Comparison between adult and pediatric populations with I/HPAH and PAH-CHD in the Bologna ARCA registry

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DIMES

European Reference Networks

European Commission

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Comprehensive clinical classification of pulmonary hypertension – Adults & Pediatrics

1. Pulmonary arterial hypertension

- 1.1 Idiopathic
- 1.2 Heritable
  - 1.2.1 BMPR2 mutation
  - 1.2.2 Other mutations
- 1.3 Drugs and toxins induced
- 1.4 Associated with:
  - 1.4.1 Connective tissue disease
  - 1.4.2 Human immunodeficiency virus (HIV) infection
  - 1.4.3 Portal hypertension
  - 1.4.4 Congenital heart diseases (Table [illegible])
  - 1.4.5 Schistosomiasis

1'. Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis

- 1'.1 Idiopathic
- 1'.2 Heritable
  - 1'.2.1 EIF2AK mutation
  - 1'.2.2 Other mutations
- 1'.3 Drugs, toxins and radiation induced
- 1'.4 Associated with:
  - 1'.4.1 Connective tissue disease
  - 1'.4.2 HIV infection

1''. Persistent pulmonary hypertension of the newborn

2. Pulmonary hypertension due to left heart disease

- 2.1 Left ventricular systolic dysfunction
- 2.2 Left ventricular diastolic dysfunction
- 2.3 Valvular disease
- 2.4 Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies
- 2.5 Congenital/acquired pulmonary veins stenosis

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 lung diseases (Web Table III)[illegible]

4. Chronic thromboembolic pulmonary hypertension and other pulmonary artery obstructions

- 4.1 Chronic thromboembolic pulmonary hypertension
- 4.2 Other pulmonary artery obstructions
  - 4.2.1 Angiosarcoma
  - 4.2.2 Other intravascular tumors
  - 4.2.3 Arteritis
  - 4.2.4 Congenital pulmonary arteries stenoses
  - 4.2.5 Parasites (hydatidosis)

5. Pulmonary hypertension with unclear and/or multifactorial mechanisms

- 5.1 Haematological disorders: chronic haemolytic anaemia, myeloproliferative disorders, splenectomy.
- 5.2 Systemic disorders, sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis
- 5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
- 5.4 Others: pulmonary tumoral thrombothic microangiopathy, fibrosing mediastinitis, chronic renal failure (with/without dialysis), segmental pulmonary hypertension

Galiè N. et al Eur Heart J 2015, Eur Respir J, 2015

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Comprehensive clinical classification of pulmonary hypertension – Expected groups prevalence Adults

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1.4.4 Congenital heart diseases (Table 5)
1.4.5 Schistosomiasis

< 5 %

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80 %

3. Pulmonary hypertension due to lung diseases and/or hypoxia

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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 lung diseases (Web Table III)[a]

10 %

4. Chronic thromboembolic pulmonary hypertension and other pulmonary artery obstructions

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4.2.2 Other intravascular tumors
4.2.3 Arteritis
4.2.4 Congenital pulmonary arteries stenoses
4.2.5 Parasites (hydatidosis)

< 5 %

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5.4 Others: pulmonary tumoral thrombothic microangiopathy, fibrosing mediastinitis, chronic renal failure (with/without dialysis), segmental pulmonary hypertension

< 5 %

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Comprehensive clinical classification of pulmonary hypertension – Expected group prevalence Pediatric (Persistent PH)

1. Pulmonary arterial hypertension

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  - 1.4.2 Human immunodeficiency virus (HIV) infection
  - 1.4.3 Portal hypertension
  - 1.4.4 Congenital heart diseases (Table [illegible])
  - 1.4.5 Schistosomiasis

23 %

27 %

77 %

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- 2.5 Congenital/acquired pulmonary veins stenosis

28 %

3. Pulmonary hypertension due to lung diseases and/or hypoxia

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- 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 lung diseases (Web Table III)[3]

44 %

4. Chronic thromboembolic pulmonary hypertension and other pulmonary artery obstructions

- 4.1 Chronic thromboembolic pulmonary hypertension
- 4.2 Other pulmonary artery obstructions
  - 4.2.1 Angiosarcoma
  - 4.2.2 Other intravascular tumors
  - 4.2.3 Arteritis
  - 4.2.4 Congenital pulmonary arteries stenoses
  - 4.2.5 Parasites (hydatidosis)

1 %

5. Pulmonary hypertension with unclear and/or multifactorial mechanisms

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0 %

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

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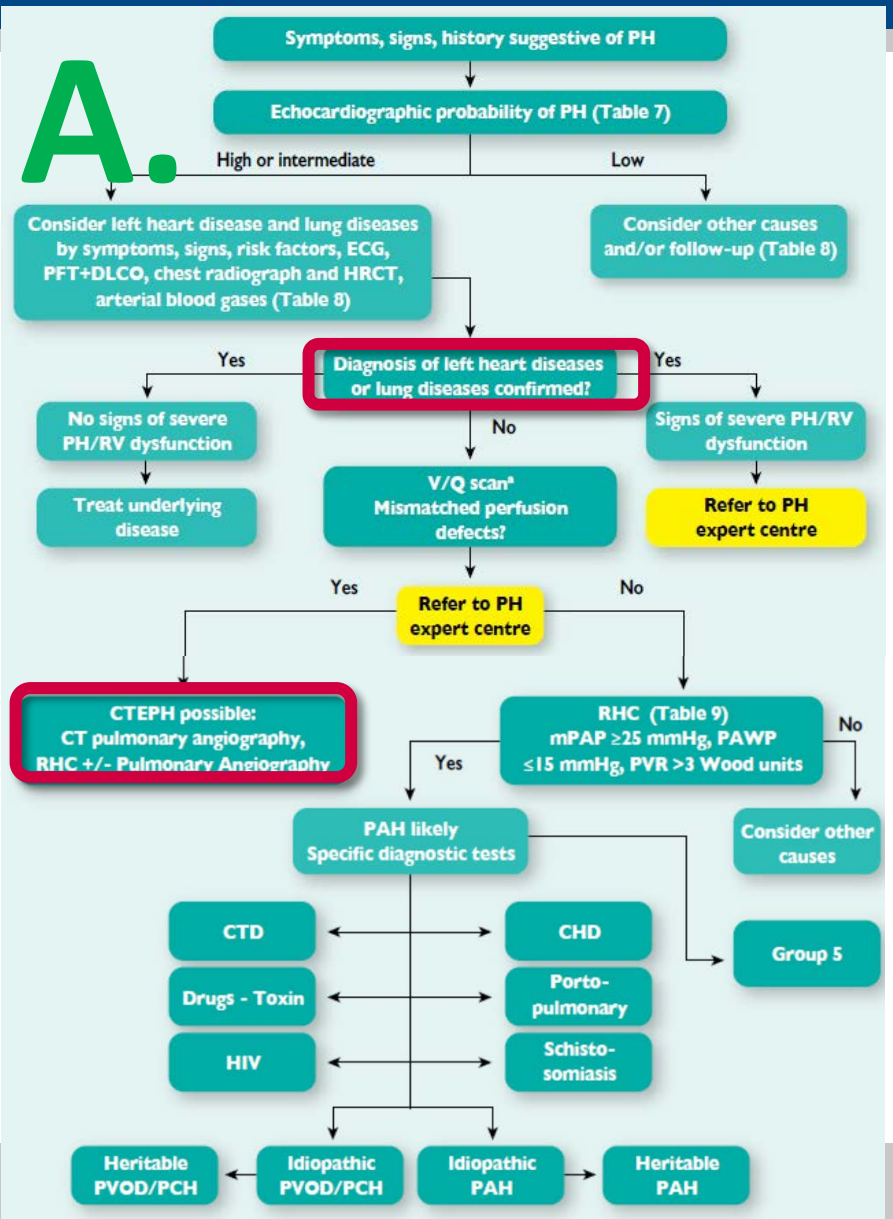
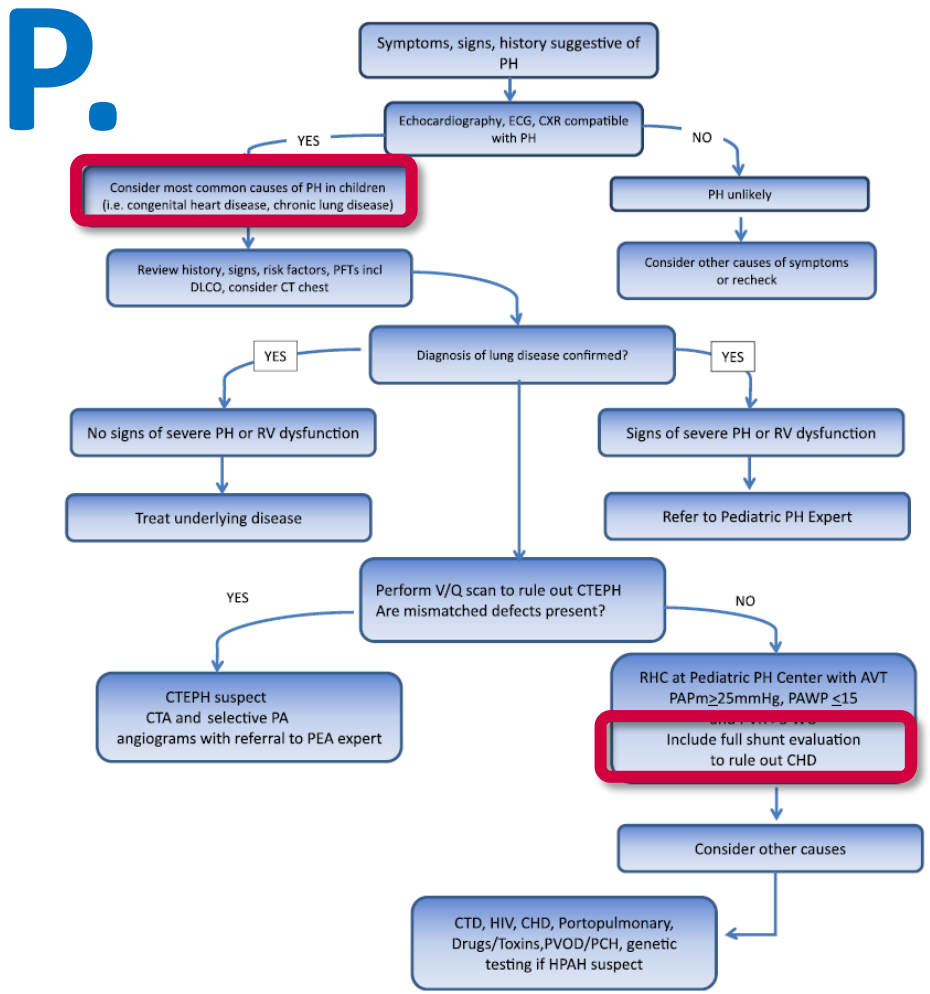
Diagnostic Algorithms



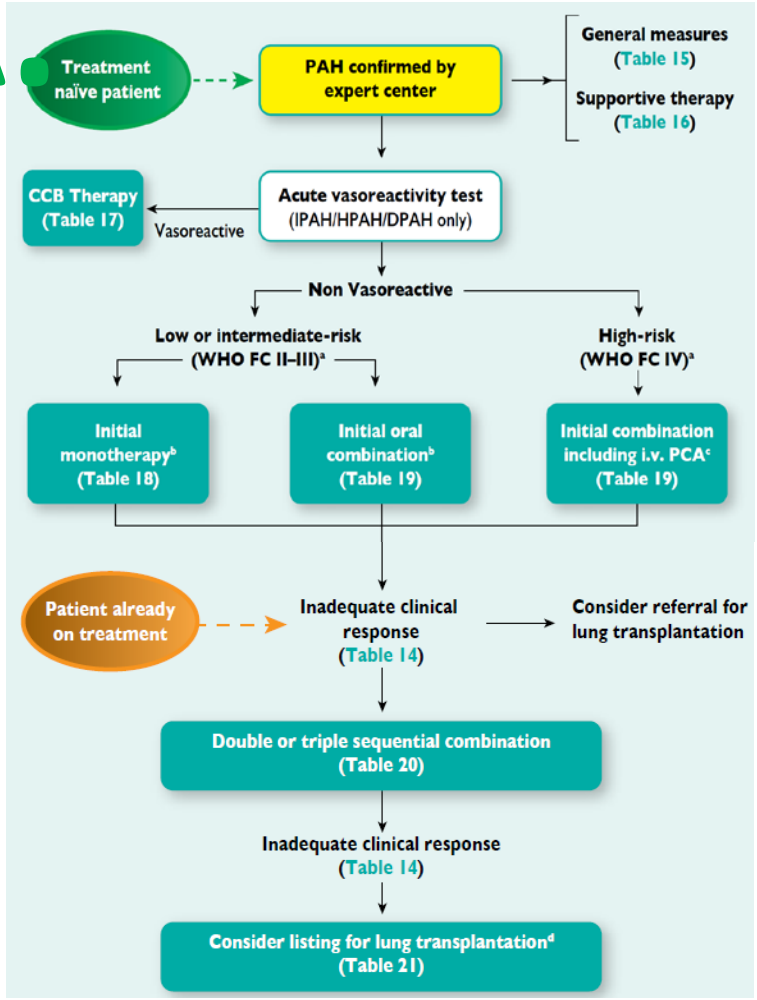


Galiè N. et al Eur Heart J 2016, Eur Respir J, 2015

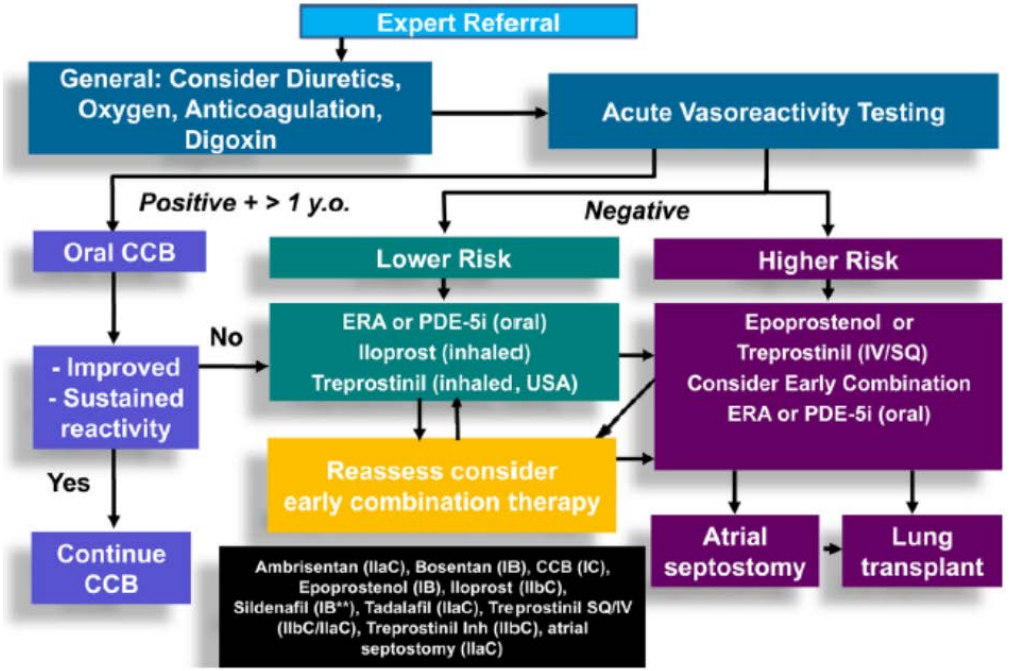
Ivy D et al, JACC 2013

Treatment Algorithms

A



P.



Galiè N. et al Eur Heart J 2015, Eur Respir J, 2015

Ivy D et al, JACC 2013

Epidemiology Pediatric PAH
Recent data from large registries

	TOPP [1]	*Reveal-children* [2]
Patients, *n*	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.

Prevalence of PAH and CTEPH in the Bologna Province area (1 Million Residents)

		Average Prevalence (21 m)
PAH	Pts / Million	60
CTEPH	Pts / Million	47

PED	2
IPAH	21
CHD	16
CTD	12
HIV/PP	10
PVOD	1

5.4%

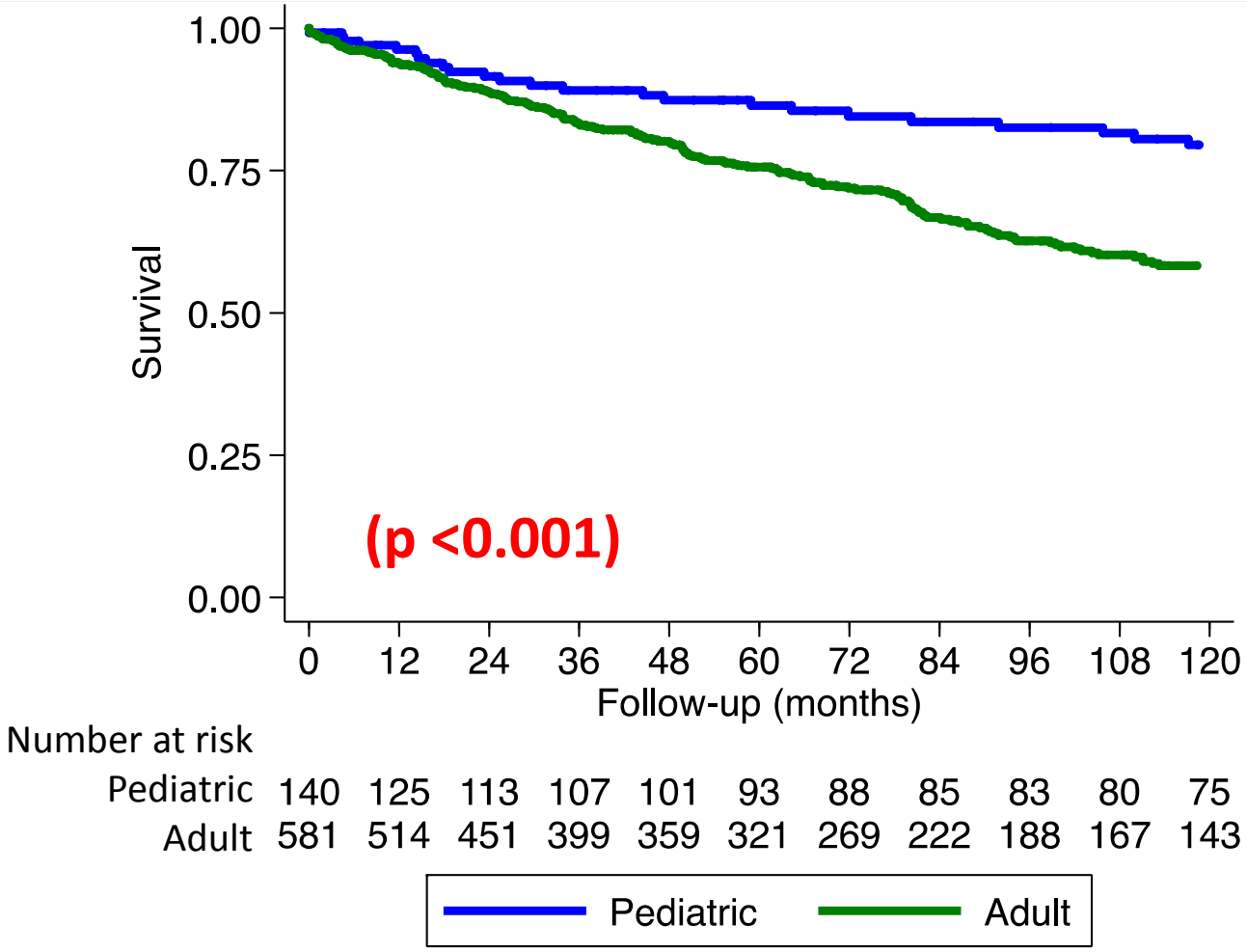
Comparison between adult and pediatric populations with I/HPAH and PAH-CHD

Methods

- **721 patients were included: 581 adult patients and 140 pediatric patients (<18 years at diagnosis)**
- **Diagnosis is established at the time of first right heart catheterization**
- **Survival is analised since diagnosis**

	I/H-PAH	CHD-PAH
Adult patients (581)	424	157
Pediatric patients (140)	53	87

Survival from diagnostic RHC (A vs P)



Immortal time bias

Months between diagnostic right heart catheterization and referral to Bologna PH centre (Registry Inclusion).

	I/H-PAH	CHD-PAH
Adult patients (581)	9 ± 33	56 ± 107
Pediatric patients (140)	31 ± 76	194 ± 175

To minimise immortal time bias

- Only Incident patients included in the Analysis
- Incident patients: distance between diagnostic right heart catheterization and referral to Bologna PH centre <6 months

	I/H-PAH	CHD-PAH
Adult patients (440)	341	99
Pediatric patients (48)	31	17

10.0%

Baseline and Demographic Characteristics – I/H-PAH

	Adult (341)	Pediatric (31)	p-value
Female gender, %	**61**	**48**	0.181
Age, years, ± SD	**52** ± 17	**9** ± 5	
6MWD, m, ± SD	**398** ± 139	**425** ± 144	0.379
WHO FC III-IV, %	**67**	**58**	0.322
Haemodynamics ± SD			
RAP (mmHg)	**8** ± 5	**6** ± 3	**0.011**
mPAP (mmHg)	**52** ± 15	**68** ± 26	**0.005**
mBP (mmHg)	**92** ± 14	**70** ± 14	**<0.001**
CI (l/min/m^2)	**2.4** ± 0.7	**3.2** ± 1.2	**0.002**
PVR (WU)	**12** ± 6	**21** ± 12	**0.001**
PVRi (WU*m^2)	**21** ± 10	**23** ± 15	0.484
SVR (WU)	**22** ± 7	**22** ± 10	0.954
PA O2 Sat (%)	**63** ± 9	**65** ± 11	0.265
Art O2 Sat (%)	**95** ± 4	**96** ± 3	0.082

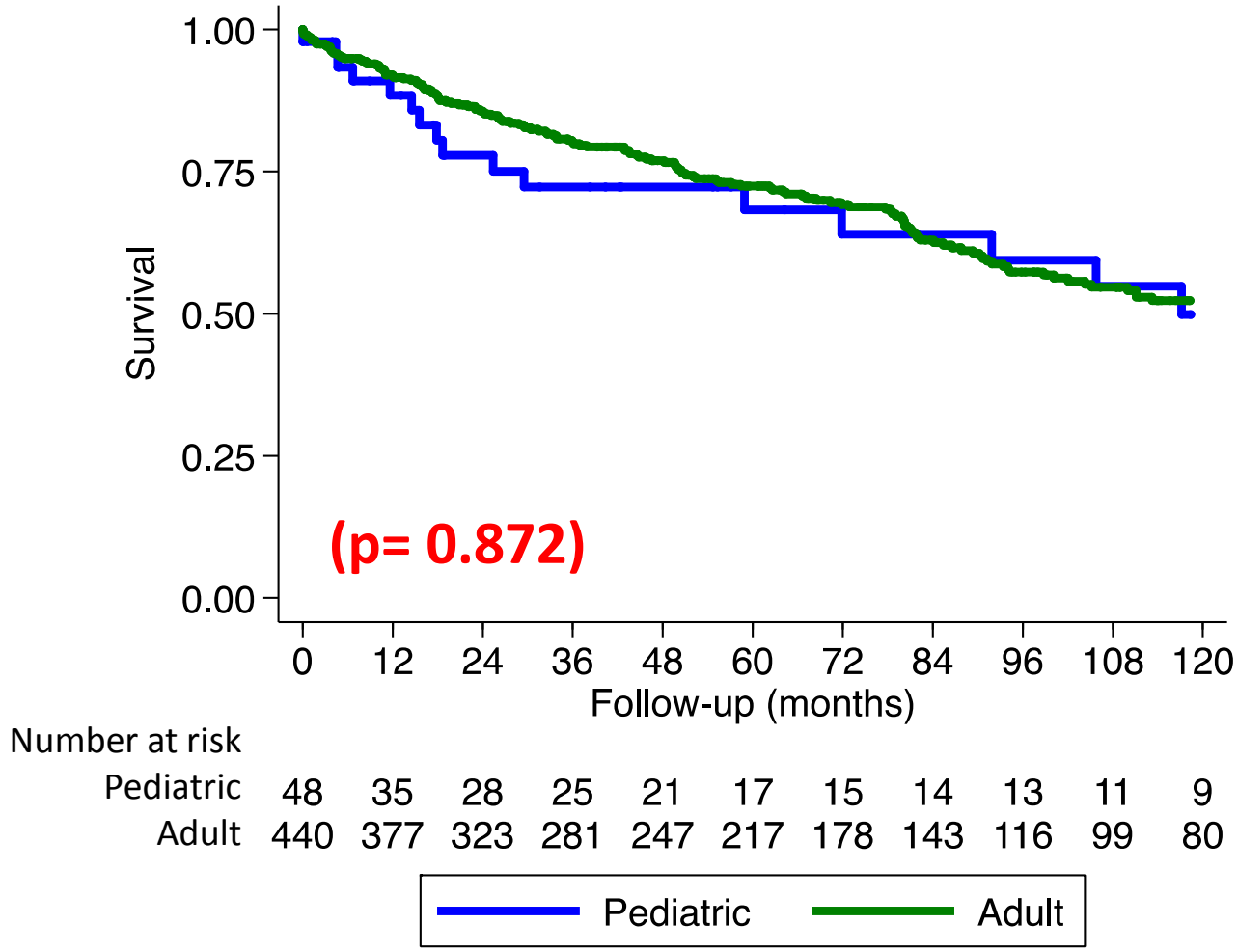
Baseline and Demographic Characteristics – CHD-PAH

	Adult (99)	Pediatric (17)	p-value
Female gender, %	**70**	**41**	**0.022**
Age, years, ± SD	**44** ± 17	**7** ± 6	
6MWD, m, ± SD	**425** ± 124	**455** ± 111	0.479
WHO FC III-IV, %	**43**	**54**	0.467
Haemodynamics ± SD			
RAP (mmHg)	**7** ± 4	**8** ± 3	0.311
mPAP (mmHg)	**60** ± 20	**60** ± 18	0.942
mBP (mmHg)	**89** ± 14	**66** ± 15	**<0.001**
CI (l/min/m^2)	**2.5** ± 0.8	**3.2** ± 1.2	**0.048**
PVR (WU)	**13** ± 9	**32** ± 29	**0.041**
PVRi (WU*m^2)	**20** ± 14	**22** ± 19	0.658
SVR (WU)	**22** ± 9	**30** ± 24	0.257
PA O2 Sat (%)	**72** ± 10	**68** ± 15	0.400
Art O2 Sat (%)	**92** ± 7	**91** ± 10	0.581

Therapy

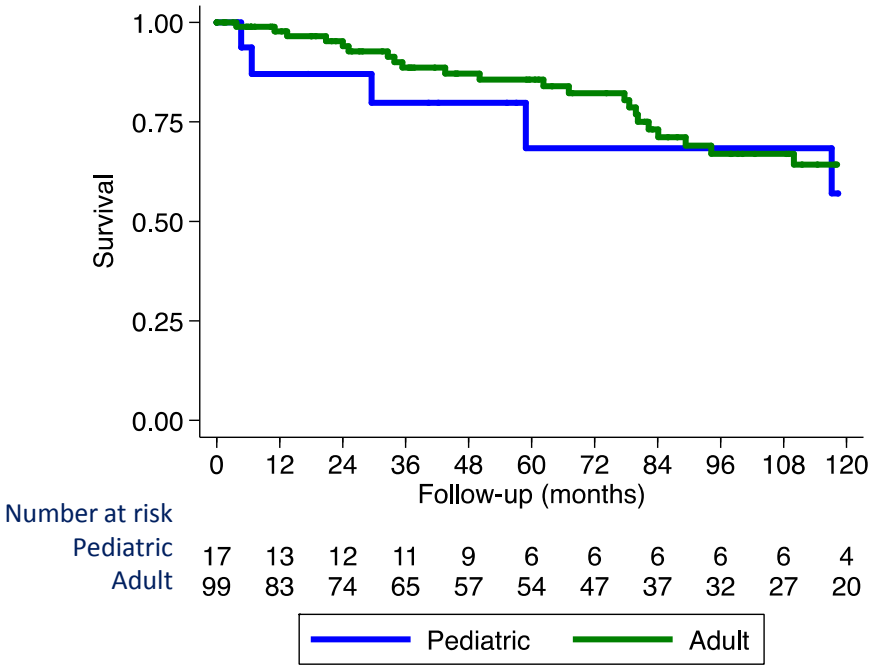
	I/H-PAH	CHD-PAH
Adult patients		
None (%)	4	15
CCB (%)	14	/
Mono (%) (% ERA/PDE5/Prost)	30 (46/27/27)	42 (41/49/10)
Double (%)	34	32
Triple (%)	18	11
Pediatric patients		
None (%)	/	/
CCB (%)	6	/
Mono (%) (% ERA/PDE5/Prost)	39 (42/25/33)	18 (67/33/0)
Double (%)	48	64
Triple (%)	7	18

Survival (A vs P)



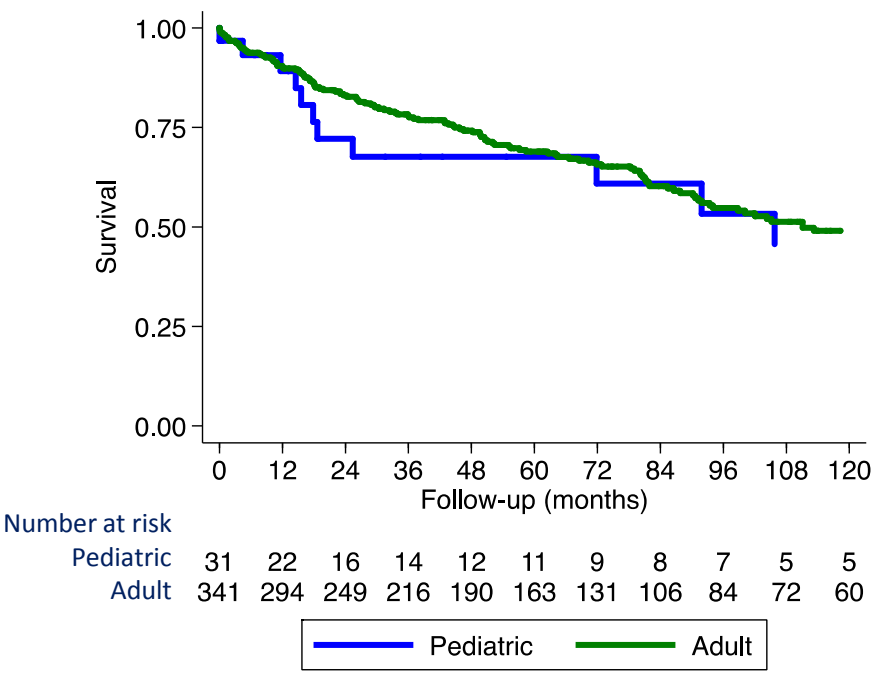
Survival (A vs P)

CHD-PAH



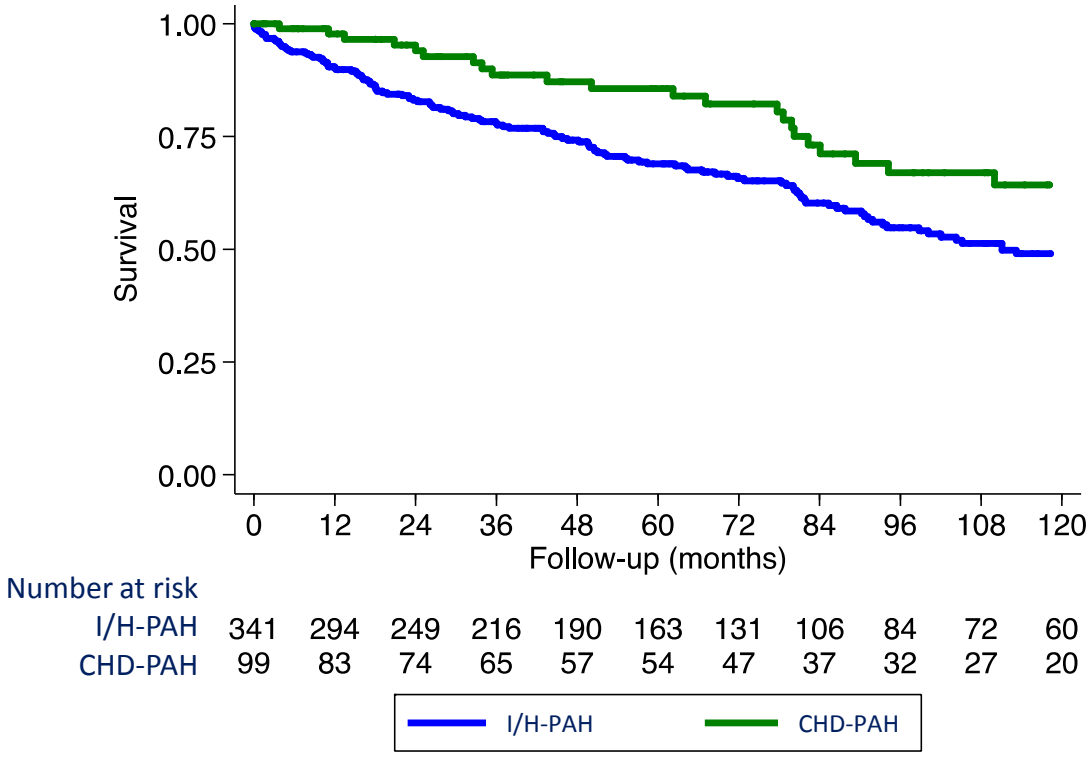
(p: 0.583)

I/H-PAH



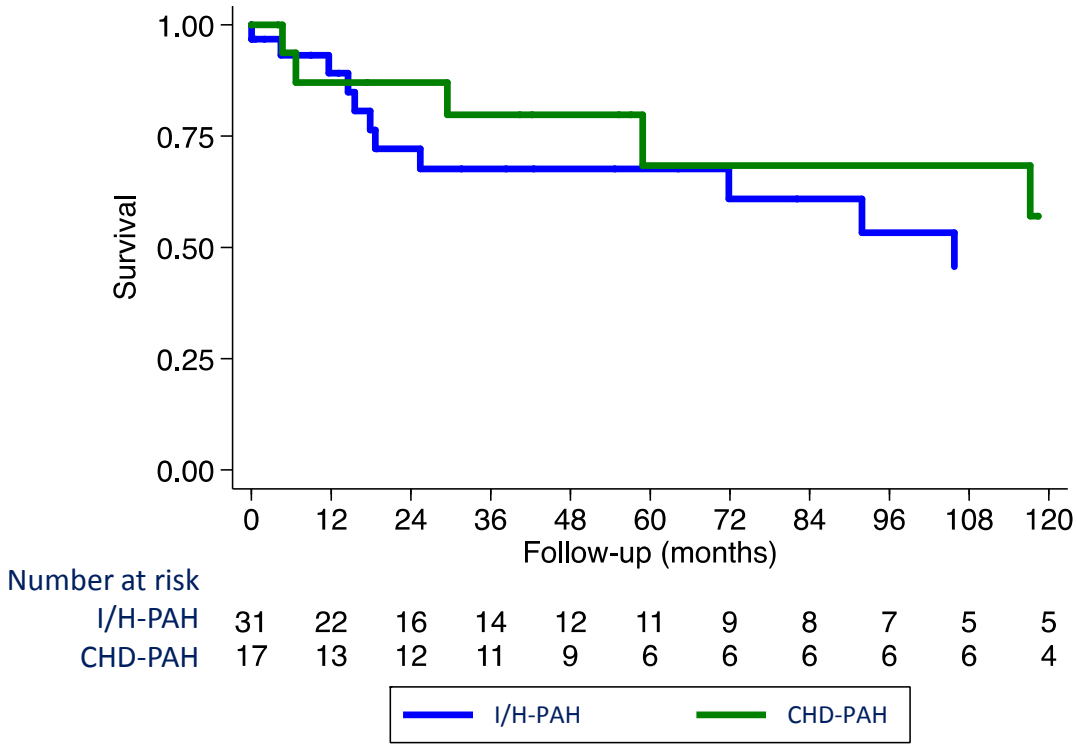
(p: 0.795)

Adult patients (I/H-PAH vs CHD-PAH)



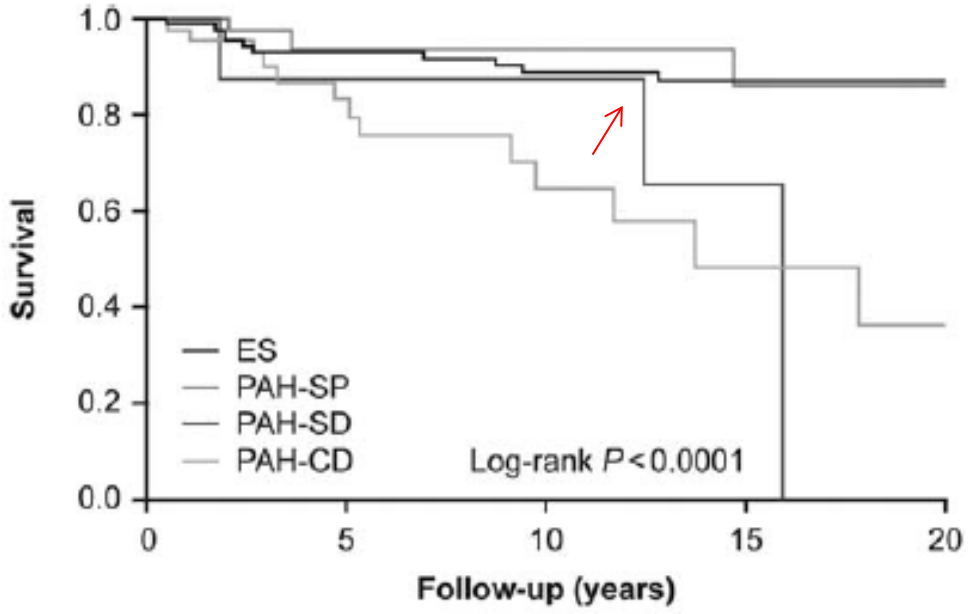
(p = 0.006)

Pediatric patients (I/H-PAH vs CHD-PAH)



(p = 0.454)

Survival by Subgroups



ES

S-P shunt

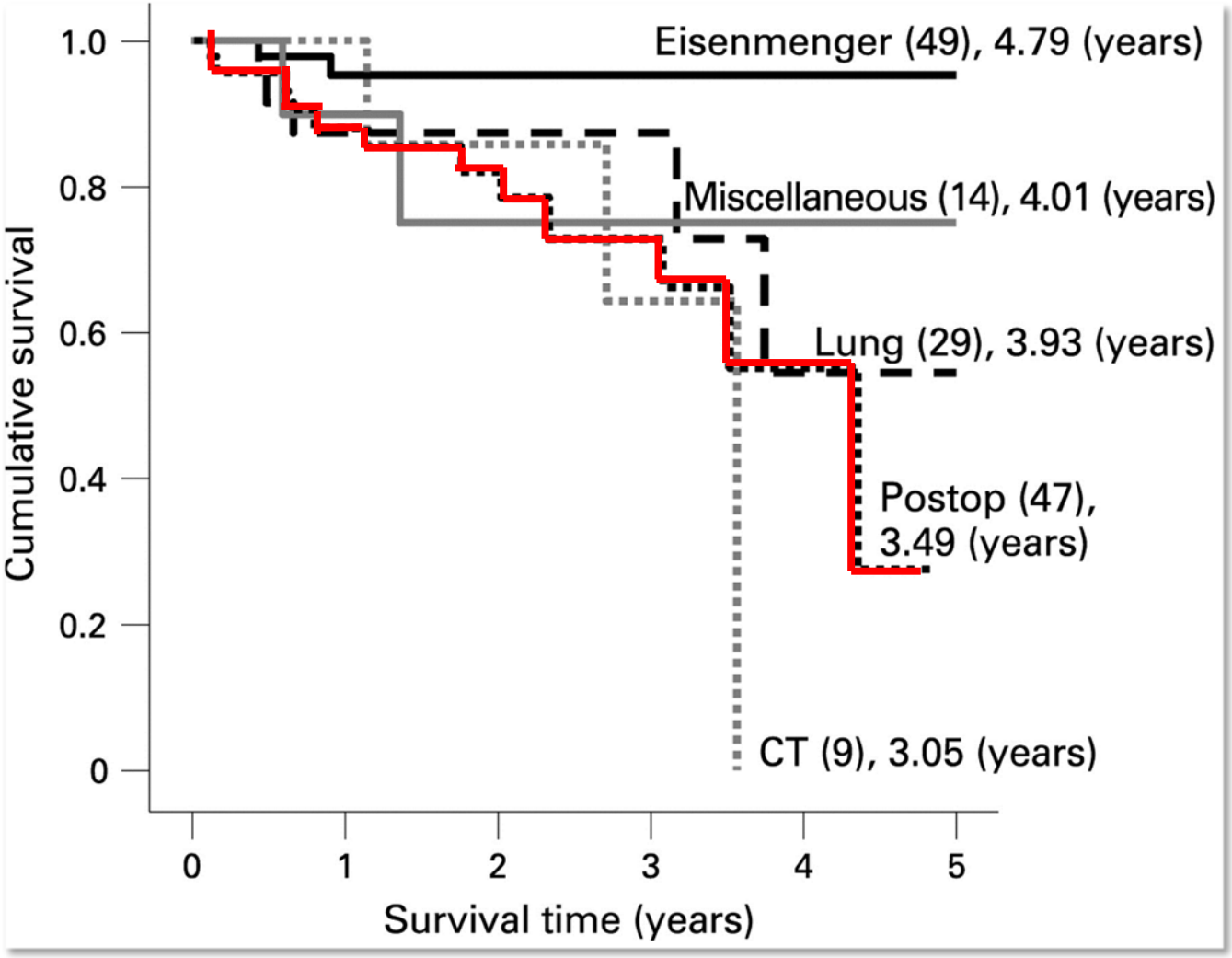
CD

SD

Patients at risk					
ES	90	71	59	52	48
PAH-SP	48	22	18	11	10
PAH-SD	10	4	4	2	0
PAH-CD	44	22	12	4	3

Manes A et al, Eur Heart J 2014

Post-operative PAH has a Worse Survival than Eisenmenger's Syndrome *In Children with CHD*



Eisenmenger

PAH + CD

Haworth SG et al. UK PH Service for Children. Heart 2009

Combining bosentan and sildenafil in pulmonary arterial hypertension patients failing monotherapy: real-world insights

Eur Respir J 2015; 46: 414–421

Fabio Dardi, Alessandra Manes, Massimiliano Palazzini, Cristina Bachetti, Gaia Mazzanti, Andrea Rinaldi, Alessandra Albini, Enrico Gotti, Enrico Monti, Maria Letizia Bacchi Reggiani and Nazzareno Galiè

TABLE 1 Baseline characteristics at initiation of combination therapy

	All patients	IPAH/HPAH	PAH-CHD	PAH-CTD
Patients n	181	[illegible]	[illegible]	29
Male %	40	48	38	17
Age at initiation of combination therapy years	50 (36–62)	50 (36–62)	45 (31–54)	66 (58–72)
Duration of monotherapy months	16 (5–39)	14 (4–35)	26 (8–51)	13 (6–27)
New York Heart Association functional class III/IV %	52	54	39	72
6-min walking distance m	425 (307–491)	441 (271–516)	428 (383–494)	360 (219–425)
Right atrial pressure mmHg	9 (7–13)	8 (7–12)	9 (7–12)	12 (7–16)
Mean pulmonary arterial pressure mmHg	62 (51–75)	59 (49–69)	78 (65–90)	50 (44–56)
Pulmonary wedge pressure mmHg	10 (8–12)	10 (8–12)	11 (9–12)	9 (6–12)
Mean systemic arterial pressure mmHg	85 (77–93)	85 (77–91)	82 (75–94)	89 (82–97)
Cardiac index $L \cdot min^{-1} \cdot m^{-2}$	2.2 (1.9–2.6)	2.3 (1.9–2.7)	2.1 (1.8–2.6)	2.1 (1.9–2.4)
Pulmonary vascular resistance WU	13 (10–18)	12 (9–16)	17 (13–27)	13 (8–14)
Systemic vascular resistance WU	20 (16–24)	18 (16–23)	21 (16–27)	20 (18–25)
Arterial oxygen saturation %	93 (90–96)	95 (92–97)	90 (84–95)	94 (92–97)
Pulmonary arterial oxygen saturation %	64 (57–69)	62 (56–67)	68 (61–73)	60 (51–64)

Data are presented as median (interquartile range) unless otherwise stated. PAH: pulmonary arterial hypertension; IPAH: idiopathic PAH; HPAH: heritable PAH; CHD: congenital heart disease; CTD: connective tissue disease; WU: Wood units.

Adult and Pediatric Patients with I/H-PAH & PAH-CHD (N = 175)

		All patients	Adult	Pediatric	p-value
n		175	156	19	
Sex M (%)		45	44	47	0.795
Age at combo (y)	Min: 2 y Max: 79 y	45 (31÷59)	48 (36÷60)	9 (5÷14)	
Time on mono (months)		16 (5÷40)	17 (5÷42)	11 (6÷26)	0.347
I/H vs CHD (%)		61 vs 39	62 vs 38	53 vs 47	0.453
Association of Bos vs Sild (%)		30 vs 70	29 vs 71	37 vs 63	0.510

Adult and Pediatric Patients with I/H-PAH & PAH-CHD (N = 175)

	All patients	Adult	Pediatric	p-value
NYHA III-IV (%)	48	49	33	0.235
6MWD (m)	428 (338÷504) (n= 163)	427 (323÷504) (n= 149)	452 (401÷486) (n= 14)	0.477
RAP (mmHg)	9 (7÷12)	9 (7÷12)	7 (4÷7)	0.003
mPAP (mmHg)	65 (54÷77)	65 (54÷76)	62(51÷96)	0.631
PWP (mmHg)	10 (8÷12)	10 (9÷12)	9 (8÷11)	0.104
mSAP (mmHg)	84 (75÷91)	85 (77÷93)	75 (62÷84)	0.002
CI (l/min/m2)	2.3 (1.9÷2.7)	2.2 (1.8÷2.6)	2.6 (2.3÷3.8)	0.006
PVR (W.U.)	14 (10÷18)	14 (10÷18)	18 (12÷31)	0.134
PVRi (WU*m^2)	23 (18÷31)	23 (18÷31)	21 (15÷36)	0.624
SVR (W.U.)	20 (16÷24)	20 (16÷24)	19 (14÷24)	0.523
Art O2 Sat (%)	93 (89÷96)	93 (89÷96)	96 (89÷99)	0.119
PA O2 Sat (%)	65 (58÷70)	65 (58÷69)	70 (58÷73)	0.110

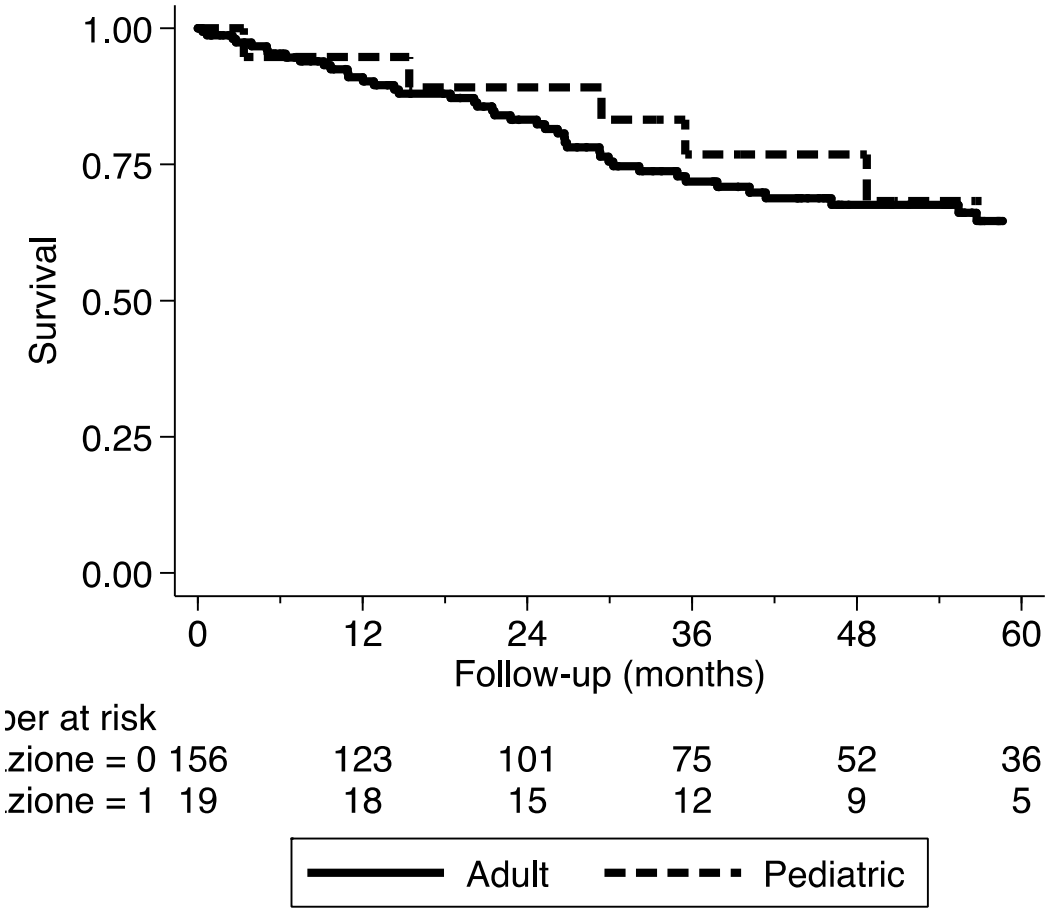
3-4 month after combo therapy (Adult, n= 145)

	Monotherapy Sildenafil or Bosentan	Sildenafil + Bosentan	p-value
NYHA III-IV (%)	47	32	<0.001
6MWD (m) (n= 140)	432 (351÷513)	471 (390÷554)	<0.001
RAP (mmHg)	9 (7÷11)	8 (6÷11)	0.003
mPAP (mmHg)	65 (54÷77)	60 (50÷73)	<0.001
PWP (mmHg)	10 (8÷12)	10 (9÷12)	0.424
mSAP (mmHg)	84 (76÷91)	82 (75÷90)	0.027
CI (l/min/m2)	2.2 (1.8÷2.6)	2.6 (2.2÷2.9)	<0.001
PVR (W.U.)	14 (10÷18)	11 (8÷14)	<0.001
SVR (W.U.)	20 (16÷24)	17 (14÷21)	<0.001
Art O2 Sat (%)	93 (88÷96)	94 (91÷96)	<0.001
PA O2 Sat (%)	65 (59÷69)	68 (62÷74)	<0.001

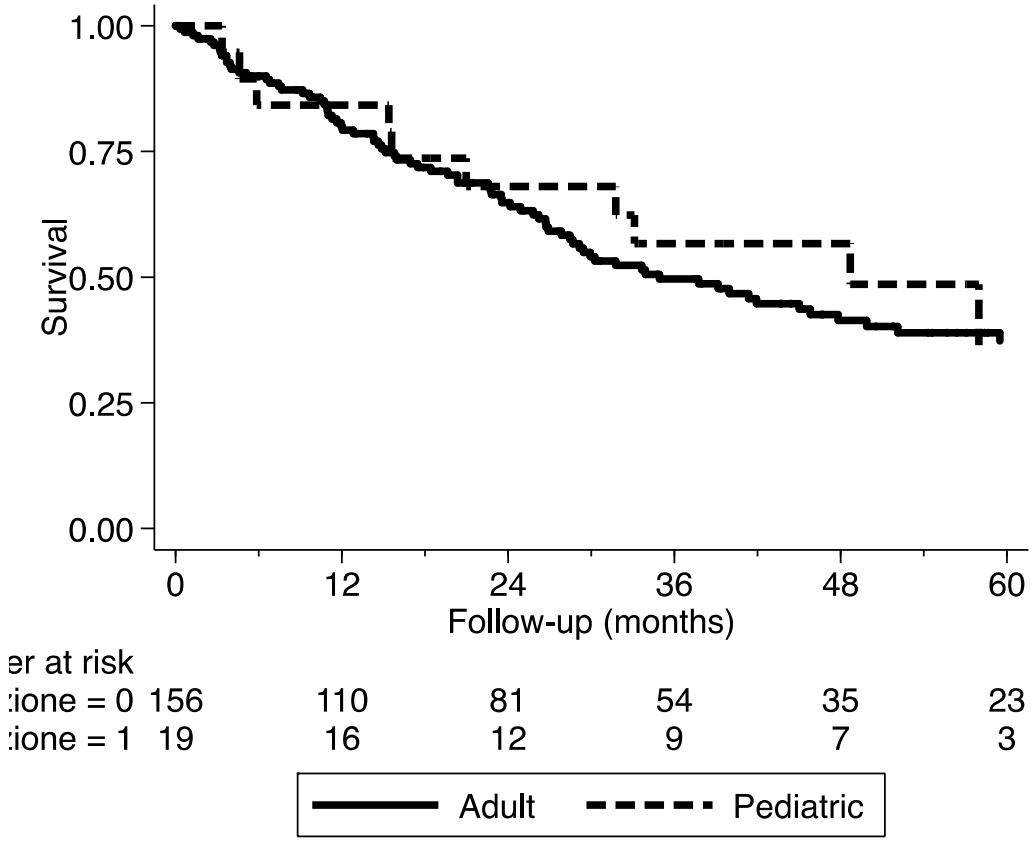
3-4 month after combo therapy (Pediatric, n= 12)

	Monotherapy Sildenafil or Bosentan	Sildenafil + Bosentan	p-value
NYHA III-IV (%)	37	21	0.083
6MWD (m)	452 (401÷513)	495 (431÷572)	0.004
RAP (mmHg)	7 (6÷7)	8 (7÷11)	0.095
mPAP (mmHg)	67 (50÷95)	63 (45÷78)	0.011
PAWP (mmHg)	10 (9÷12)	10 (9÷13)	0.904
mBP (mmHg)	80 (73÷86)	74 (69÷78)	0.009
CI (l/min/m2)	3.2 (2.3÷4.0)	2.7 (2.5÷3.5)	0.272
PVR (W.U.)	13 (6÷24)	10 (6÷20)	0.041
SVR (W.U.)	14 (13÷20)	14 (14÷17)	0.308
Art O_2 Sat (%)	97 (90÷99)	97 (94÷98)	0.873
PA O_2 Sat (%)	70 (67÷75)	69 (65÷76)	0.530

175 Patients with I/H-PAH & CHD-PAH
All Cause Death

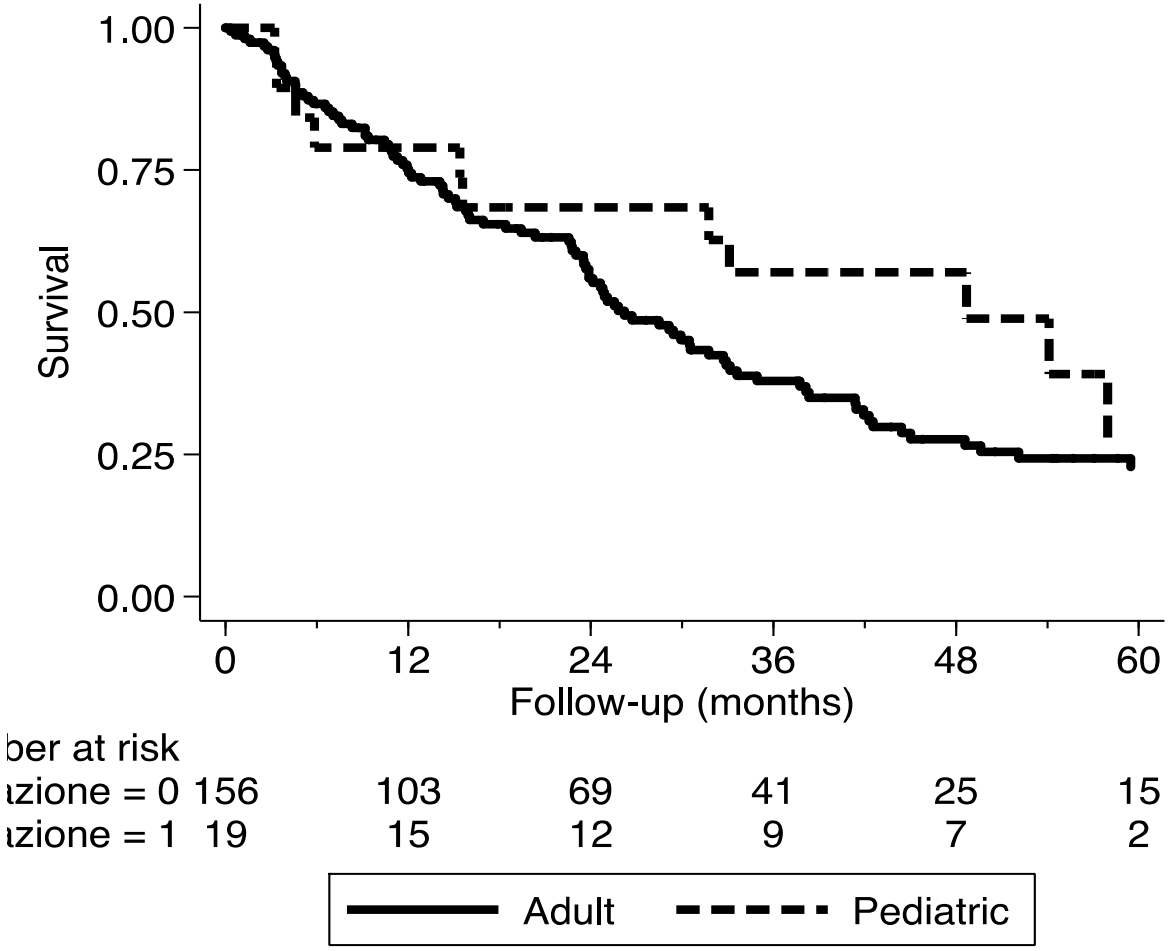


175 Patients with I/H-PAH & CHD-PAH
All Cause Death and Not-Elective Hospitalization



175 Patients with I/H-PAH & CHD-PAH

All Cause Death and Not-Elective Hospitalization and Triple Combination Therapy



Conclusions-1

- **The epidemiology of the PH clinical groups is different between A (G2-LHD predominance) and P population (G3-LD predominance)**
- **G1-PAH is relatively larger (27%) in P as compared with A (< 5%) but as absolute prevalence G1-PAH in P patients are about 5-6% of G1-PAH A patients**
- **I/H-PAH and PAH-CHD are the predominant etiologies of P G1-PAH (23% and 77%, respectively)**
- **Meaningful data can be obtained by the comparison of I/H-PAH and PAH-CHD in A and P populations**

Conclusions-2

- At baseline I/H-PAH P patients tend to have higher PAP and CI, lower BP and similar PVRI as compared with A
- At baseline CHD-PAH P patients tend to have higher CI, lower BP and similar PVRI as compared with A
- Treatment strategies (mono, double, triple) and survival tend to be quite similar in A and P patients populations
- The 3-4 months haemodynamic and exercise comparative effect of sequential double combo therapy (sildenafil and bosentan) are similar in A and P patients populations
- Time to clinical worsening and all cause mortality are also comparable

Conclusions-3

- **Safety data (not shown) are very similar in A and P populations and reflect those observed in the RCTs**
- **The above data support the extrapolation of the efficacy data observed in the A PAH population to PAH P populations**