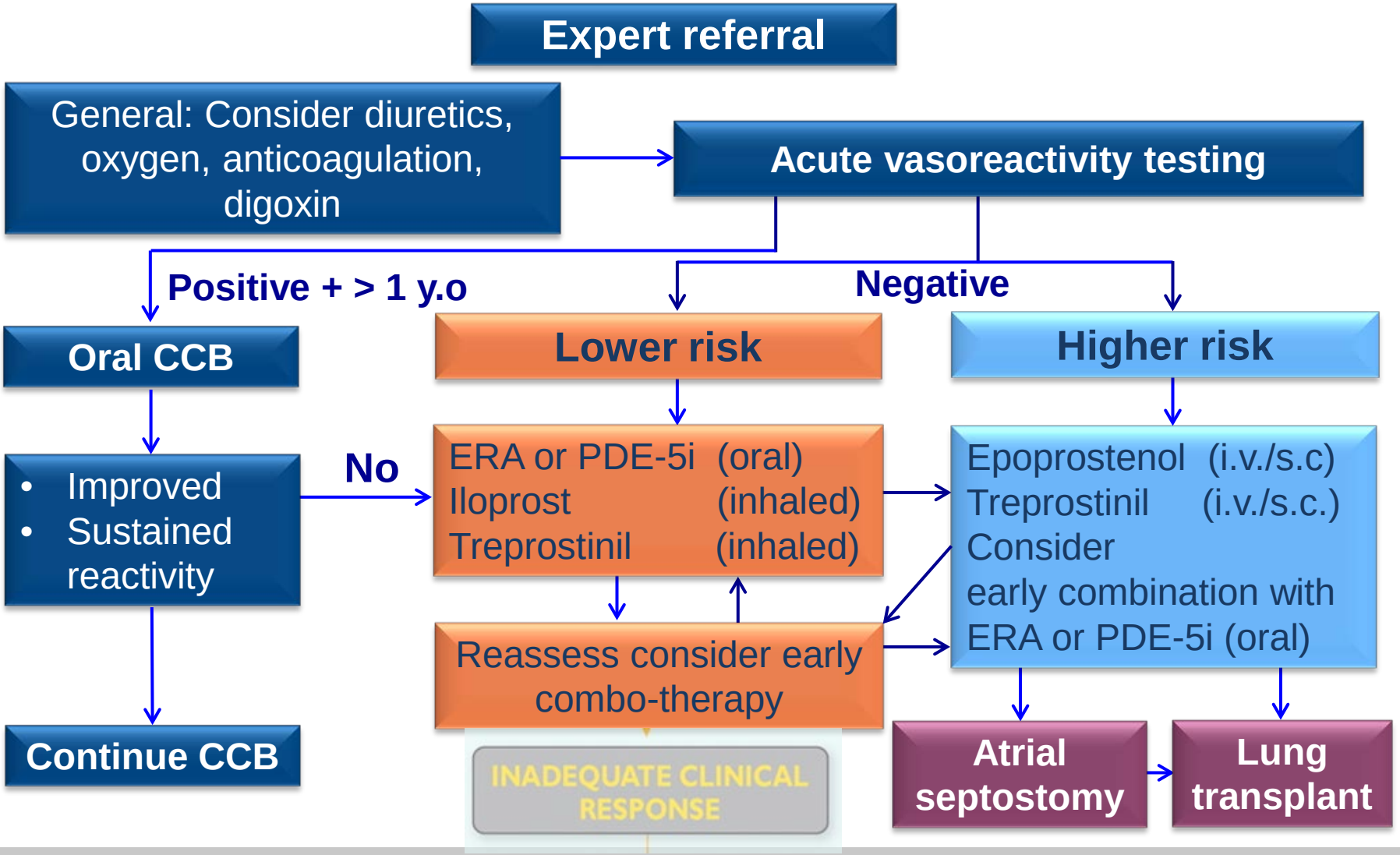
D'Alonzo (NIH) Ann Int Med1991
Barst ,Circulation 1999
Haworth: Heart 2009
Ivy Am J Cardiol 2010
Yung Circulation 2004
Barst, Circulation 2012

Van Loon et al, Am J Cardiol, 2010

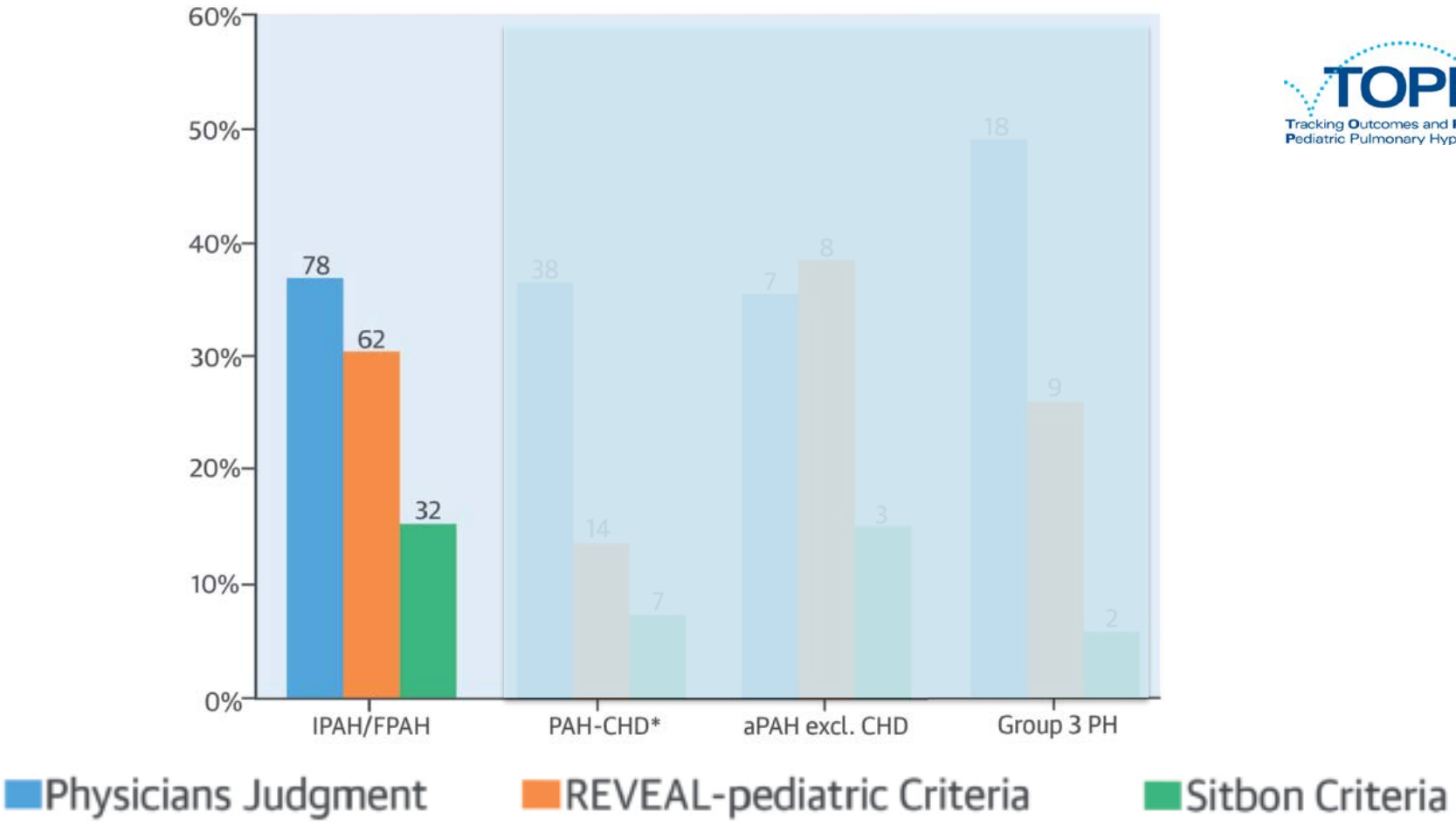
Consensus paediatric IPAH/HPAH treatment algorithm*
5th WSPH (Nice 2013):



- Use of all agents is considered off label in children aside from sildenafil in Europe

Ivy D, *et al. J Am Coll Cardiol* 2013

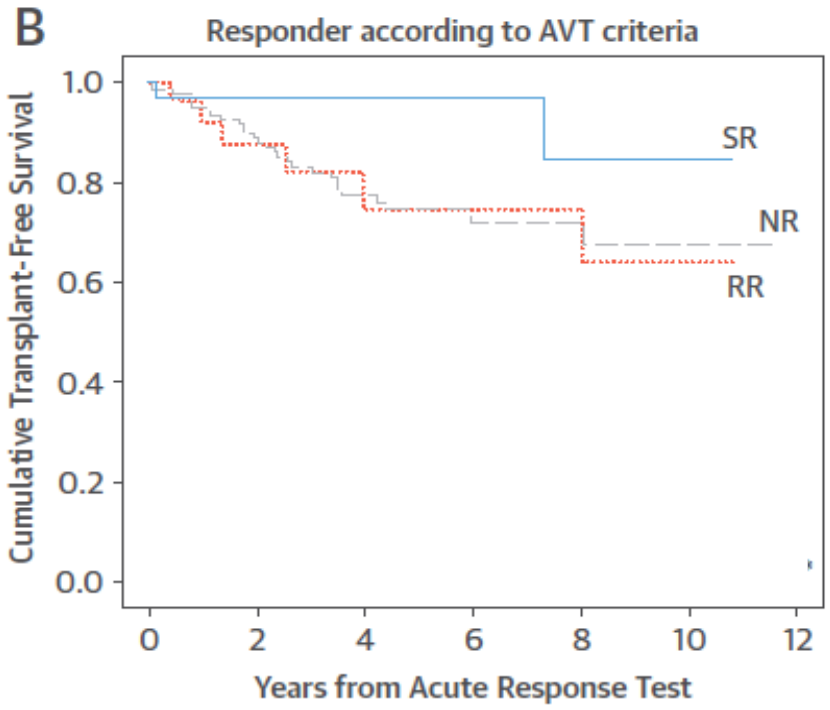
AVT in pediatric pulmonary hypertension



TOPP
Tracking Outcomes and Practice in Pediatric Pulmonary Hypertension

Douwes et al; J Am Coll Cardiol 2016
Douwes et al; Eur Heart J 2011

Survival stratified for AVT response status



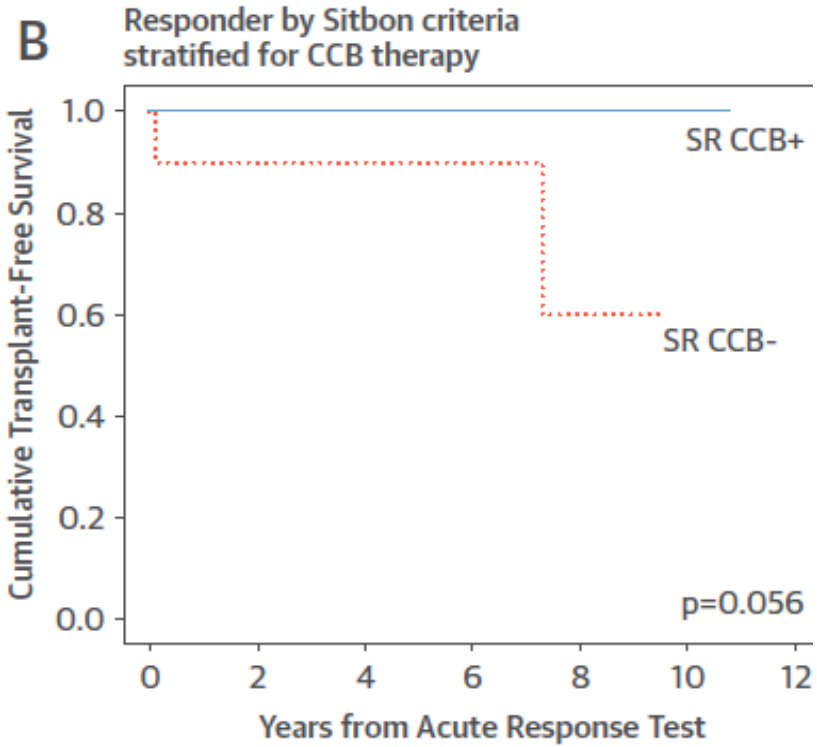
Number of cases:

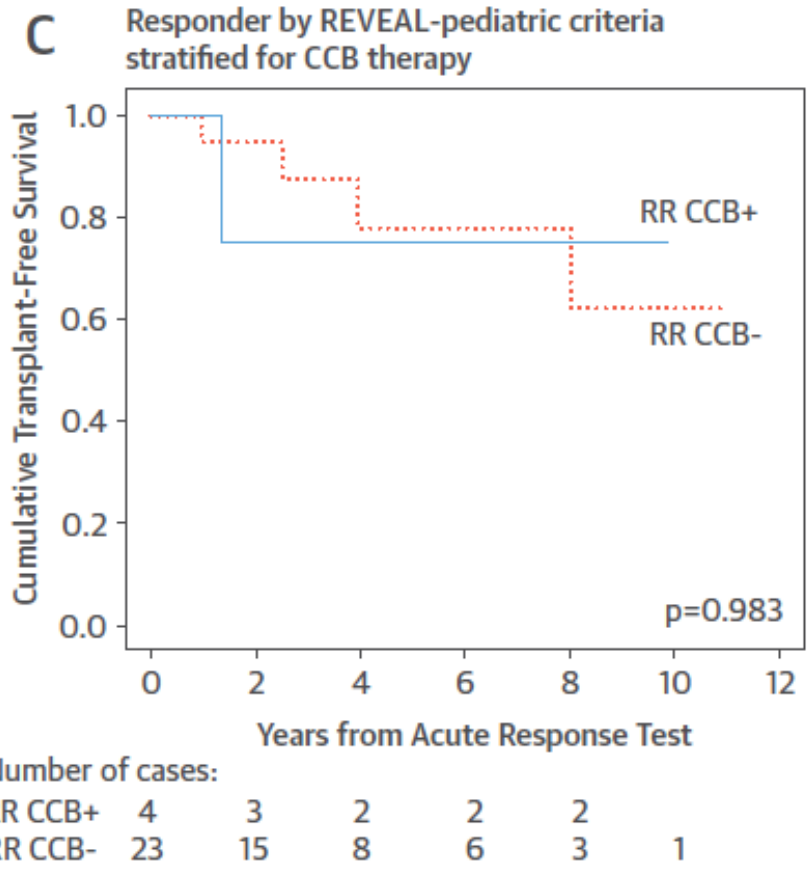
SR	32	23	16	10	5	3
NR	143	96	60	27	18	10
RR	30	18	10	8	7	1

TOPP
Tracking Outcomes and Practice in Pediatric Pulmonary Hypertension

Douwes et al; J Am Coll Cardiol 2016

Survival of AVT responders stratified for CCB treatment





Douwes et al; J Am Coll Cardiol 2016

AVT in Paediatric PAH

For children with IPAH/FPAH,

the Sitbon criteria seem to be

the criteria of choice to identify

acute vasodilator responders

who show a sustained beneficial response to CCB therapy.

TOPP
Tracking Outcomes and Practice in Pediatric Pulmonary Hypertension

Douwes et al; J Am Coll Cardiol 2016

Consensus paediatric IPAH/HPAH treatment algorithm*
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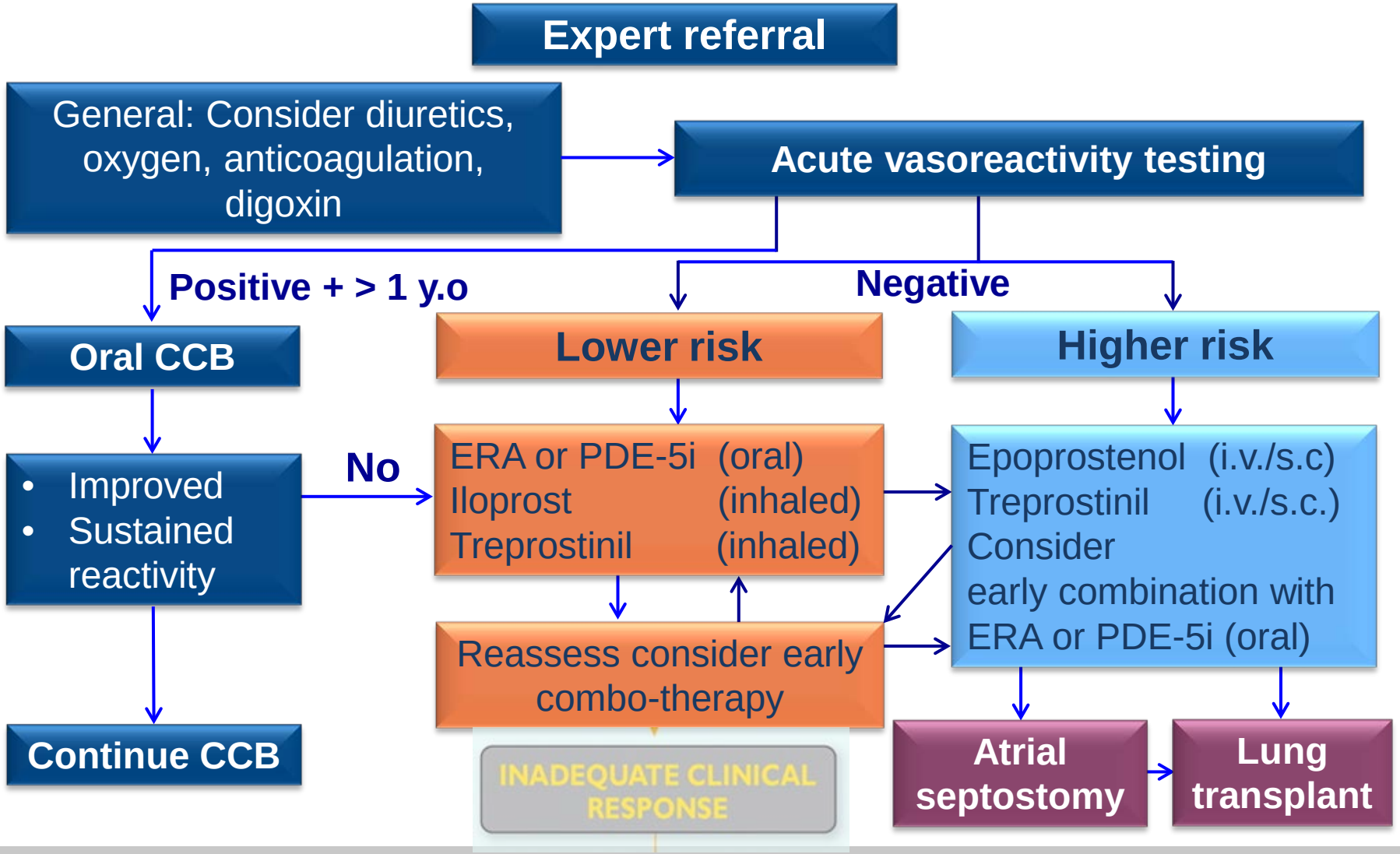


- Use of all agents is considered off label in children aside from sildenafil in Europe

Ivy D, *et al. J Am Coll Cardiol* 2013

Predictors of Outcome

New York/Denver/NL-cohort

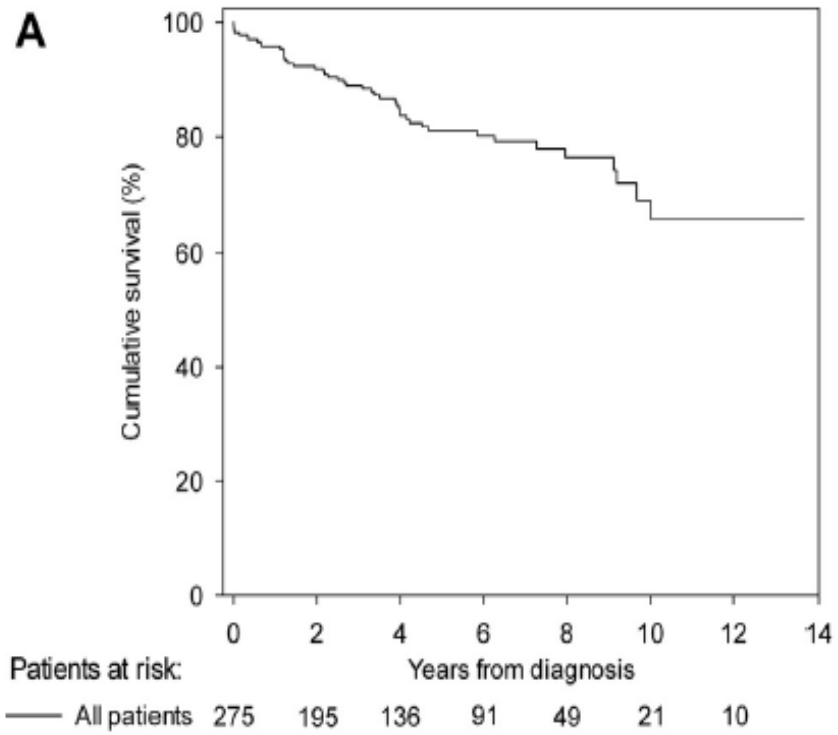


Table 4 Multivariate Backward Stepwise Cox Regression Analysis of Parameters Associated With Survival (N = 196)

	Backward Stepwise Cox Regression Analysis	
	Hazard Ratio (95% CI)	p Value
Diagnosis		
IPAH/HPAH	1.00	
PAH-CHD	0.103 (0.027–0.396)	0.001
APAH-non-CHD	15.974 (4.402–57.960)	<0.001
WHO functional class III–IV versus I–II	3.251 (1.316–8.028)	0.011
PVRi	1.053 (1.017–1.090)	0.003
mPAP/mSAP*	1.282 (1.104–1.489)	0.001
Treatment strategy		
PAH-targeted monotherapy	1.00	
No specific PAH therapy†	19.311 (3.682–101.274)	<0.001
CCB monotherapy	0.385 (0.047–3.191)	0.377
PAH-targeted dual therapy	0.156 (0.057–0.422)	<0.001
PAH-targeted triple therapy	0.094 (0.029–0.302)	<0.001

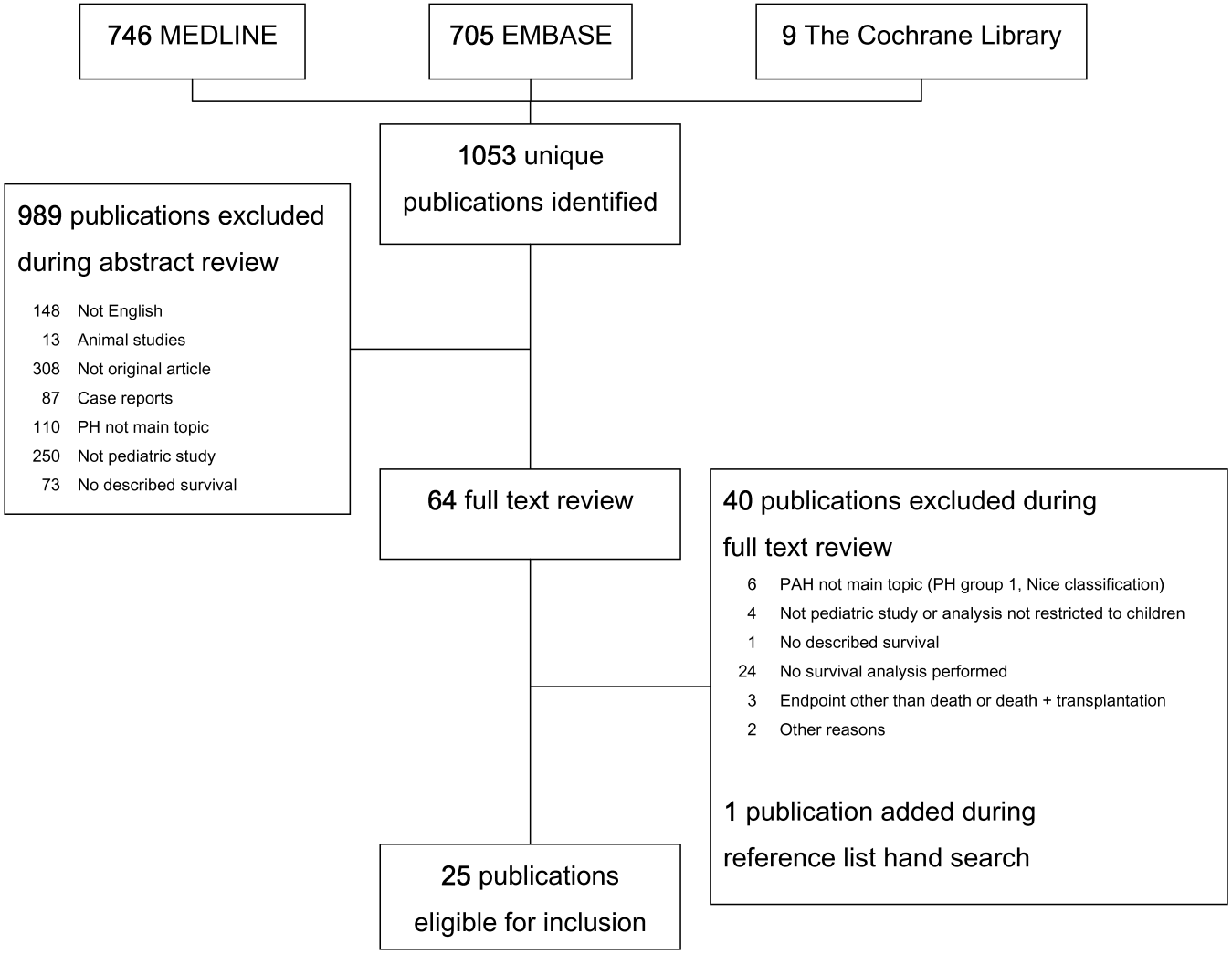
Zijlstra et al; JACC 2014

Risk factors, treatment goals and clinical end points

in Pediatric PAH

- **Risk factors**
  - for risk stratification
- **Treatment goals**
  - to evaluate treatment response
  - To adapt treatment strategies
- **Clinical End points**
  - for trial design

Predictors of Outcome in Pediatric PAH
A systematic review and meta-analyses



Ploegstra MJ et al Int J Cardiol 2015

40
candidate
predictors

	Sandoval 1995, Mexico City, n=18	Ciabby 1997, US multicenter, n=50	Barst 1999, New York, n=77	Nakayama 2007, Tokyo, n=31	Van Albada 2008, Netherlands, n=29	Bernus 2009, Denver, n=78	Haworth 2009, London, n=216	Lammers 2009, London, n=50	Van Loon 2010, Netherlands, n=52	Lammers 2010, London, n=47	Alkon 2010, Toronto, n=47	Moledina 2010, London, n=64	Ivy 2010, New York / Denver, n=86	Hislop 2011, London, n=101	Moledina 2011, London, n=31	Van Loon 2011, Netherlands, n=154	Barst 2012, US multicenter, n=216	Chida 2012, Japan/China, n=54	Apitz 2012, Giessen, n=43	Douwes 2013, Netherlands, n=52	Moledina 2013, London, n=100	Kassem 2013, Toronto, n=54	Wagner 2013, Denver, n=83	Chida 2014, Tokyo, n=59	Zijlstra 2014, Multinational, n=275	N times studied	N times significant	N extractable HR's[a]	N HR's non-overlapping cohorts
Demographic predictors																													
Age	×	×	✓						×			×	×				×			×			✓		×	10	2	6	5
Sex	×	×	✓						×			✓	×				×	×					×		×	10	2	5	5
Etiology		×					×		×				×	×		✓	×			×					✓	9	2	7	3
Clinical predictors																													
WHO-FC	×								✓	✓		✓	✓		×		×			✓	✓		✓		✓	11	8	10	4
6MWT									×	✓					×						×		×		×	6	1	2	1
Heartrate	×								×											✓	✓		×			5	2	2	2
Systolic RR									✓								×						×		✓	4	2	3	2
Diastolic RR									✓																✓	2	2	2	1
Height												✓					×						×		×	4	1	2	2
Weight									×			✓					×						×			4	1	2	2
BSA																							✓			1	1	1	1
Heartrate variability										✓																1	1	1	1
peak VO2																							✓			1	1	1	1
VE/VCO2 slope																							✓			1	1	1	1
BMPR2 mutation																		✓								1	1	1	1
Biochemical predictors																													
(NT-pro)BNP				✓	✓	✓		✓	✓								✓						×	✓	✓	9	8	8	4
Uric Acid					✓				✓														✓			3	3	3	2
Hb		×																					✓			2	1	1	1
Norepinephrine					✓																					1	1	1	1
Apo-A1																							✓			1	1	1	1
TIMP-1																							✓			1	1	1	1
sST2																								✓		1	1	1	1
Hemodynamic predictors																													
mRAP	×	✓	✓						×	×		×	×										×		✓	9	3	6	3
mPAP	×	✓	✓						×	×		×	×							×	×		✓		×	11	3	7	4
mPAP/mSAP		×							✓								✓			✓			×		✓	6	4	4	2
PVRi	×	✓	✓						×	✓		×	✓		×		✓			×			✓		✓	12	7	9	4
Cardiac index	×	×	✓						✓			×	×				✓			×			×		✓	10	4	7	4
Qp(i)		✓													×					×						3	1	2	2
SvO2			✓						✓																	2	2	2	2
PAC(i)																				✓			×			2	1	1	1
PVR/SVR	×																✓									2	1	2	2
Acute vasodilator response	×		✓						×			×					×		✓						✓	7	3	4	4
PVR during VRT										✓		✓														2	2	2	1
mPAP during VRT												✓							✓							2	2	2	2
PFR during VRT																			✓							1	1	1	1
mRAP x PVRi		✓																								1	1	1	1
PSVi																				✓						1	1	1	1
Imaging predictors																													
Echocardiography										✓	✓	✓									×	✓	✓			6	5	6	3
CMR																					✓					1	1	1	1
CT, fractal dimensions															✓											1	1	1	1

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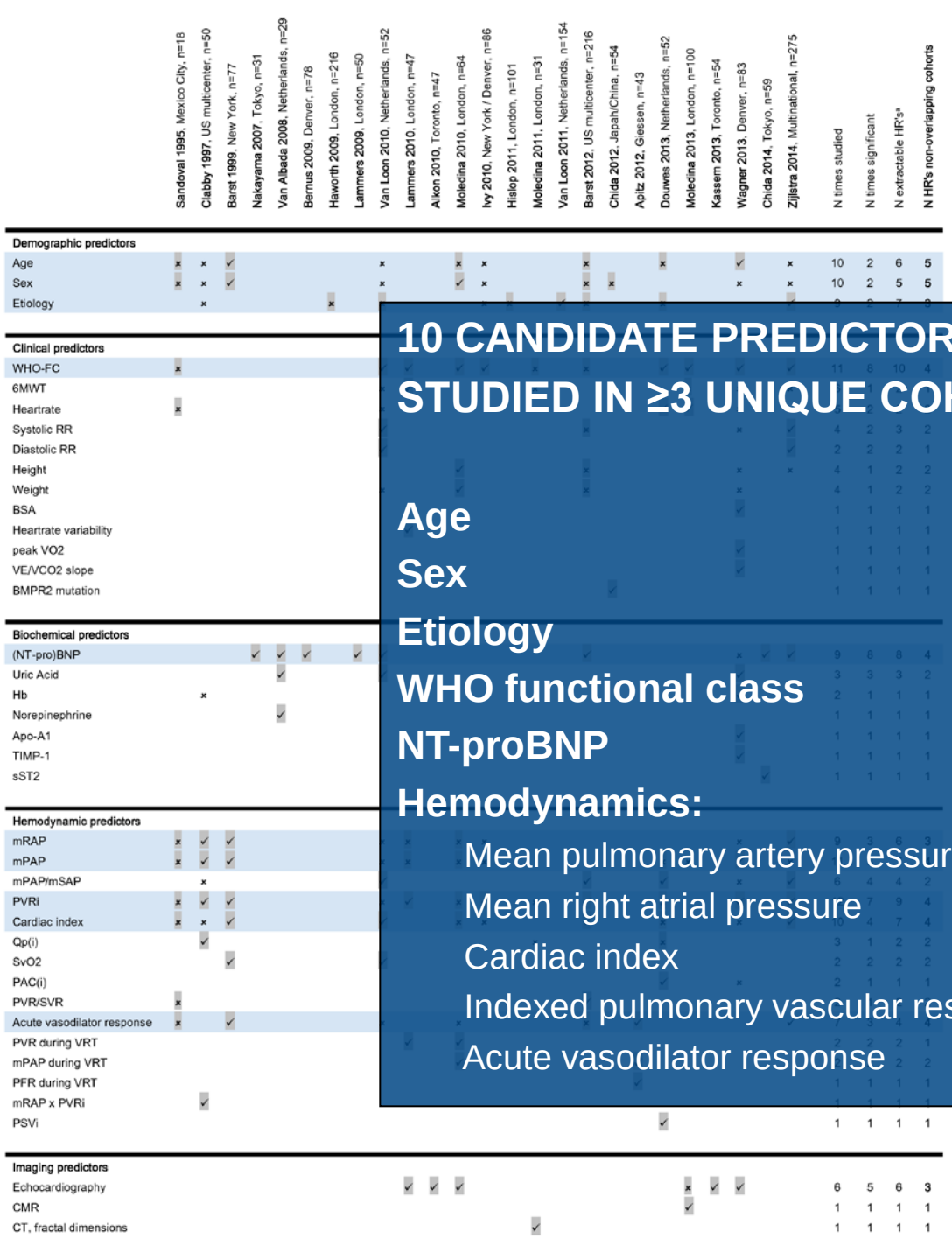
candidate
predictors



10 CANDIDATE PREDICTORS STUDIED IN ≥3 UNIQUE COHORTS:

- **Age**
- **Sex**
- **Etiology**
- **WHO functional class**
- **NT-proBNP**
- **Hemodynamics:**
  - Mean pulmonary artery pressure
  - Mean right atrial pressure
  - Cardiac index
  - Indexed pulmonary vascular resistance
  - Acute vasodilator response

Predictors of outcome in pediatric PAH

A systematic review and meta-analysis

- Six consistently reported predictors of outcome in pediatric PAH:
  - WHO functional class
  - NT-proBNP
  - Mean right atrial pressure
  - Cardiac Index
  - Pulmonary vascular resistance
  - Acute vasodilator response

ESC/ERS Guidelines adult PAH

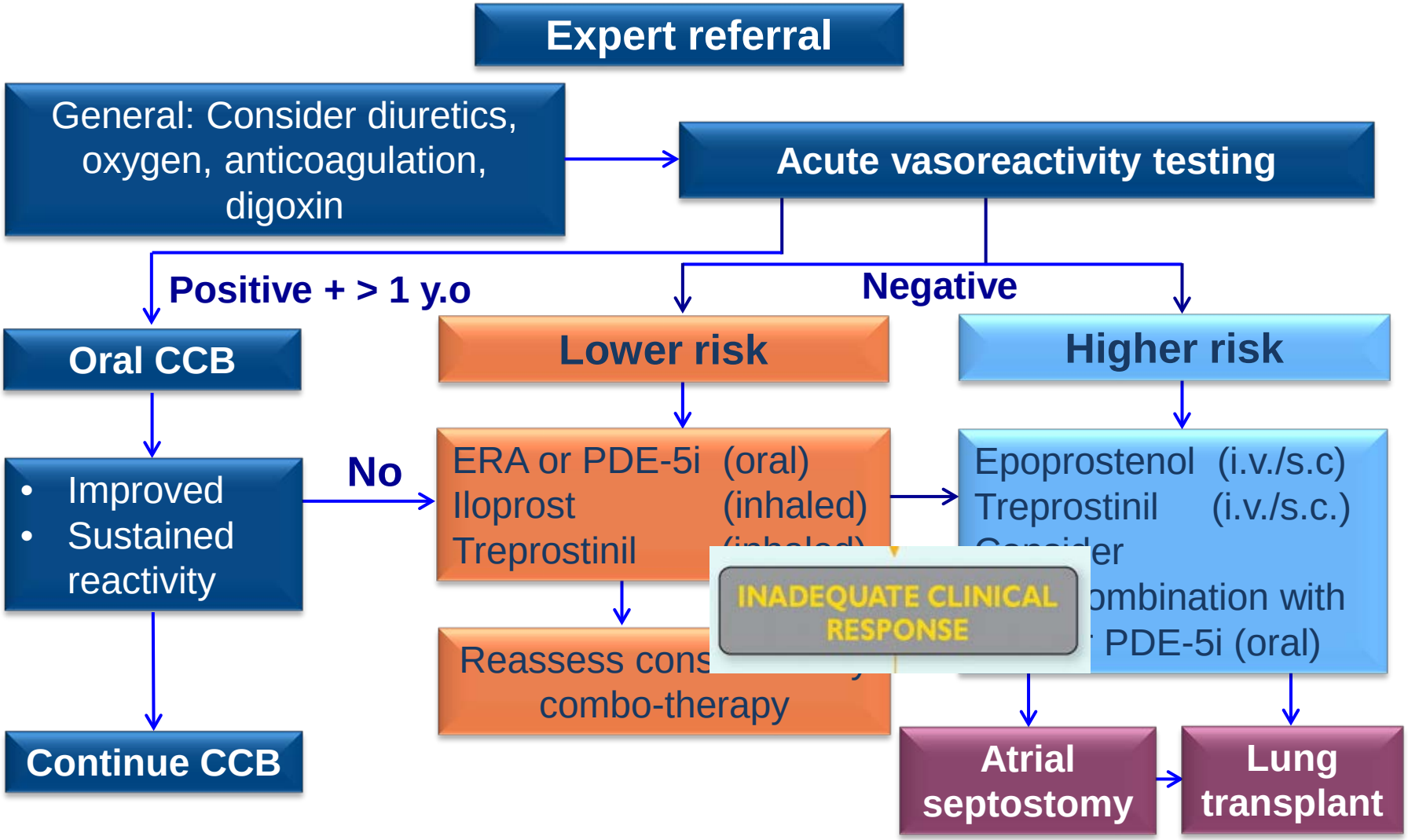
Determinants of prognosis[a] (estimated 1-year mortality)	Low risk <5%	Intermediate risk 5–10%	High risk >10%
Clinical signs of right heart failure	Absent	Absent	Present
Progression of symptoms	No	Slow	Rapid
Syncope	No	Occasional syncope[b]	Repeated syncope[c]
WHO functional class	I, II	III	IV
6MWD	>440 m	165–440 m	<165 m
Cardiopulmonary exercise testing	Peak VO_2 >15 ml/min/kg (>65% pred.) VE/VCO_2 slope <36	Peak VO_2 11–15 ml/min/kg (35–65% pred.) VE/VCO_2 slope 36–44.9	Peak VO_2 <11 ml/min/kg (<35% pred.) VE/VCO_2 slope ≥45
NT-proBNP plasma levels	BNP <50 ng/l NT-proBNP <300 ng/l	BNP 50–300 ng/l NT-proBNP 300–1400 ng/l	BNP >300 ng/l NT-proBNP >1400 ng/l
Imaging (echocardiography, CMR imaging)	RA area <18 cm^2 No pericardial effusion	RA area 18–26 cm^2 No or minimal, pericardial effusion	RA area >26 cm^2 Pericardial effusion
Haemodynamics	RAP <8 mmHg CI ≥2.5 l/min/m^2 SvO_2 >65%	RAP 8–14 mmHg CI 2.0–2.4 l/min/m^2 SvO_2 60–65%	RAP >14 mmHg CI <2.0 l/min/m^2 SvO_2 <60%

Galie et al Eur Heart J 2015

- This study:
  - Does not preclude the potential of other variables
  - Provides direction for further research

Ploegstra MJ et al Int J Cardiol 2015

Consensus paediatric IPAH/HPAH treatment algorithm*
5th WSPH (Nice 2013):



- Use of all agents is considered off label in children aside from sildenafil in Europe

Ivy D, *et al. J Am Coll Cardiol* 2013

Treatment Goals

Clinically meaningful:

- Clinical event relevant to the patient
  - Death, Tx, Hospitalisation for PAH
- Measures directly how a patient feels, functions or survives
  - Symptoms, Functional class, excercise testing, 6MWD, (ADL-)activities?

    (provided no negative impact mortality/morbidity)

Surrogate:

- Used as a substitute for a clinically meaningful endpoint
- Changes induced by a therapy on such variable are expected to reflect changes in a clinically meaningful endpoint

Flemming and Powers. Stat in Med 2012

Pediatric PAH Treatment Goals

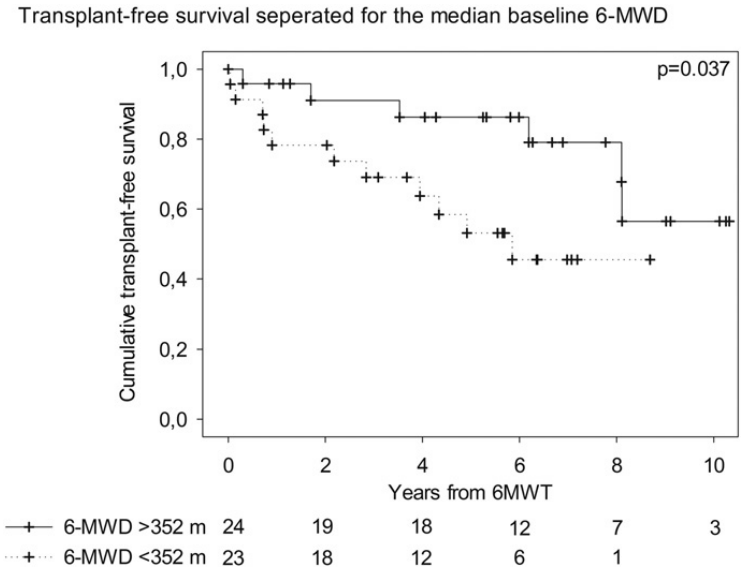
WSPH Pediatric Task Force, 2013

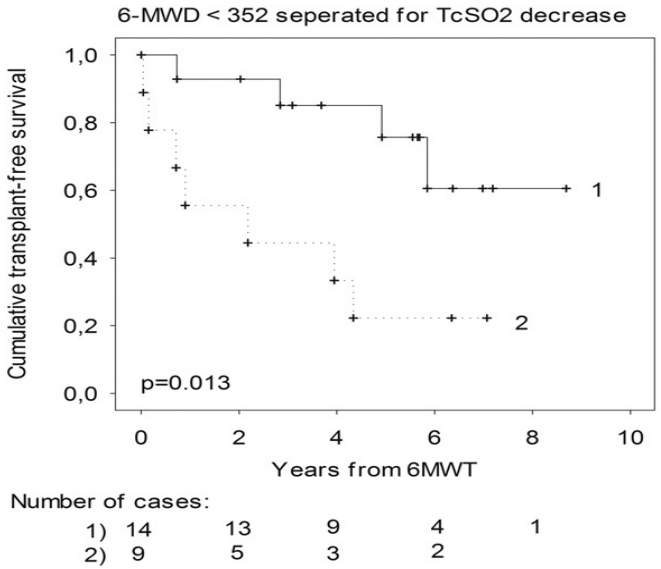
LOWER RISK	DETERMINANTS OF RISK	HIGHER RISK
No	Clinical evidence of RV failure	Yes
No	Progression of symptoms	Yes
No	Syncope	Yes
	Growth	Failure to thrive
I,II	WHO functional class	III,IV
Minimally elevated	BNP / NTproBNP	Significantly elevated, rising
syst CI > 3.0 L/min/m^2 mPAP/mSAP < 0.75 Acute Vasoreactivity	Hemodynamics	syst CI < 2.5 L/min/m^2 mPAP/mSAP > 0.75, rising RAP > 10mmHg PVRI > 20 WU*m^2
	Echocardiography	Severe RV dysfunction, PE
> 450 m, stable (> z-2 ; % predicted)	6MWD (if ≥ 8 yr and developmentally able)	≤ 350m decreasing

Level of evidence C

Ivy et al J Am Coll Cardiol 2013

6MWT in Paediatric PAH





The 6-MWD is feasible in children > 7yrs with PAH

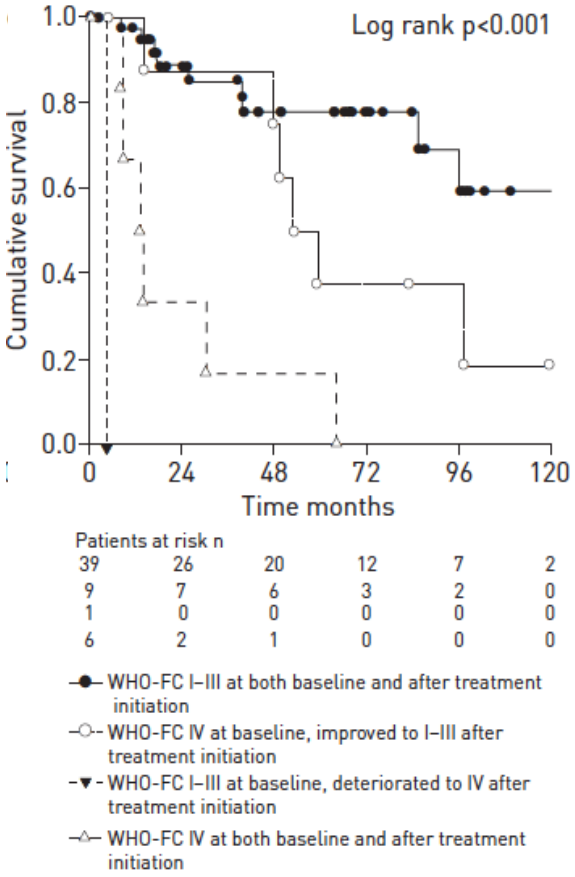
Both absolute values and z-scores:

- represents directly “how a child feels, functions”
- correlates with WHO-FC and NTproBNP and CPET
- +/- Predicts transplant free survival

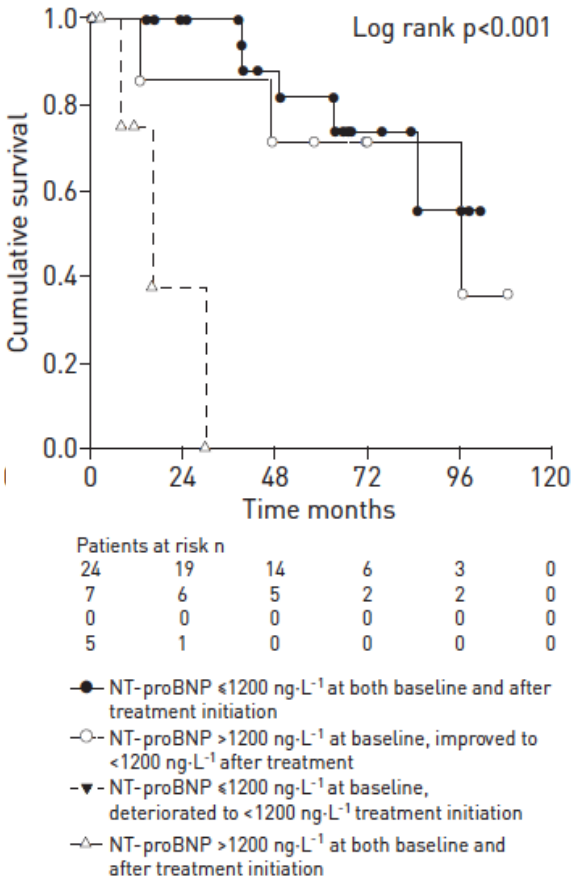
Douwes JM, et al. Heart 2014
Zuk et al; Ped Cardiol 2017
Lammers et al; Arch Dis Child 2011

Treatment Goals in Pediatric PAH

WHO-FC



NT-pro-BNP



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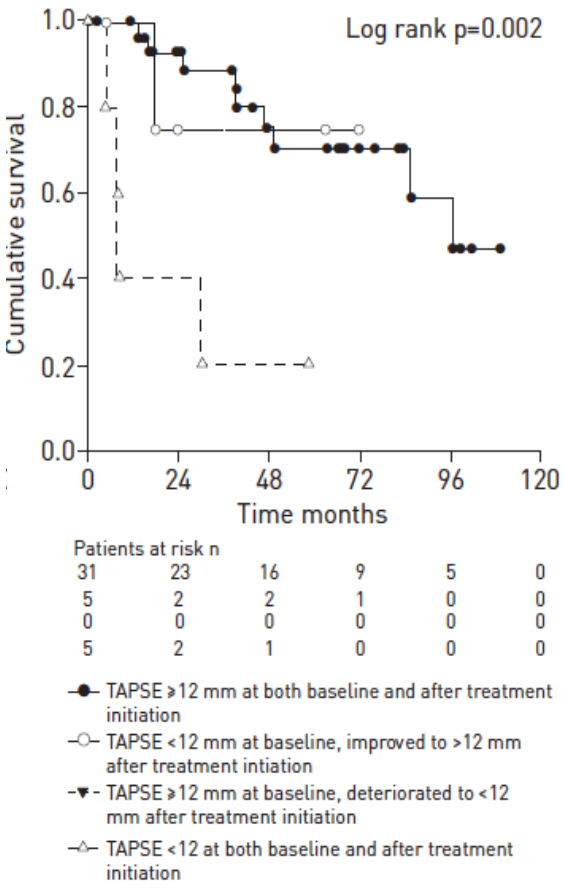


Ploegstra MJ et al. Eur Resp J 2015

Pediatric PAH
Clinical Endpoints

- Adult trials are currently shifting towards long-term trials with an event-driven design
  - Feasibility in children to have a 3-5 year trial?

- We are still searching for an endpoint for the paediatric population that is acceptable, reproducible, without risks and feasible with a reasonable number of patients!

Time to clinical worsening in paediatric PAH

5th WSPH (Nice 2013):

- Death
- Transplantation
- Hospitalisation for PAH, unplanned
  - Includes instalment of i.v. epoprostenol therapy
- Deterioration of PAH
  - Increased functional class

  and

  - Signs/symptoms of RHF

  and/or

  - Decreased exercise capacity (6MWD, CPET) (if applicable)

Ivy D, *et al. J Am Coll Cardiol* 2013

Endpoint event rates

Total group (n=70)

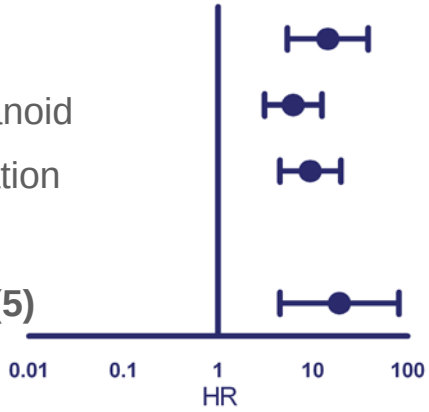
	Patients n (%)	Event rate n/100 py
(1) Death	28 (40%)	10.1
(2) Lung-transplantation	7 (10%)	2.5
(3) Hospitalization	38 (54%)	21.4
(4) Initiation of IV prostanoids	26 (37%)	9.4
(5) Functional deterioration	50 (71%)	48.1
Combination of (1)(2)(3)(4)(5)	59 (84%)	**91.5**

Stratified by diagnostic groups

	Event rate n/100 py
Idiopathic PAH (n=37)	102.1
Associated PAH – CHD (n=25)	63.5
Associated PAH – Other (n=8)	264.4

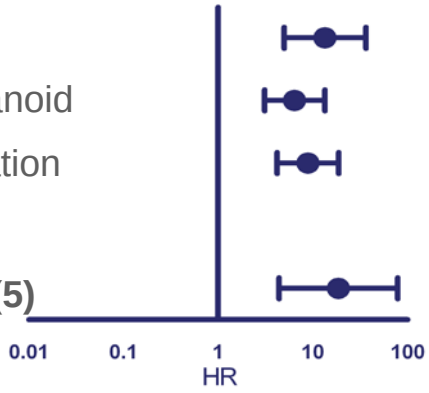
Association of *soft* endpoint components with *hard* endpoints

Time-dependent Cox regression analysis



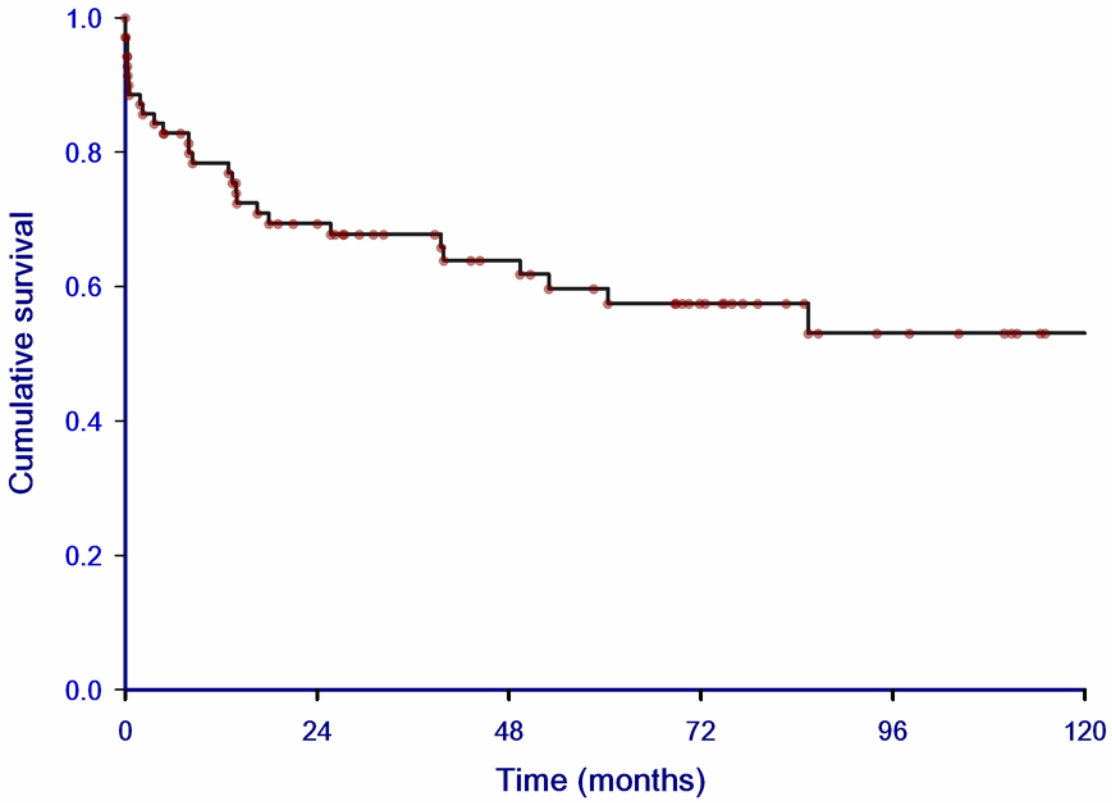
(3) Hospitalization	9.4 (4.5-19.8)	P<0.001
(4) Initation of IV prostanoid	6.2 (3.1-12.5)	P<0.001
(5) Functional deterioration	14.4 (5.4-38.6)	P<0.001
Combination of (3)(4)(5)	**19.1 (4.5-81.2)**	**P<0.001**

Adjusted for diagnosis



(3) Hospitalization	8.9 (4.2-18.8)	P=0.003
(4) Initation of IV prostanoid	6.4 (3.1-13.4)	P=0.008
(5) Functional deterioration	13.4 (5.0-36.3)	P=0.005
Combination of (3)(4)(5)	**18.6 (4.4-79.1)**	**P=0.014**

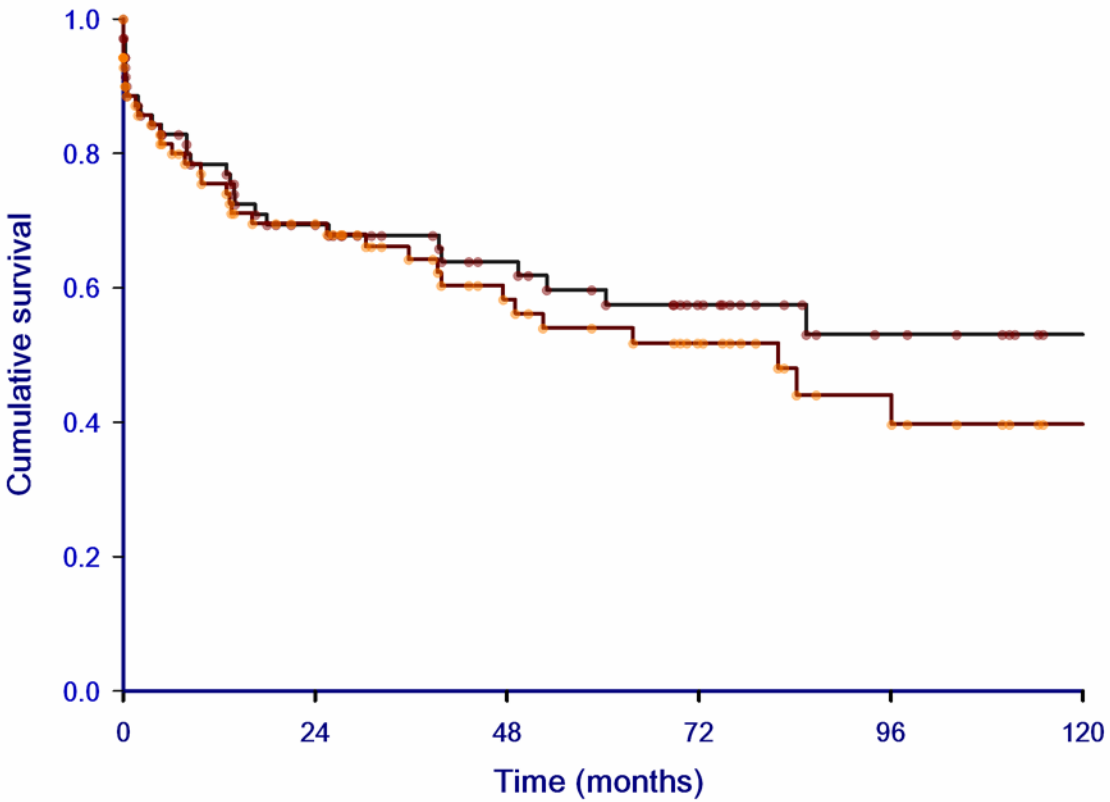
Timing of events



Freedom from **death**

MJ Ploegstra et al. Chest 2015

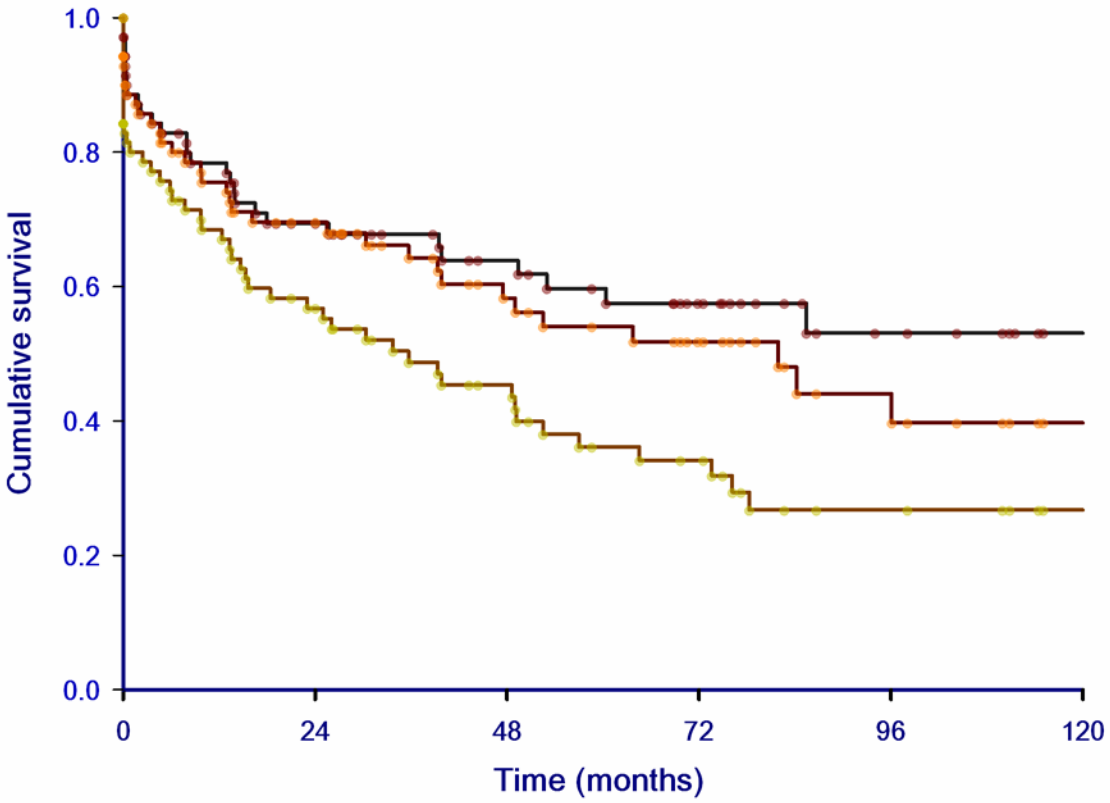
Timing of events



Freedom from **death + lung-transplantation**

MJ Ploegstra et al. Chest 2015

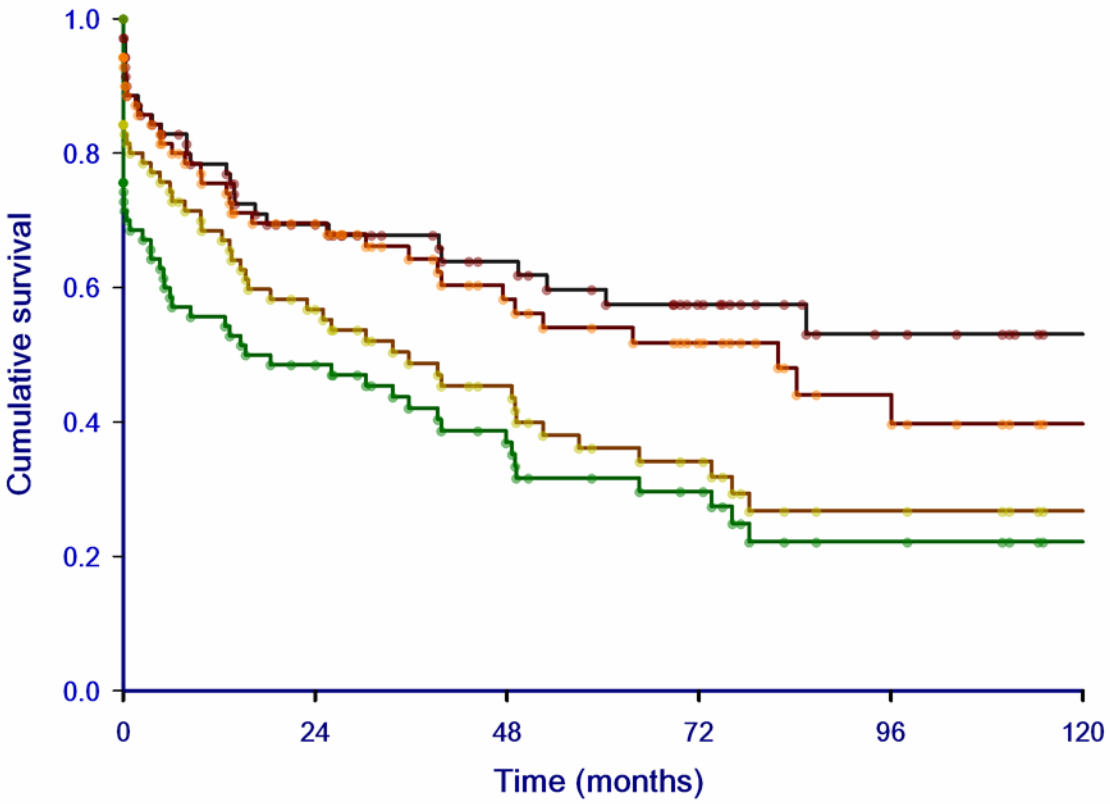
Timing of events



Freedom from **death + lung-transplantation + hospitalization**

MJ Ploegstra et al. Chest 2015

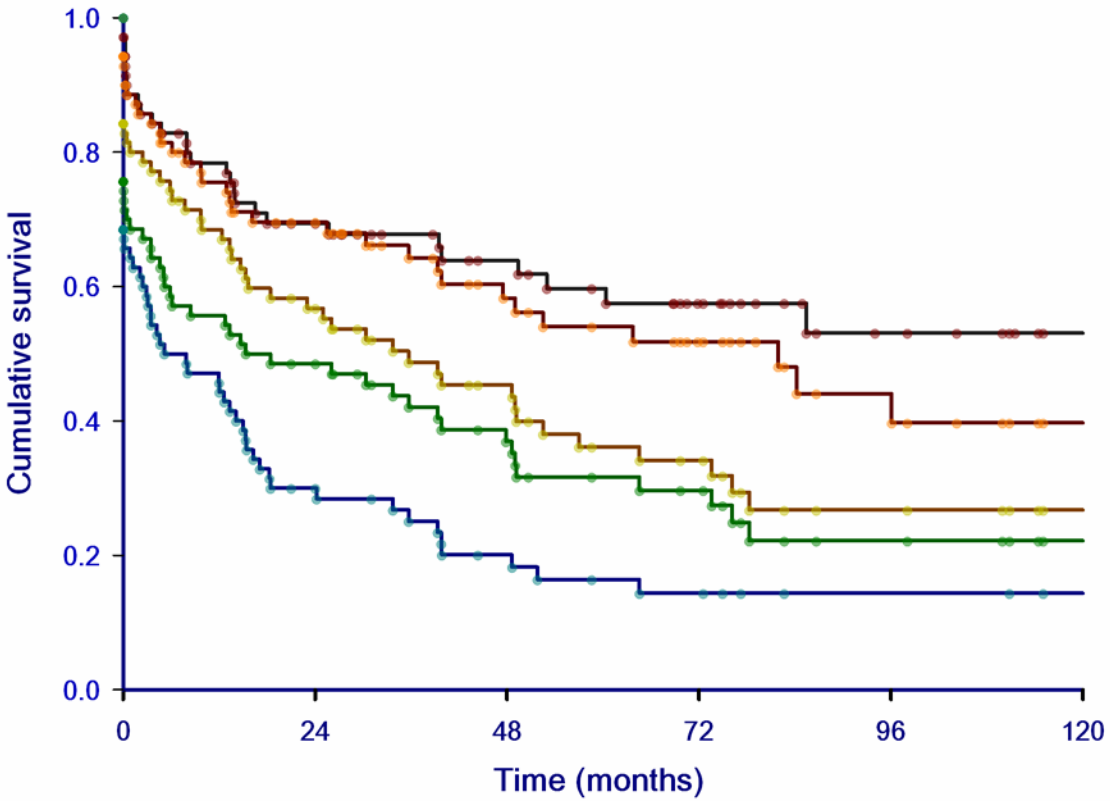
Timing of events



Freedom from **death + lung-transplantation + hospitalization + initiation of IV prostanoids**

MJ Ploegstra et al. Chest 2015

Timing of events



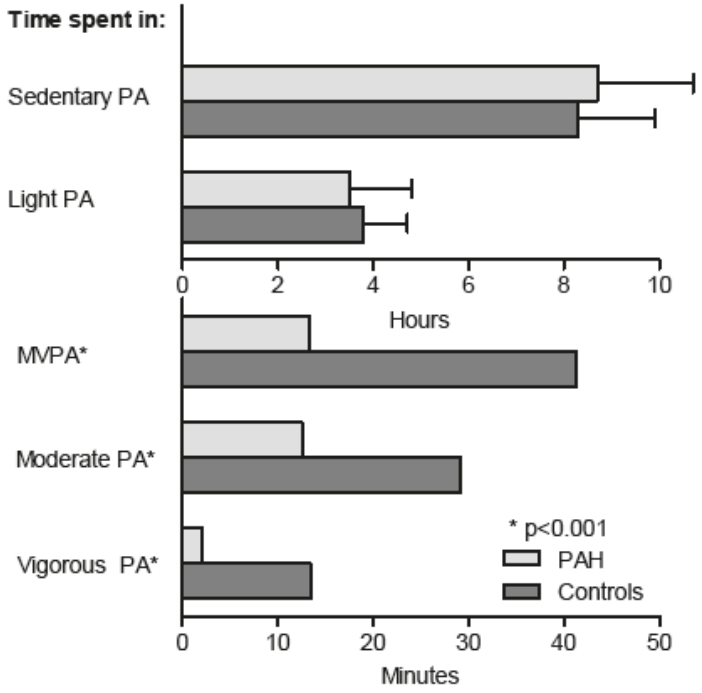
TOPP
Tracking Outcomes and Practice in Pediatric Pulmonary Hypertension

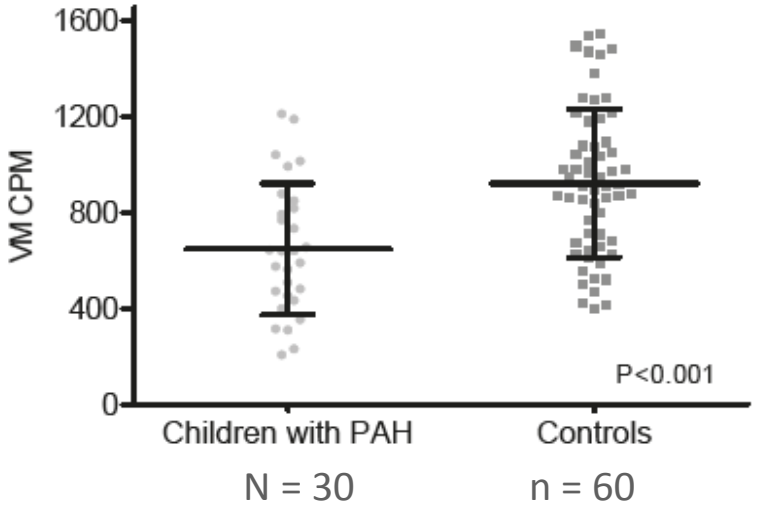
Freedom from **death + lung-transplantation + hospitalization + initiation of IV prostanoids + functional deterioration**

= TIME TO CLINICAL WORSENING

MJ Ploegstra et al. Chest 2015
M Beghetti et al. submitted

Physical activity in Ped PAH measured by accelerometry:
a candidate clinical endpoint?





Time spent in vigorous or moderate PA:

- correlated with WHO-FC and 6MWD
- Predicted event-free survival
- Further validation warranted

Zijlstra et al; Am J Resp Crit Care Med 2017

Pediatric Formularium for Bosentan: The FUTURE progam

over 100 children with IPAH/HPAH

Pharmacokinetic and clinical profile of a novel formulation of bosentan in children with pulmonary arterial hypertension: the FUTURE-1 study

PHARMACOKINETICS

A bosentan pharmacokinetic study to investigate dosing regimens in paediatric patients with pulmonary arterial hypertension: FUTURE-3

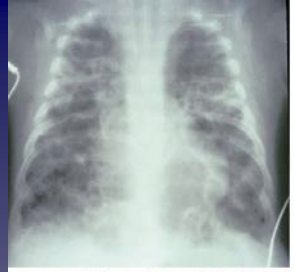
FUTURE-2: Results from an open-label, long-term safety and tolerability extension study using the pediatric FormUlation of bosenTan in pUlmonary arterial hypeRtEnsion

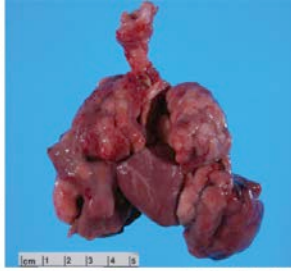
- PK/PD, dosing, different age groups
- Tolerabilty
- Safety
- (Exploratory Efficacy??)
- Simulation and modeling!

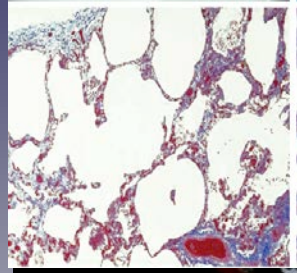
Beghetti et al Br J Clin Pharmacol 2009
Berger et al, Int J Cardiol 2016
Berger et al Br J Clin Pharmacol 2017

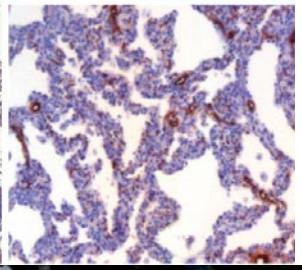
Challenges in Pediatric PAH

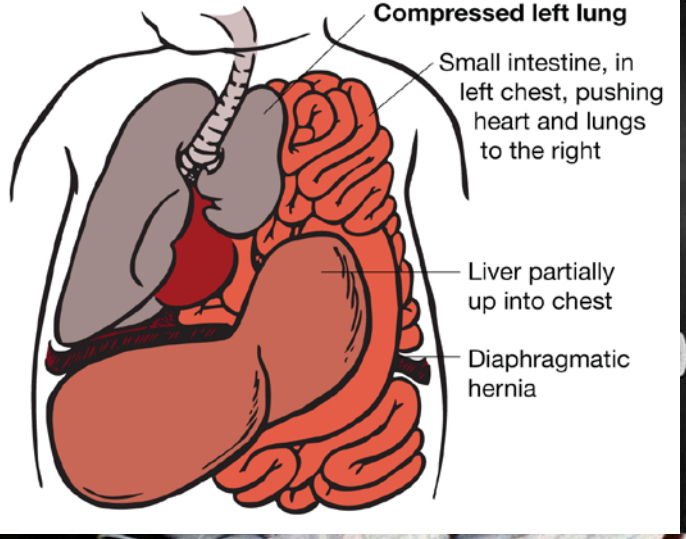
- **Agree on Treatment Goals and Clinical Endpoints**
- **Agree on Study Population**
  - Definition IiPAH/HPAH +/- PAH-CHD)
  - Rarity / Heterogeneity?
- **Study designs**
  - RCT? (Standard of care (80%)
  - Alternative designs
    - SMART
    - Adaptive / Bayesian
    - Valuable information from: cohort studies, registries, historical controls and meta-analyses

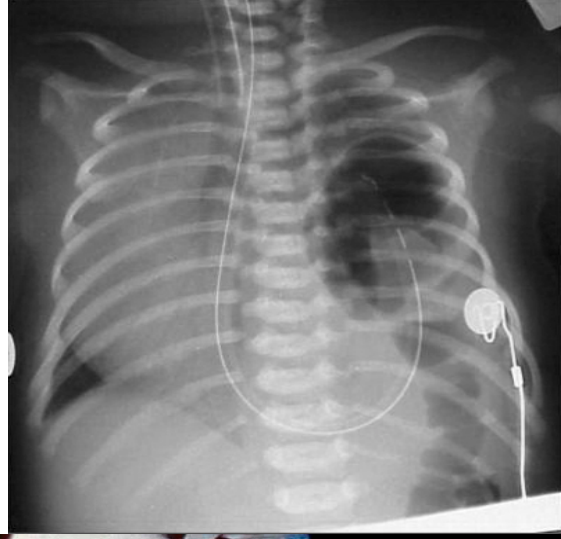


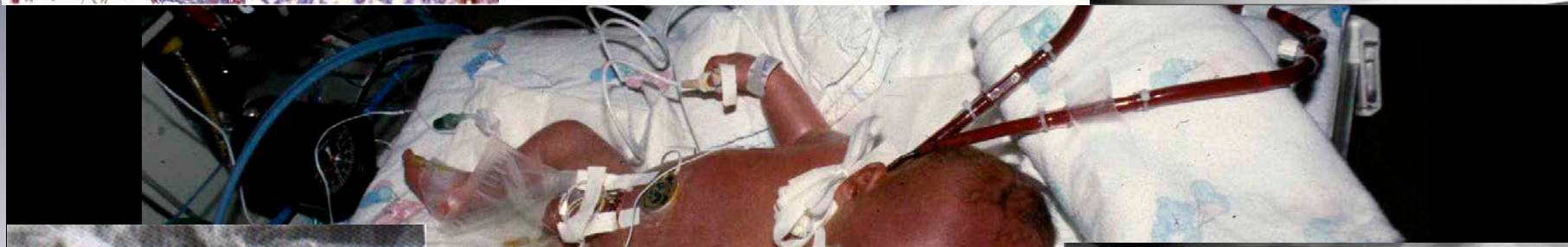


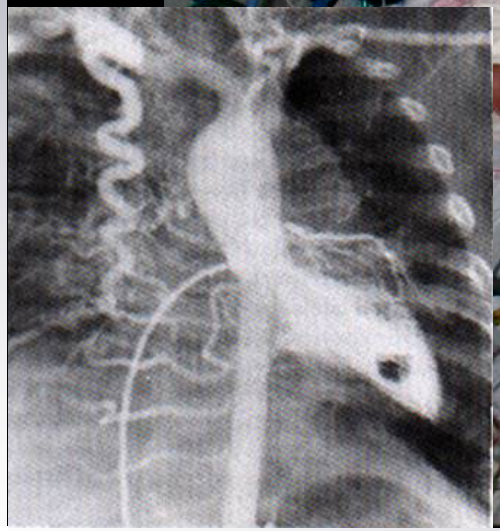


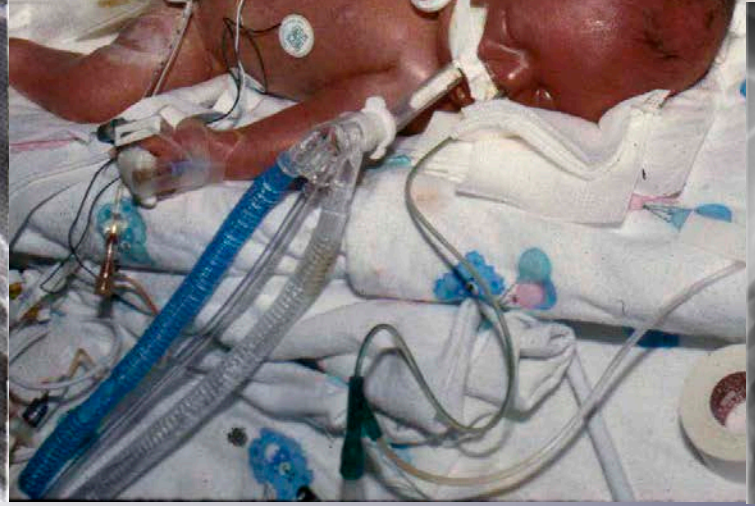


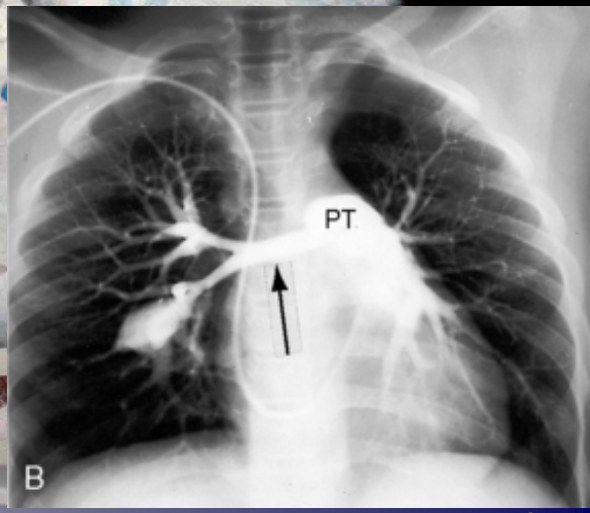

Compressed left lung
Small intestine, in left chest, pushing heart and lungs to the right
Liver partially up into chest
Diaphragmatic hernia







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