

Epidemiology and Clinical Characteristics: Registries

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Pediatric P”A”H

Learning from registries

- Epidemiology
- Clinical presentation and characteristics
- Outcome
- Prognostic parameters

Pediatric P”A”H

Learning from registries

- **Epidemiology**
- **Clinical presentation and characteristics**
- **Outcome**
- **Prognostic parameters**

Pediatrics

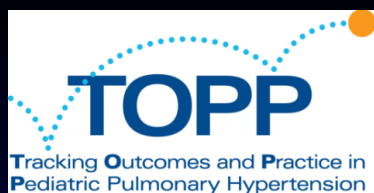
- **Single or 2 two centers studies**
- **Post marketing survey**
- **National registries**
- **Large scale registries**
 - **Reveal US**
 - **TOPP (world wide registry)**

Diagnostic Work-up

	All patients (N=456)		
	All (n=456)	Incident (n=135)	Prevalent (n=321)
ECG, n (%)	430 (94)	131 (97)	299 (93)
Abnormal, n (%)	385 (90)	116 (89)	269 (90)
Chest X-ray, n (%)	406 (89)	126 (93)	280 (87)
Abnormal, n (%)	325 (80)	103 (82)	222 (80)
Echocardiogram, n (%)	439 (96)	132 (98)	307 (96)
Abnormal, n (%)	436 (99)	132 (100)	304 (99)
All 3 tests normal	0	0	0
2 tests normal	15 (3)	6 (4)	9 (3)
1 test normal	81 (18)	23 (17)	58 (18)

Haemodynamics at diagnosis

	All PH confirmed patients	PH Group 3	PAH Group 1					APAH-Other
			IPAH / FPAH	APAH-CHD				
				All	Shunt (unrepaired / partial)	Repaired shunt	Never shunt	
Pts with HC at DX, n (%)	357 (99)	42 (100)	178 (98)	115 (100)	61 (100)	45 (100)	9 (100)	19 (95)
mPAP (mmHg)	58 (56, 59)	44 (39, 48)	59 (57, 62)	61 (57, 64)	64 (59, 69)	56 (49, 62)	62 (49, 75)	53 (45, 61)
Cardiac index (L/min/m²)	3.7 (3.5, 3.8)	4.2 (3.6, 4.8)	3.4 (3.2, 3.6)	3.9 (3.5, 4.3)	3.8 (3.3, 4.3)	3.7 (3.2, 4.2)	5.4 (2.6, 8.3)	4.0 (2.8, 5.2)
PVRi	16.0 (14.9, 17.0)	9.8 (8.1, 11.5)	17.2 (15.8, 18.6)	16.3 (14.3, 18.3)	16.8 (14.6, 19.0)	15.0 (11.7, 18.3)	19.3 (4.0, 34.7)	14.9 (11.1, 18.7)



Complications at diagnostic cardiac catheterisation

Number of Patients* (n/N%)	Incident Patients (n = 135)	Prevalent Patients (n = 321)	All Patients (n = 456)	p value ~
Heart Catheterisation*	131 (97)	314 (98)	445 (98)	
Patients with significant complications during/after HC	5 (4)	21 (7)	26 (1)	0.28
Hypotension requiring intervention	3 (2)	9 (3)	12 (1)	
Pulmonary hypertensive crisis	2 (2)	3 (1)	5 (1)	
Arrhythmia requiring intervention	1 (1)	3 (1)	4 (1)	
Unexpected ICU admission after HC	1 (1)	3 (1)	4 (1)	
Other	0	4 (1)	4 (1)	
Cardiac Arrest	1 (1)	1 (<1)	2 (<1)	
Death/Stroke/Hemothorax/ Pneumothorax/Pericardial effusion/ Cardiac perforation/Bleeding requiring transfusion/Inotropic support required	0	0	0	

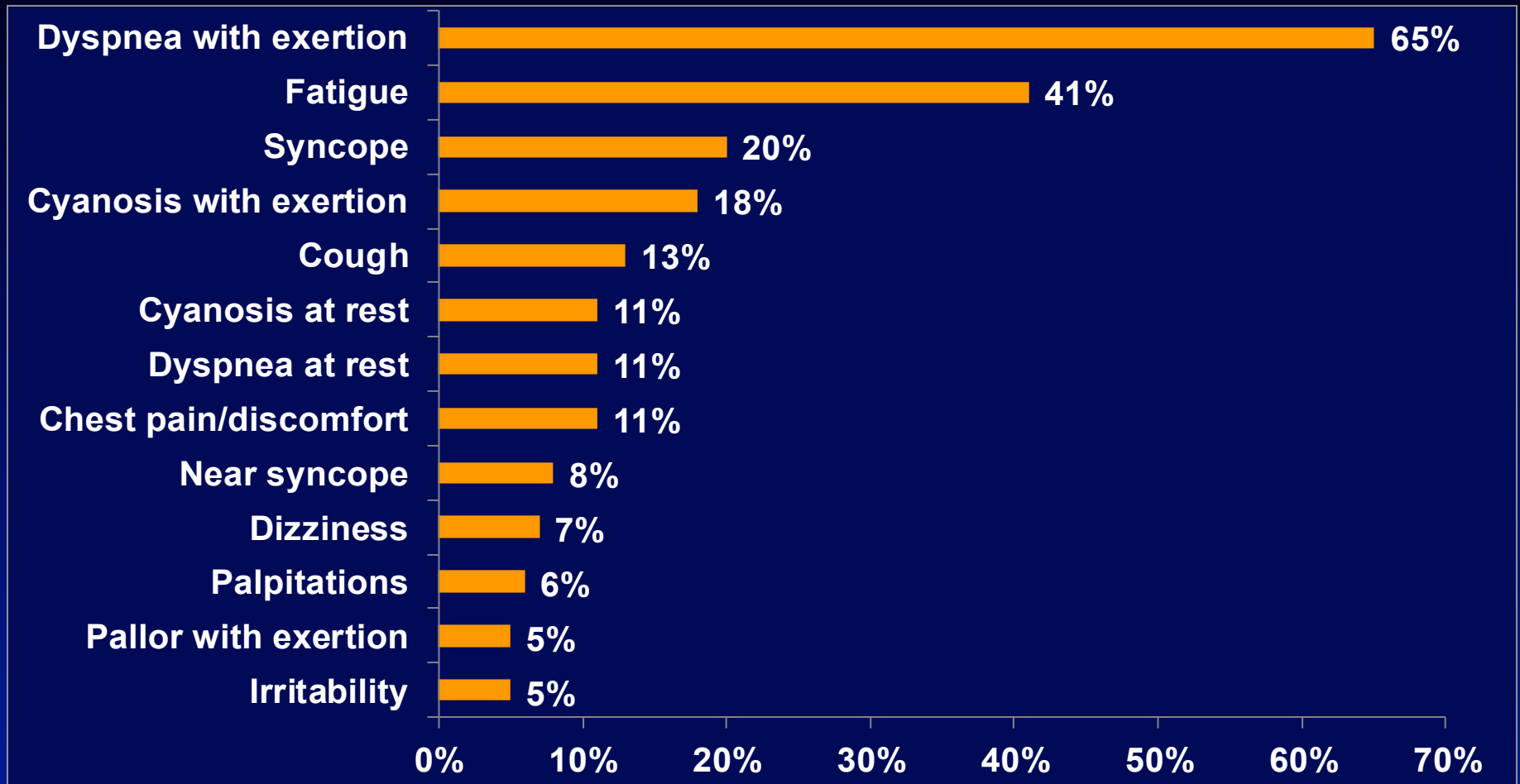
~ Fisher's Exact test

* It was intended that all patients would undergo heart catheterization, but 21 patients had missing confirmation on the case report form. Percentages based on denominator of patients undergoing heart catheterization

Incidence and prevalence

- **France PAH excluding CHD**
 - Prevalence Overall 4.2 per million
 - Prevalence IPAHA 2.4 per million
- **UK only IPAHA**
 - Incidence 0.48 per million
 - Prevalence 2.07 per million
- **Netherlands PH**
 - IAPH incidence 0.7 and prevalence 4.4 per Mio
 - CHD-PAH incidence 2.2 and prevalence 15.6

Pediatric PAH Presenting Symptoms: Global TOPP Registry



N=362. TOPP: Tracking Outcomes and Practice in Pediatric Pulmonary Hypertension
Berger, Beghetti, Humpl, Raskob, Ivy, Jing, Bonnet, Schulze-Neick, Barst.
Lancet 2012;379:537-546

Epidemiology: Current Knowledge

	Fasnacht Swiss Med wkly 2007	Beghetti Pediatr Res 2008	Van Loon J Ped 2009	Fraisse Arch Cardiovasc Dis 2010	Rosenzweig JACC 2005	Haworth Heart 2010
Number of patients	23	146	63	50	86	216
Age (median in years)	3.5	2 to 11	5.8	8.9	5	NA
Female (%)	52	48.6	62	48	57	62/52 ⁺
Group 1 PAH (%)	20 (87%)	131 (90%)	54 (86%)	50 (100%)	86 (100%)	173 (80%)
Idiopathic PAH (%)	8 (35%)	59 (40%)	29 (46%)	30 (60%)	36 (42%)	60 (28%)
Heritable (%)				5 (10%)		
CHD (%)	12 (52%)	66 (45%)	23 (37%)	12(24%)*	48 (56%)	104 (48%) §
CTD (%)		4 (2.8%)	2 (3%)		2 (2%)	9 (4%)
Portopulmonary (%)		1 (0.7%)				
HIV(%)						
Group 3: lung disease (%)	3(13%)	2 (1%)	8 (12%)	NI		29 (14%)
Other (%)		13 (9%)	1 (2%)			14 (7%)

Functional Class: Current Knowledge

	NYHA 1	NYHA 2	NYHA 3	NYHA 4
Van Loon et al	2	27	47	24
Fraisse et a	17	54	26	2
Fasnacht et al	0	16	76	8
Beghetti et al	6	28	51	10
Rosenzweig et al	8	43	41	8
Badesch et al	21	52	24	3
Haworth et al	0	19	53	28

NYHA; New York Heart Association

Results are in %

For Beghetti, 5% were not classified

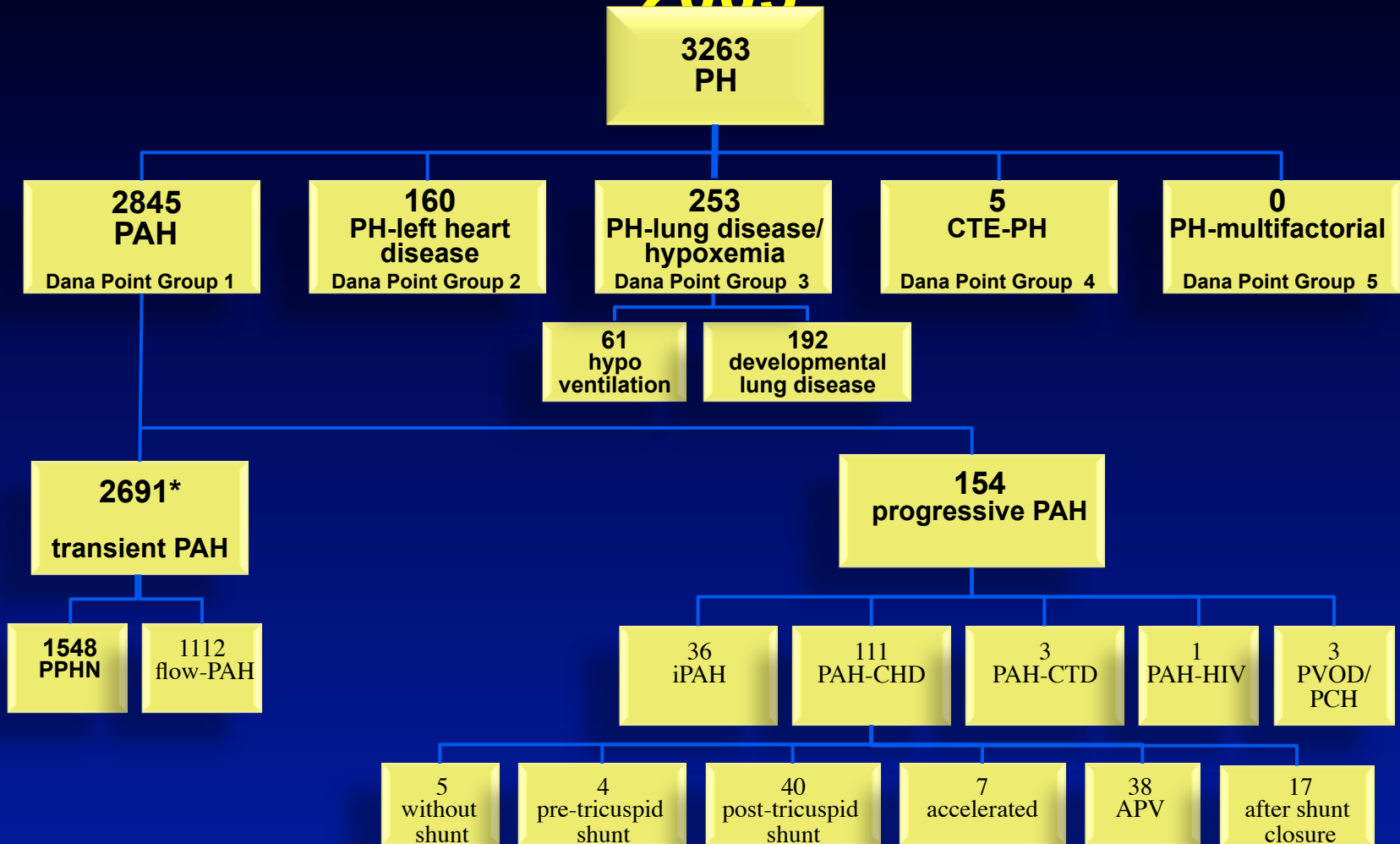
Van Loon J Ped 2009, Fraisse Arch Cardiovasc Dis 2010, Fasnacht Swiss Med Wkly 2007,
Beghetti Pediatr Res 2008, Rosenzweig JACC 2005, Badesch Chest 2010, Haworth Heart 2010

Pediatric Pulmonary Hypertension

Limitations of these studies

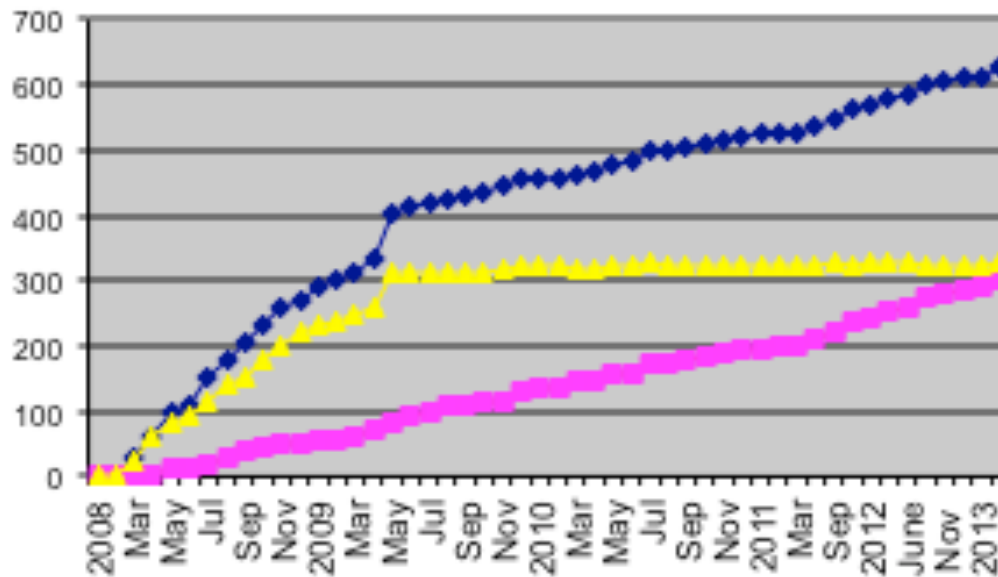
- **Small patient numbers (50–216)**
- **Unclear enrolment criteria, selection bias**
- **Insufficient disease characterisation**
- **Non-exhaustive nature of the cohort**
- **No representation of different PH groups according to the clinical classification of PH**
- **Retrospective nature of studies**

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



Enrollment into TOPP

- First international registry in pediatric pulmonary hypertension (PePH)
- 22 Countries participating (world wide):
- 38 Sites registered for participation
- *Ongoing recruitment for incident patients*



Clinical symptoms at diagnosis

- **Dyspnea with exertion: 65%**
- **Fatigue: 41%**
- **Syncope: 20%**
- **Cyanosis with exertion: 18%**
- **Cyanosis with rest: 12%**
- **Dyspnea with rest: 11%**
- **Chest pain: 11%**

Symptoms

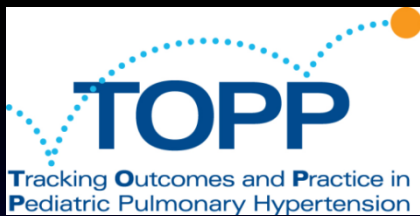
	NL ¹	TOPP ²	REVEAL ⁵
Patients, <i>n</i>	63	362	216
Age (yrs), median	5.8	8.9	7
Dyspnea at exertion, %	62 (98)	235 (65)	100 (46)
Syncope	8 (13)	73 (20)	51 (24)
Idiopathic PAH	7 (11)	57 (31)	44(36)
CHD (shunt)	1 (2)	0 (0)	3 (4)
WHO functional class (%)			
I	2	12	7
II	27	51	45
III	47	30	37
IV	24	7	12
mPAP (mmHg)	52	58	56
PVRi (WU.m ²)	18	16	17
CI (L/min/m ²)	2.8	3.7	3.7

Symptoms

Comorbidities

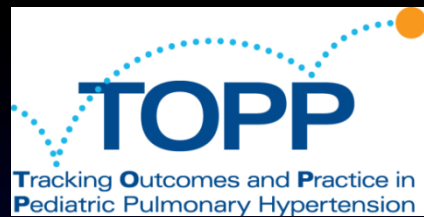
	NL ¹	TOPP ²	REVEAL ³
Patients, <i>n</i>	63	362	216
Age (yrs), median	5.8	8.9	7
Comorbidities	27 (43)	86 (24)	NR
Trisomy 21	13 (21)	42 (12)	NR
Other	14 (22)	44 (12)	NR
chromosomal, non-chromosomal, syndromes			
PPHN	NR	8 (2*)	NR
		≥ 10 times normal; ≥ 2.5 times higher controlling for trisomy 21	

1. van Loon *et al. J Pediatr* 2009; 2. Berger *et al. Lancet* 2012; 3. Barst *et al. Circulation* 2012.



Demographics

	PH confirmed patients		
	All	Incident	Prevalent
Patients, n (%)	362 (79)	102 (28)	260 (72)
Female	214 (59)	58 (57)	156 (60)
Pre-term	47 (13)	16 (16)	31 (12)
Age at Dx (yrs)	7.5 (7.0, 8.1)	8.5 (7.5, 9.5)	7.2 (6.5, 7.8)
Time from onset of symptoms to PH Dx (mos)			
Mean (95% CI)	17 (14, 20)	24 (16, 31)	15 (12, 18)
Median (range)	6 (0 – 146)	6 (0 – 129)	5 (0 -146)



PH classification

	PH confirmed patients		
	All	Incident	Prevalent
Group 1 PH (PAH)	317 (88)	88 (86)	229 (88)
IPAH/FPAH	182 (57)	55 (63)	127 (55)
APAH-CHD	115 (36)	26 (30)	89 (39)
APAH-Other	20 (7)	7 (7)	17 (6)
Group 3 PH	42 (11)	13 (13)	29 (11)
Group 4/5 PH	3 (1)	1 (1)	2 (1)

Functional class at diagnosis

	PH confirmed patients		
	All	Incident	Prevalent
I	45 (12)	11 (11)	34 (13)
II	185 (51)	52 (51)	133 (51)
III	108 (30)	28 (27)	80 (31)
IV	24 (7)	11 (11)	13 (5)

REVEAL[®]

Registry to Evaluate Early and Long Term PAH Disease Management

Pediatric Cardiology

Survival in Childhood Pulmonary Arterial Hypertension Insights From the Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management

Robyn J. Barst, MD; Michael D. McGoon, MD; C. Gregory Elliott, MD; Aimee J. Foreman, MA;
Dave P. Miller, MS; D. Dunbar Ivy, MD

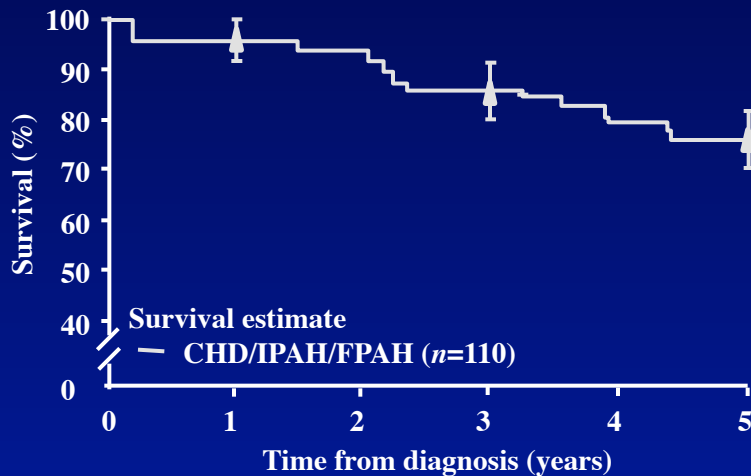
Circulation 2012

PAH-CHD: Paediatrics vs adults

- Same outcome?
- Same response to treatment??
- Are adults paediatric survivors with better prognosis???

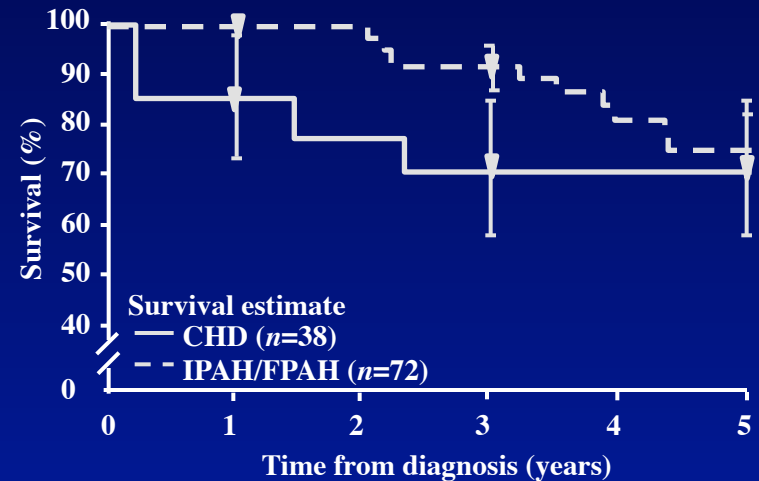
Data from REVEAL

5-yr survival from diagnostic RHC, total cohort



No. at risk: 27 40 50 53 52 49

5-yr survival from diagnostic RHC, PAH-CHD vs IPAH/FPAH



No. at risk:
CHD 7 9 11 14 23 25
IPAH/FPAH 20 31 39 39 29 24

Reveal: Potential risk factors

- **PVR**
- **FPAH**
- **Functional Class**
- **Z score for weight**
- **BNP**
- **Vasoreactivity testing**

Adult versus children

Table 2. Comparison of Childhood-onset and Adult-onset IPAH

Variable	Childhood-onset IPAH	Adult-onset IPAH	P-value
	N = 99	N = 1287	N/A
Time from IPAH diagnosis to PAH treatment initiation, months			
Mean \pm SD	11 \pm 35	2 \pm 26	0.001
Median (IQR)	0 (0, 6)	1 (0, 4)	
Heart rate at enrollment, bpm	90, 88 \pm 17	1183, 82 \pm 15	0.001
Time from symptom onset to diagnosis, months n, Mean \pm SD	95, 22 \pm 29	1277, 29 \pm 39	0.068
Acute Vasoreactivity at IPAH diagnosis, n (%)	11/66 (17) 33 missing data points	69/651 (11) 636 missing data points	0.14
Hemodynamics at IPAH diagnosis, n, Mean \pm SD			
mRAP, mmHg	95, 7 \pm 3	1158, 10 \pm 6	<0.001
mPAP, mmHg	99, 58 \pm 20	1287, 52 \pm 13	<0.001
mPCWP, mmHg	99, 9 \pm 3	1285, 10 \pm 4	0.003
PVRI, Wood units \times m ²	77, 19 \pm 18	928, 23 \pm 12	0.013
Cardiac Index, L/min/m ²	74, 3.6 \pm 1.7	929, 2.2 \pm 0.8	<0.001
SVO ₂ , %	76, 67 \pm 10	721, 62 \pm 10	<0.001

Note: Significantly different parameters are highlighted in gray. IQR, interquartile range; mRAP, mean right atrial pressure; PVRI, pulmonary vascular resistance index; SD, standard deviation; SVO₂, mean venous oxygen saturation.

- Adult-onset IPAH was associated with an earlier start of PAH treatment after diagnosis compared with childhood-onset IPAH.
- There were significantly higher heart rate at enrollment, and mPAP, cardiac index, and SVO₂ values at diagnostic RHC in childhood-onset IPAH patients vs adult-onset IPAH patients.
- There were significantly higher mRAP, mPCWP, and PVRI values at diagnostic RHC in adult-onset IPAH patients vs childhood-onset IPAH patients.
- There were no differences in acute vasoreactivity testing for childhood-onset IPAH patients vs adult-onset IPAH patients.
- These results suggest:
 1. Time from IPAH diagnosis to PAH treatment is longer for pediatric patients, perhaps due to either a) reluctance to use parenteral or complex medications with potential adverse events as readily in this group or b) because of less exercise intolerance at the time of diagnosis in childhood-onset IPAH patients.
 2. Pediatric patients have a higher cardiac index, lower mRAP, and lower PVRI than adult-onset IPAH patients at the time of diagnosis, consistent with better overall right heart function in children with IPAH compared with adult-onset IPAH patients.

Table 1. Patient Characteristics: CHD-APAH vs IPAH/FPAH

Characteristic	IPAH/FPAH N = 122	CHD-APAH N = 77	P-value
Age at diagnosis (yrs), mean ± SD	9 ± 6	6 ± 6	0.002
Age at enrollment (yrs), mean ± SD	14 ± 7	15 ± 10	0.47
Female, n (%)	73 (60)	53 (69)	0.20
Newly diagnosed, n (%)	20 (16)	7 (9)	0.14
Race, n (%)			0.050
White	82 (68)	58 (76)	—
Black	14 (12)	1 (1)	—
Hispanic	15 (13)	10 (13)	—
Other	9 (8)	7 (9)	—
WHO/NYHA functional class at PAH diagnosis, n (%)			0.64
I	7 (7)	2 (5)	—
II	38 (40)	19 (51)	—
III	41 (43)	12 (32)	—
IV	10 (10)	4 (11)	—
WHO/NYHA functional class at enrollment, n (%)			0.26
I	28 (26)	9 (14)	—
II	52 (48)	39 (59)	—
III	26 (24)	16 (24)	—
IV	3 (3)	2 (3)	—
Time from onset of initial symptoms to PAH diagnosis, months			0.020
N	118	72	—
Mean ± SD	19 ± 26	31 ± 44	—
25, 50, 75 percentile	2, 8, 24	2, 8, 58	—
6MWD at enrollment,* m			0.058
N	97	45	—
Mean ± SD	447 ± 124	405 ± 115	—
Initial symptoms attributed to PAH, n (%)			—
Dyspnea on exertion	64 (53)	23 (30)	0.002
Pre-syncope/syncope	44 (36)	3 (4)	<0.001
Fatigue	30 (25)	16 (21)	0.53
Chest pain/discomfort	20 (16)	2 (3)	0.002
Dizziness, lightheadedness	18 (15)	1 (1)	0.001
Dyspnea at rest	9 (7)	9 (12)	0.30
Palpitations	9 (7)	6 (8)	0.91
Edema	8 (7)	3 (4)	0.53
Cough	7 (6)	1 (1)	0.15
Seizures	4 (3)	1 (1)	0.65
Abdominal distension	2 (2)	0 (0)	0.52
Raynaud's phenomenon	0 (0)	0 (0)	—
No reported symptoms	4 (3)	5 (7)	0.31
Prior diagnosis of asthma, [†] n (%)	5 (4)	2 (3)	0.71

Reveal CHD versus IPAH

Epidemiology Pediatric PAH

Recent data from large registries

	<i>TOPP</i> ¹	<i>Reveal-children</i> ²
Patients, <i>n</i>	362	216
Age at Dx (yrs), median	7.5	7
Female, %	59	64
Group 1: PAH	317 (88)	216 (100)
IPAH/HPAH	212 (53)	122 (56)
CHD	160 (40)	23 (36)
CTD	9 (3)	10 (5)
Portopulmonary	2 (1)	3 (1)
Other	14 (4)	4 (2)
Group 3: Lung disease	42 (12)	NE
Other	3 (1)	NE

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

1. Berger et al. *Lancet* 2012.
2. Barst et al. *Circulation* 2012.

Summary

- **Pediatric PAH is a rare disease**
 - **(Incidence 3/mil; Prevalence 20/mil)**
- **Although many similarities, pediatric PAH differs from adult disease**
 - **Associated conditions (e.g. heterogenous CHD)**
 - **Presenting symptoms at diagnosis (syncope, functional class)**
 - **Comorbidities (Down syndrome, BPD)**
 - **Genetic basis**
- **More important data are coming from current registries**