EUROPEAN HEART HOUSE
Pulmonary Hypertension:
Challenging The 2015 PH Guidelines
Friday 14 – Saturday 15 October 2016

Associated PAH – Comments and proposals

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DHU Thorax Innovation

Disclosures

- Olivier Sitbon acknowledges the following associations during the past 3 years:

- Honoraria and clinical trials:
  Actelion Pharmaceuticals, Bayer HealthCare, GlaxoSmithKline, Merck, United Therapeutics

- Advisory boards:
  Actelion Pharmaceuticals, Bayer HealthCare, GlaxoSmithKline, Merck

Associated forms of pulmonary arterial hypertension

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 disease (Table 6)
  - 1.4.5 Schistosomiasis

Galiè N, Humbert M, *et al.* 2015 ESC/ERS Guidelines. *Eur Respir J 2015 & Eur Heart J* 2016.

Associated forms of pulmonary arterial hypertension

- Idiopathic (1.1), heritable (1.2), D & T induced (1.3) and associated PAH (1.4) in the same PH group because they share:
  - similar pathophysiological mechanism
  - similar pathological findings
  - similar clinical presentation
  - similar management

- Is it really true?
  - YES for idiopathic and heritable PAH
  - Maybe for D & T-induced PAH
    - YES for appetite suppressants,
    - Debatable for some other drugs (dasatinib, interferon…)
  - Probably NO for associated forms of PAH

Galiè N, Humbert M, *et al.* 2015 ESC/ERS Guidelines. *Eur Respir J 2015 & Eur Heart J* 2016.

Recommendations for PAH associated with connective tissue diseases (CTD)

	Recommendations	Class[a]	Level[b]	Ref.[c]
Treatment algorithm	In patients with PAH associated with CTD, the same treatment algorithm as for patients with IPAH is recommended	I	C	46
Screening (Echo)	Resting echocardiography is recommended as a screening test in asymptomatic patients with SSc, followed by annual screening with echocardiography, DLCO and biomarkers	I	C	46
Diagnosis (RHC)	RHC is recommended in all cases of suspected PAH associated with CTD	I	C	46,327
Anticoagulant issue	Oral anticoagulation may be considered on an individual basis and in the presence of thrombophilic predisposition	IIb	C	175,339

Galiè N, Humbert M, *et al.* 2015 ESC/ERS Guidelines. *Eur Respir J 2015 & Eur Heart J* 2016.

PAH associated with connective-tissue diseases: Questions

- Are all PAH associated with CTD the same?
  - SSc
  - Lupus erythematosus
  - MCTD
  - Others…
- They are different…
  - Mechanisms
  - Clinical presentation
  - Response to immunosuppressive therapy
  - Survival (poorer in PAH-SSc)

PH associated with connective-tissue diseases: various possible mechanisms

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 — SSc, LES, others…
  - 1.4.2 Human immunodeficiency virus (HIV) infection
  - 1.4.3 Portal hypertension
  - 1.4.4 Congenital heart disease (Table 6)
  - 1.4.5 Schistosomiasis

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

- 1'.1 Idiopathic
- 1'.2 Heritable
  - 1'.2.1 EIF2AK4 mutation
  - 1'.2.2 Other mutations
- 1'.3 Drugs, toxins and radiation induced
- 1'.4 Associated with:
  - 1'.4.1 Connective tissue disease — SSc
  - 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 — SSc
- 2.3 Valvular disease — LES
- 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 — SSc, others…
- 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)

4. Chronic thromboembolic pulmonary hypertension and other pulmonary artery obstructions

- 4.1 Chronic thromboembolic pulmonary hypertension — LES
- 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, neurofibromatosis
- 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

Simonneau G, *et al. J Am Coll Cardiol* 2013; 62: D34–41.
Galiè N, Humbert M, *et al.* 2015 ESC/ERS Guidelines. *Eur Respir J 2015 & Eur Heart J* 2016.

PH incidence in SSc is > 1%
Almost a half are post-capillary PH…

The Three-Year Incidence of Pulmonary Arterial Hypertension Associated With Systemic Sclerosis in a Multicenter Nationwide Longitudinal Study in France

	Estimated incidence (No. of cases per 100 patient-years)	**95% CI**
All forms of PH	1.37	0.74 – 2.00
PAH	0.61	0.26 – 1.20
Among patients with limited SSc	0.40	0.11 – 1.03
Among patients with diffuse SSc	1.25	0.34 – 3.20
Postcapillary PH	0.61	0.26 – 1.20
PH secondary to pulmonary fibrosis	0.15	0.02 – 0.55

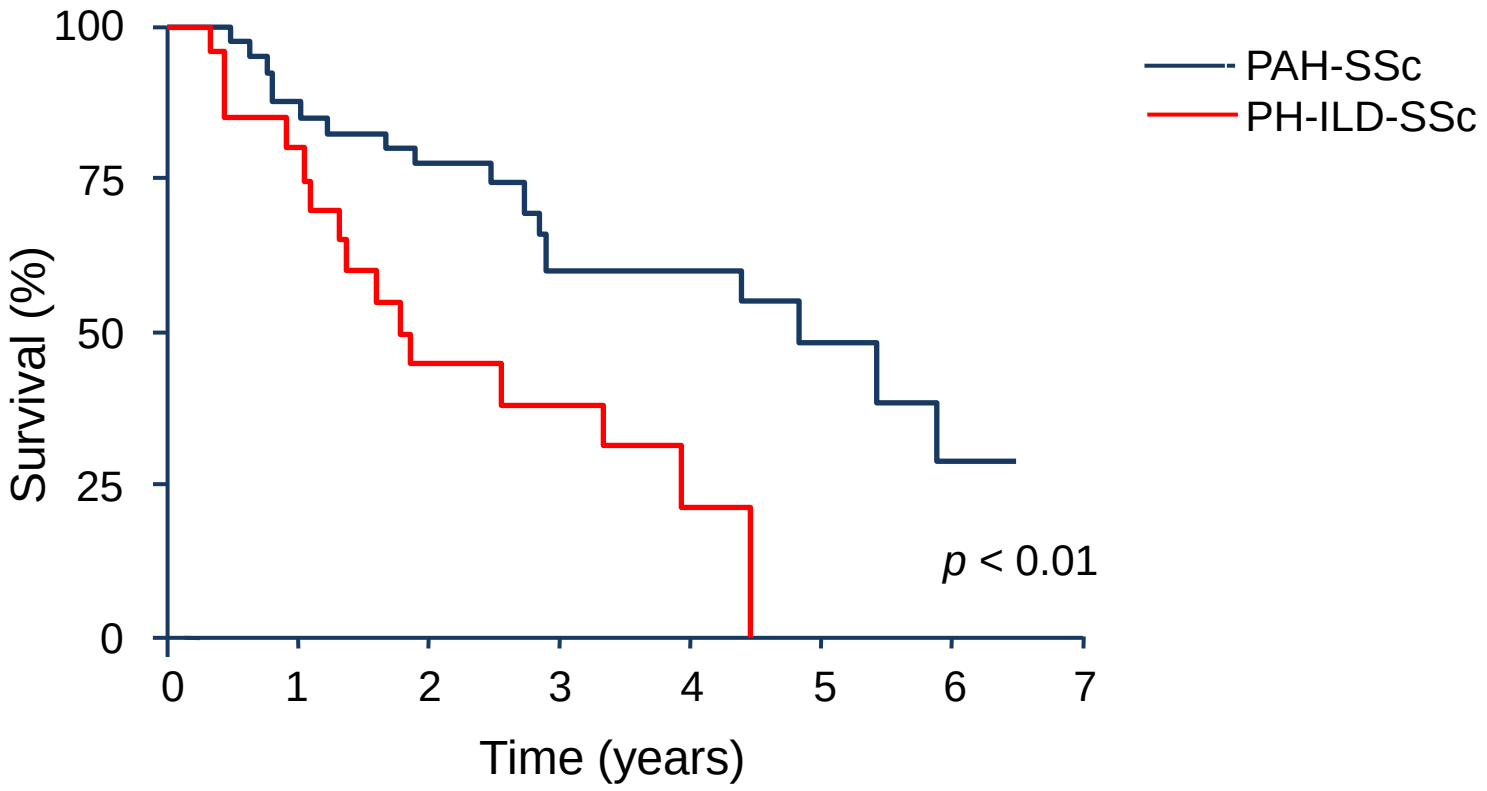
Hachulla E, *et al. Arthritis Rheum* 2009;60:1831–1839.

Why is prognosis so poor in PAH-SSc?

- Older patients (>10 years / IPAH)
- Lower RV compliance
- Mechanisms may be multiple
  - Frequent occult LV dysfunction
  - Association with ILD
  - Pulmonary vein involvement

Mathai S, *et al. Arthritis Rheum* 2009;60:569-77.
Mathai S, *et al. Eur Respir J* 2010;35:95-104.
Le Pavec J, *et al. Arthritis Rheum* 2011;63:2456-64.
Günther S, *et al. Arthritis Rheum* 2012; 64:2995-3005.

Survival is worse for SSc patients with PH-ILD than for SSc patients with PAH alone

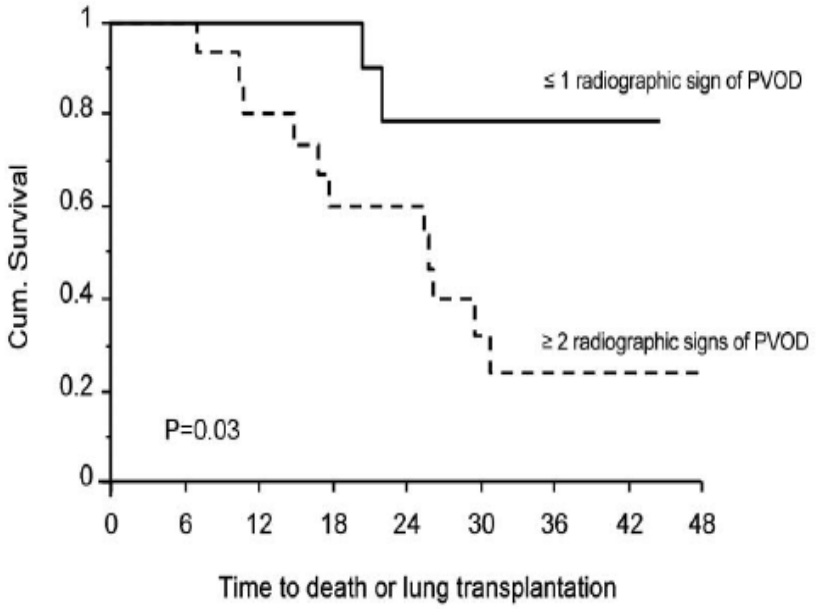


Mathai SC, *et al. Arthritis Rheum* 2009; 60:569-77.

“PVOD” is frequent in severe PH associated with SSc and prognosis is poor

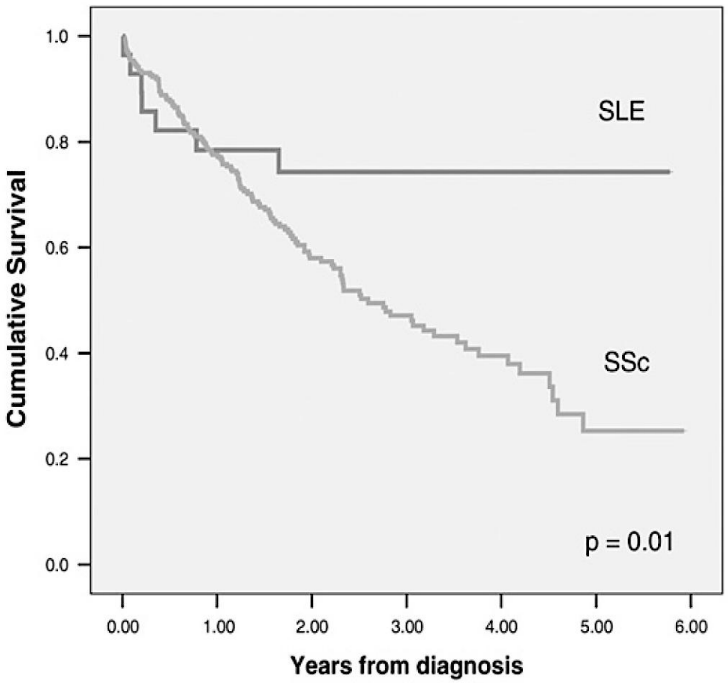
Suggests pulmonary vein involvement in patients with severe PH & SSc

- Clinical
  - More severe (NYHA III-IV)
  - History of pulmonary oedema (on PAH therapy +++)
- HRCT
  - Lymph node enlargement
  - Centrilobular ground-glass opacities
  - Septal lines
- PFTs & ABG
  - Lower DLCO
  - Lower PaO_2
- BAL
  - Hemosiderin-laden macrophages



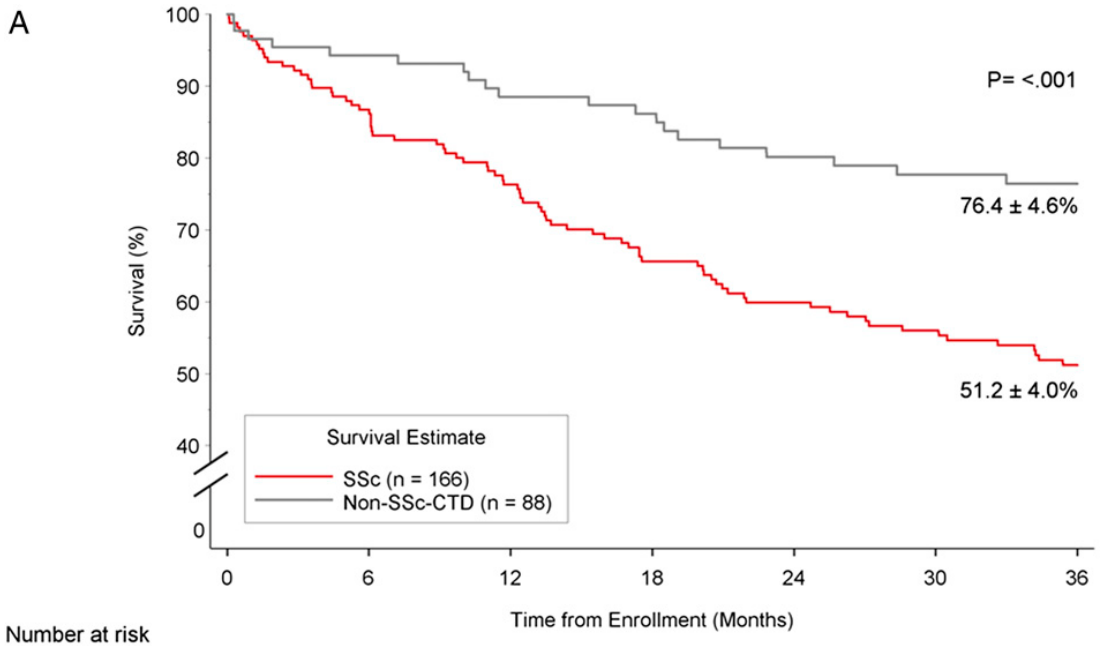
Günther S, *et al. Arthritis Rheum* 2012; 64:2995-3005.

Survival is much better in PAH associated with systemic lupus erythematosus (SLE)



Patients at risk

28	21	15	12	9	2	SLE
259	179	94	53	27	6	SSc

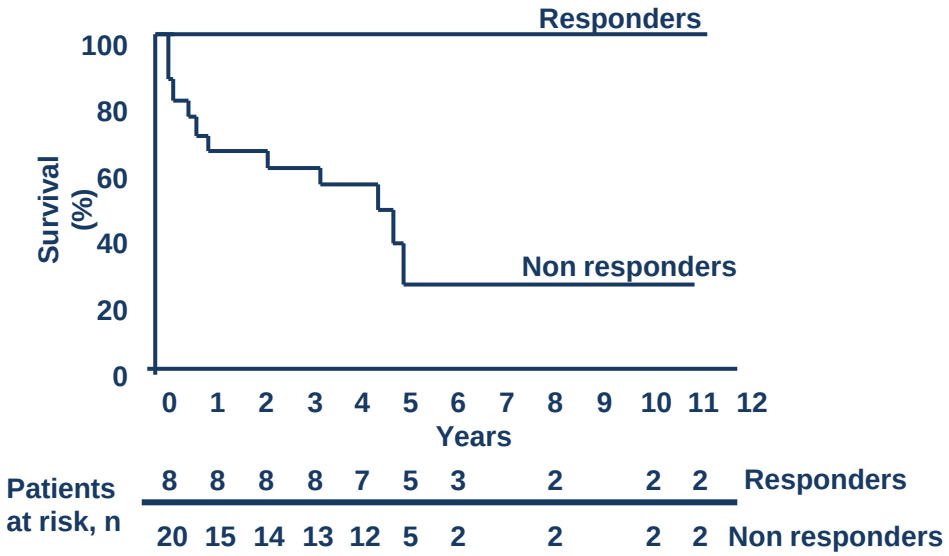


Number at risk							
SSc	166	144	123	104	94	83	74
Non-SSc-CTD	88	82	77	73	66	63	60

Condliffe R, *et al. Am J Respir Crit Care Med* 2009;17:151–7.
Chung L, *et al. Chest* 2014;146:1494-504.

And a substantial proportion of patients with SLE- or MCTD-PAH respond to immunosuppressive therapy

- First line immunosuppressive therapy
  - Monthly IV cyclophosphamide pulses (600 mg/m^2)
  - Steroids (prednisone 0.5 - 1 mg/kg/j)
- Eight out of 28 patients (32%) were “responders” (NYHA I-II after 1 yr)
- No patient with systemic sclerosis responded
- 38% of SLE and MCTD patients responded after 7 ± 6 CYC pulses
  - SLE n = 5 / 13
  - MCTD n = 3 / 8
  - SSc n = 0 / 6



Sanchez O, *et al. Chest* 2006;130:182–9.

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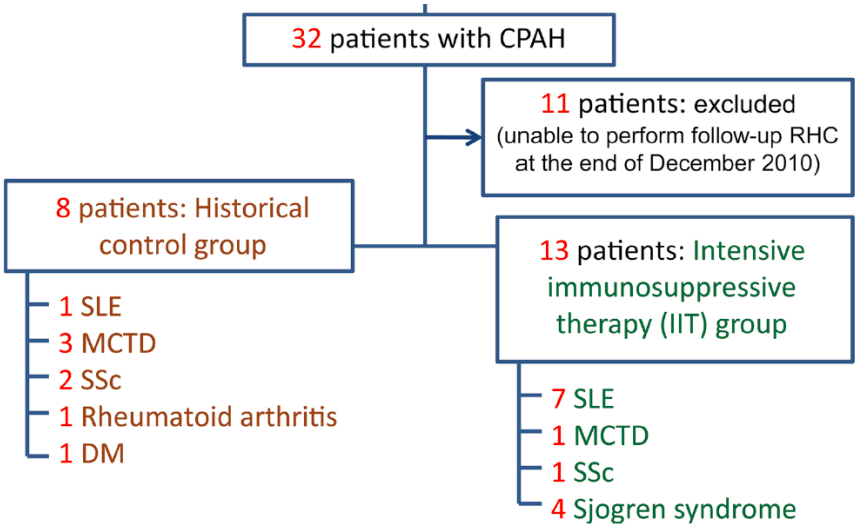
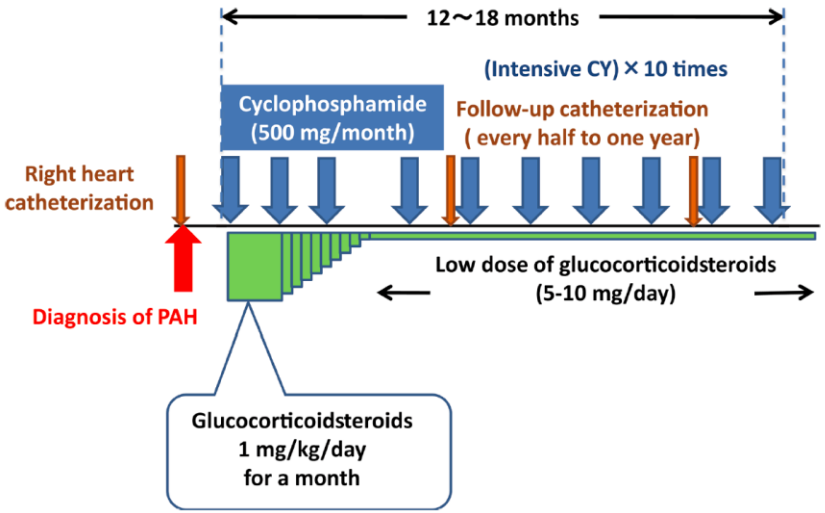
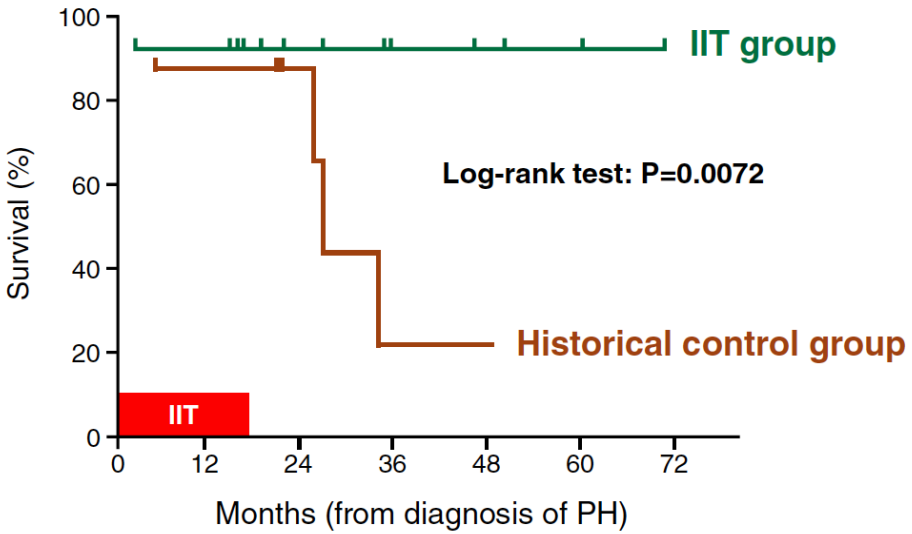
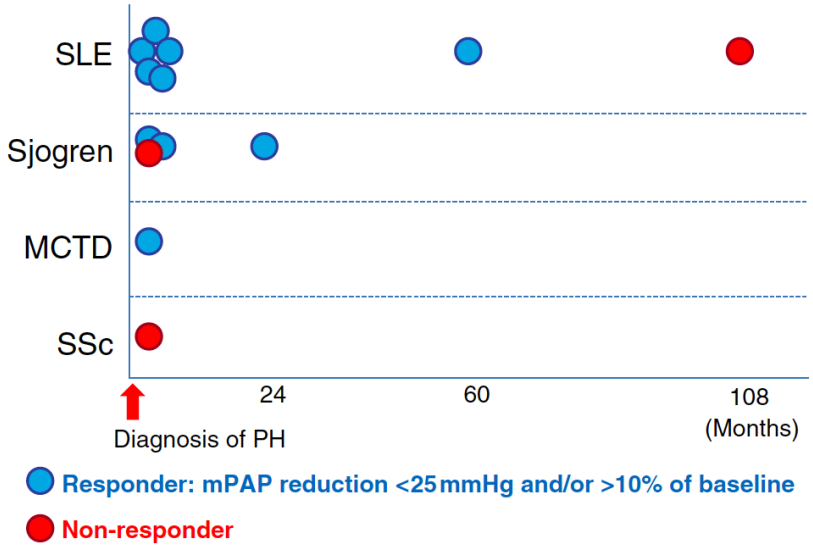








Miyamichi-Yamamoto, *et al. Circ J.* 2011;75:2668-74.

PAH associated with connective-tissue diseases: Proposal

- Improve classification of PH associated with SSc
  - Group 1 or Group 3 when ILD?
  - How to handle with LV dysfunction when associated with pre-capillary PH?
  - How to handle with PH with venous involvement?

    → Better selection of patients before inclusion in RCTs

- Non-SSc CTD (Lupus, MCTD…) are different
  - Much better survival
  - Efficacy of immunosuppressive therapy
  - Cases of haemodynamic normalization

    → Not to merge with SSc in RCTs

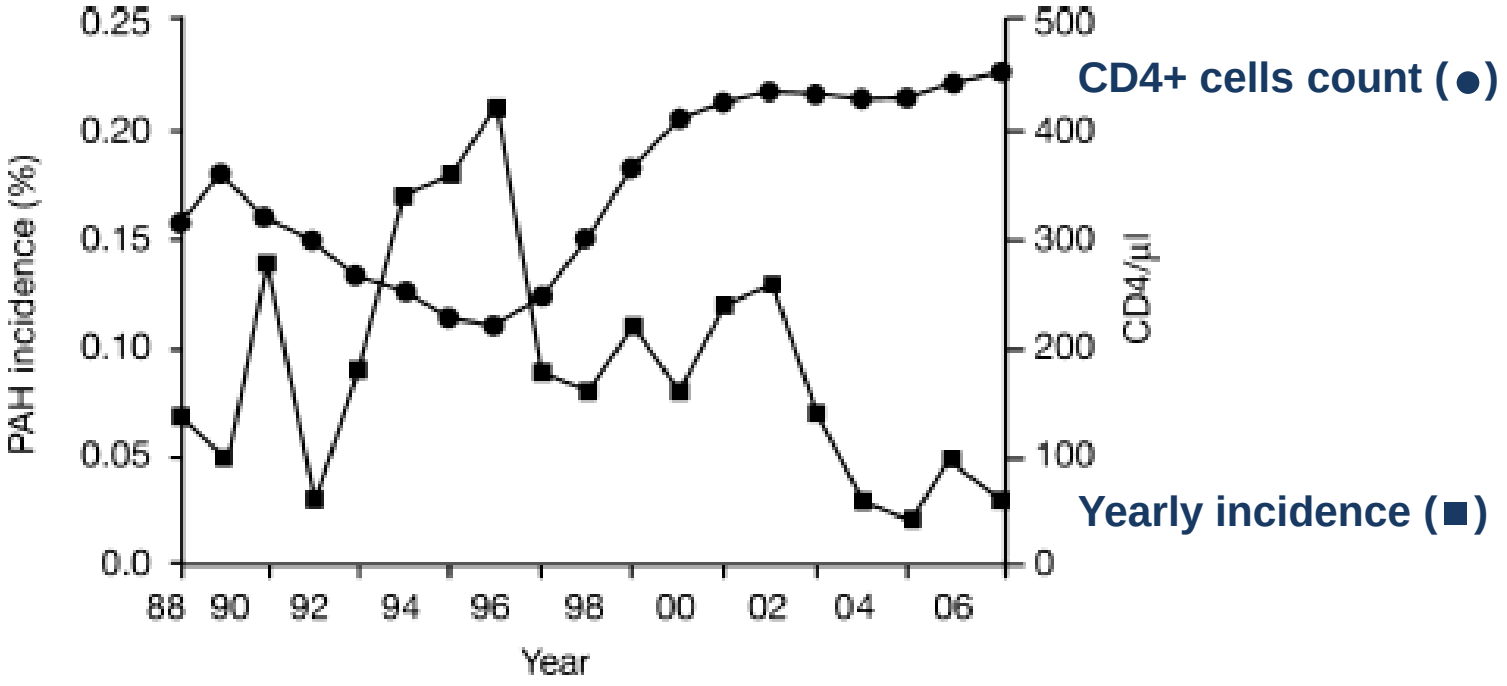
Recommendations for PAH associated with HIV infection

	Recommendations	Class[a]	Level[b]	Ref.[c]
Screening (Echo)	Echocardiographic screening in asymptomatic HIV patients to detect PH is not recommended	III	C	369
Treatment algorithm	In patients with PAH associated with HIV infection, the same treatment algorithm used for patients with PAH should be considered, taking into consideration co-morbidities and drug–drug interactions	IIa	C	194, 367
Anticoagulant issue	Anticoagulation is not recommended because of a lack of data on the efficacy:risk ratio	III	C	175,367

Galiè N, Humbert M, *et al.* 2015 ESC/ERS Guidelines. *Eur Respir J 2015 & Eur Heart J* 2016.

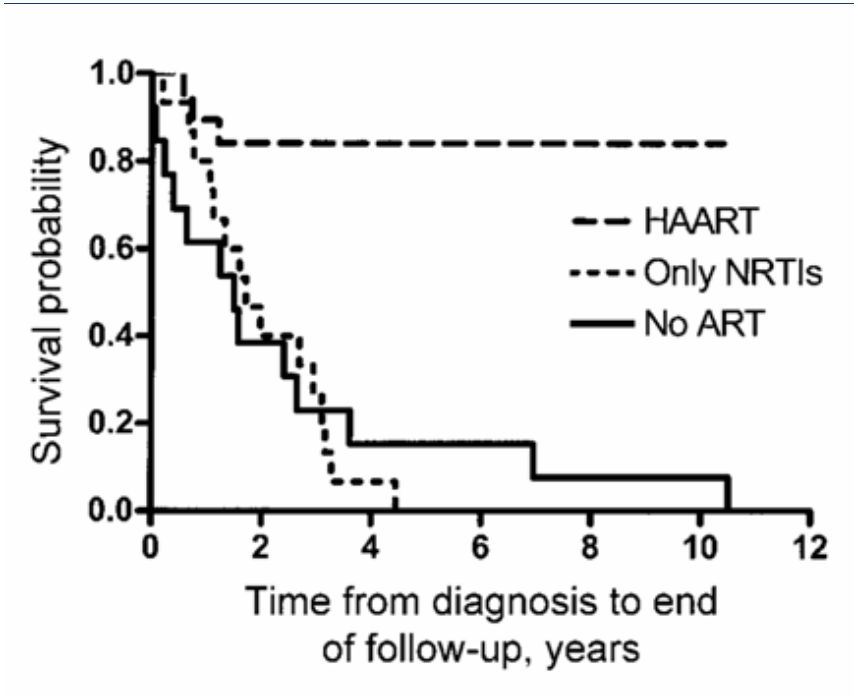
PAH-HIV: stable prevalence (0.5%) but much lower incidence…

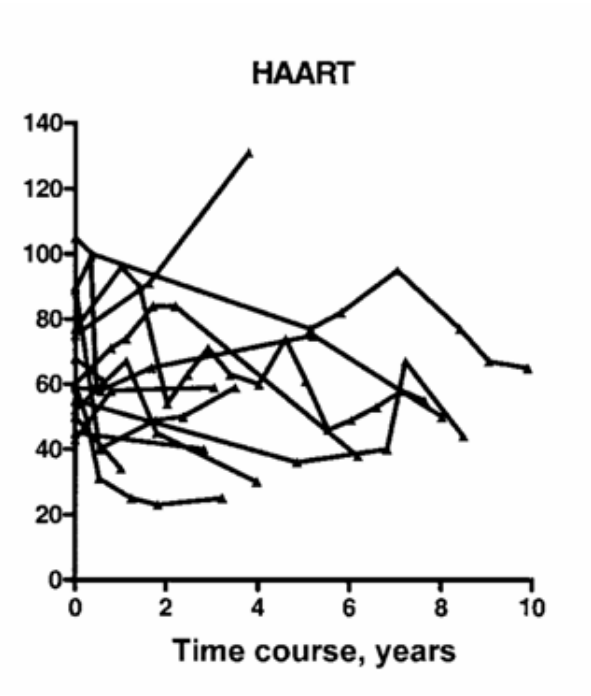
Incidence of PAH-HIV as a function of time and CD4+ cells count



Opravil M, *et al. AIDS* 2008; 22: S35-S40.

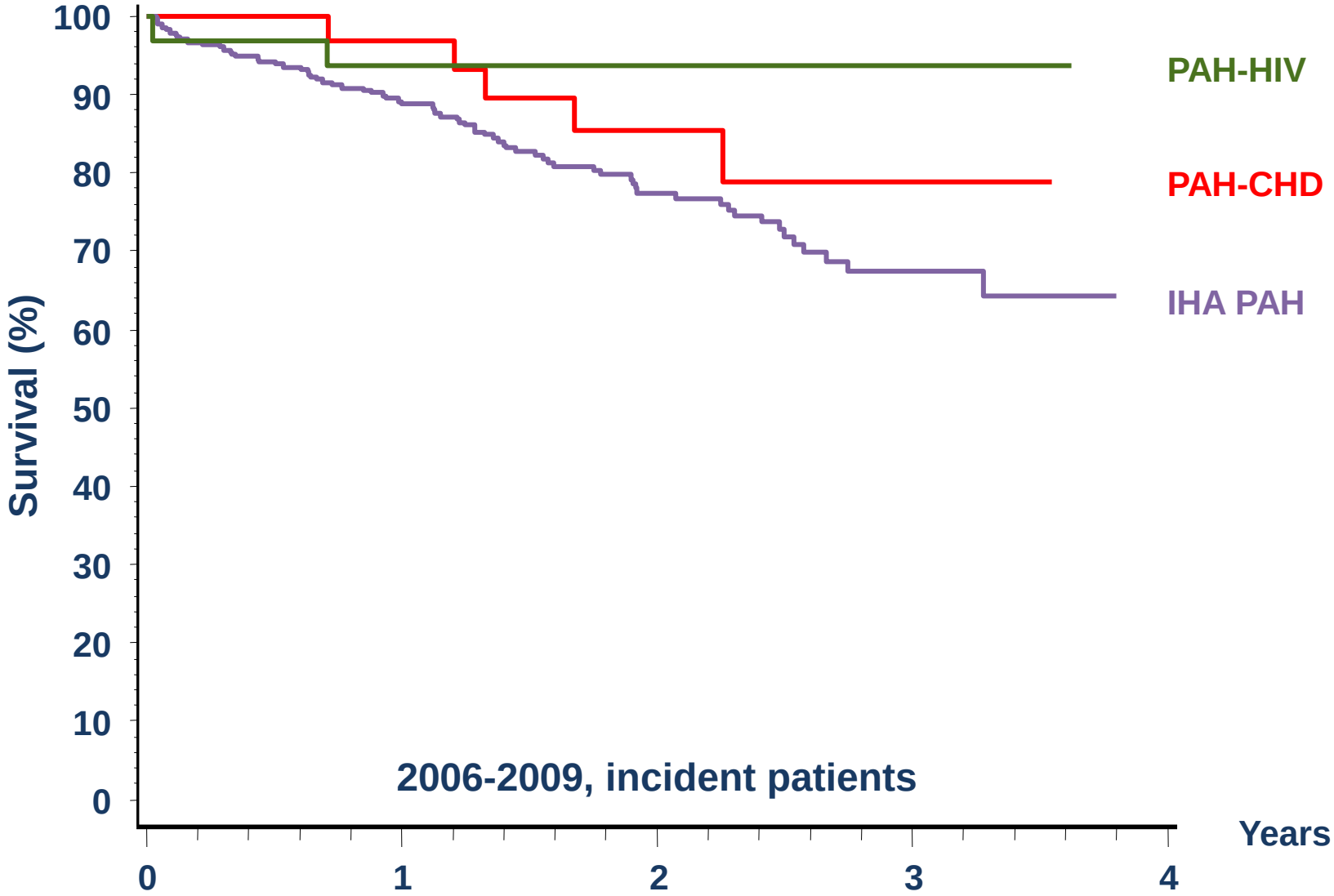
PAH-HIV: Positive effect of highly active antiretroviral therapy (HAART)





Zuber JP, *et al. Clin Infect Dis* 2004; 38:1178–85.

PAH-HIV: Today the best form of PAH! At least in western world…



CHD: congenital heart diseases
IHA: idiopathic, heritable and anorexigen-induced PAH

Sitbon O, *et al*. Presented at ERS Congress 2011.

Recommendations for PAH associated with portal hypertension (PoPH)

Screening and assessment

Recommendations	Class[a]	Level[b]	Ref.[c]
Echocardiographic assessment for signs of PH is recommended in symptomatic patients with liver disease or portal hypertension and in all candidates for liver transplantation	I	B	344
It is recommended that patients affected by PAH associated with portal hypertension should be referred to centres with expertise in managing both conditions	I	C	344

Treatment

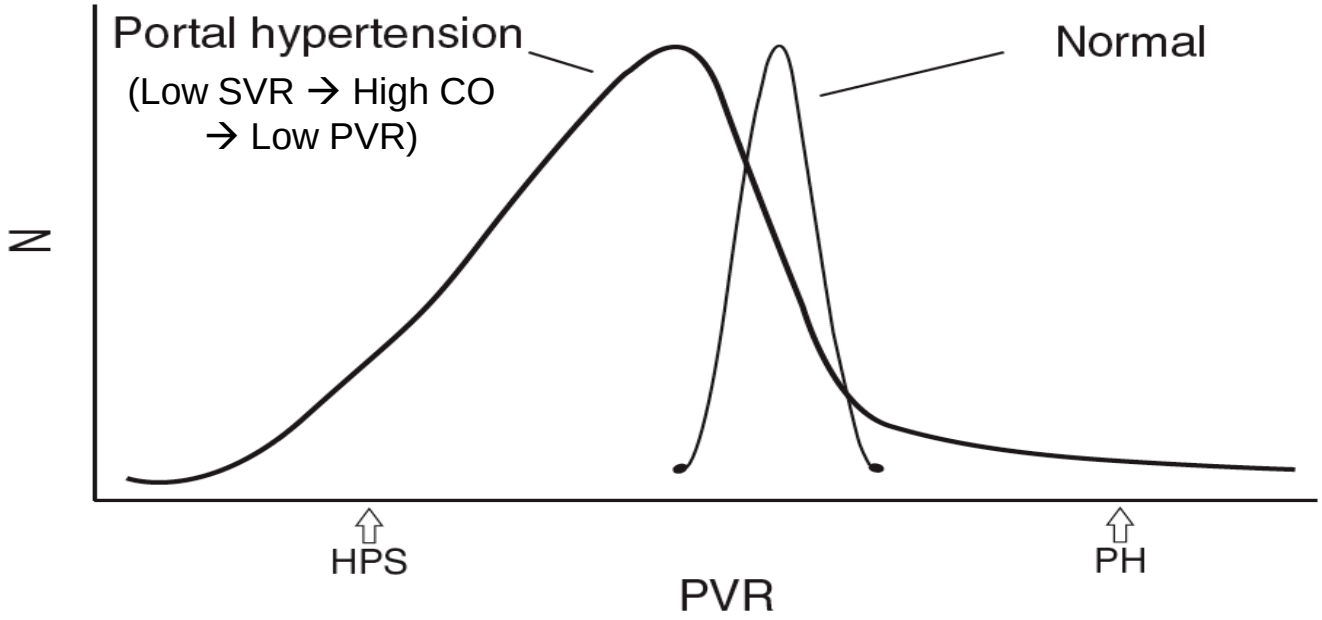
Recommendations	Class[a]	Level[b]	Ref.[c]
It is recommended that the treatment algorithm for patients with other forms of PAH should be applied to patients with PAH associated with portal hypertension, taking into account the severity of liver disease	I	C	214, 350–356
Anticoagulation is not recommended in patients with PH associated with portal hypertension	III	C	365

Liver transplantation issue

Recommendations	Class[a]	Level[b]	Ref.[c]
Liver transplantation may be considered in selected patients responding well to PAH therapy	IIb	C	361–363
Liver transplantation is contraindicated in patients with severe and uncontrolled PAH	III	C	361–363

Galiè N, Humbert M, *et al.* 2015 ESC/ERS Guidelines. *Eur Respir J 2015 & Eur Heart J* 2016.

Distribution of PVR in Portal Hypertension



Hepatopulmonary syndrome

- Pulmonary vasodilatation
- Right-to-left intrapulmonary shunt
- Diffusion impairment

Portopulmonary hypertension

- Precapillary pulmonary hypertension
- Vascular remodelling

Hervé P, *et al*. *Eur Respir J* 1998; 11: 1153–66.

Pulmonary hemodynamics in portal hypertension

	PAP	PAWP	CO	PVR
Hyperdynamic	↗	N or ↗	↗↗	↘
Volume overload	↗	N or ↗	N or ↗	↘
PoPH	↗↗	N	↗, N, or ↘	↗

Current definition of portopulmonary hypertension

- Portal hypertension (with or w/o cirrhosis).
  HPG > 5 mmHg if intrahepatic block
- Resting mPAP > 25 mmHg
- PAWP < 15 mmHg
- PVR > 3 Wood units

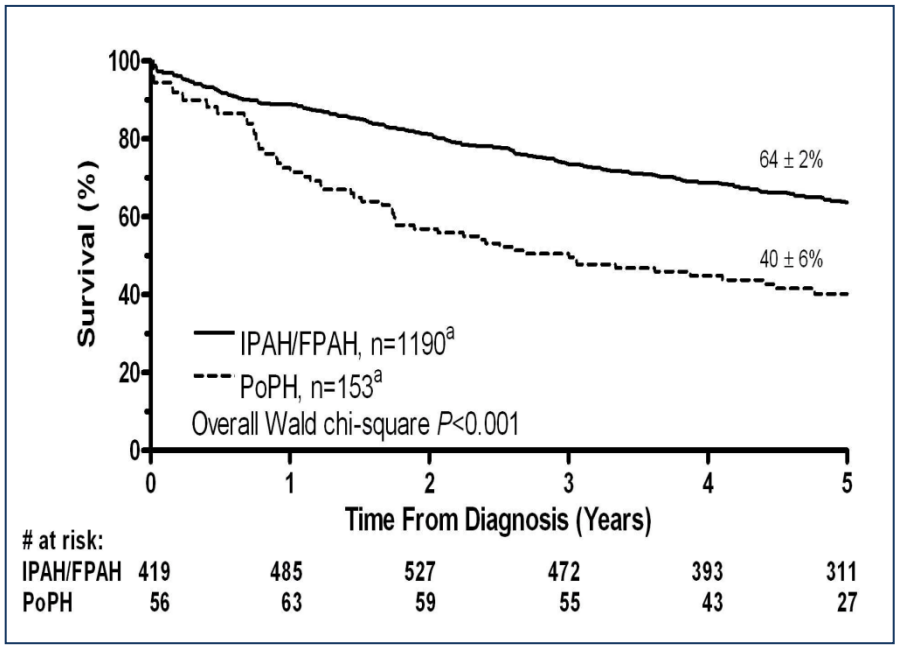
Patients with portal HT usually have a high CO

→ Do we have to choose a PVR threshold of 2 WU to define PoPH?

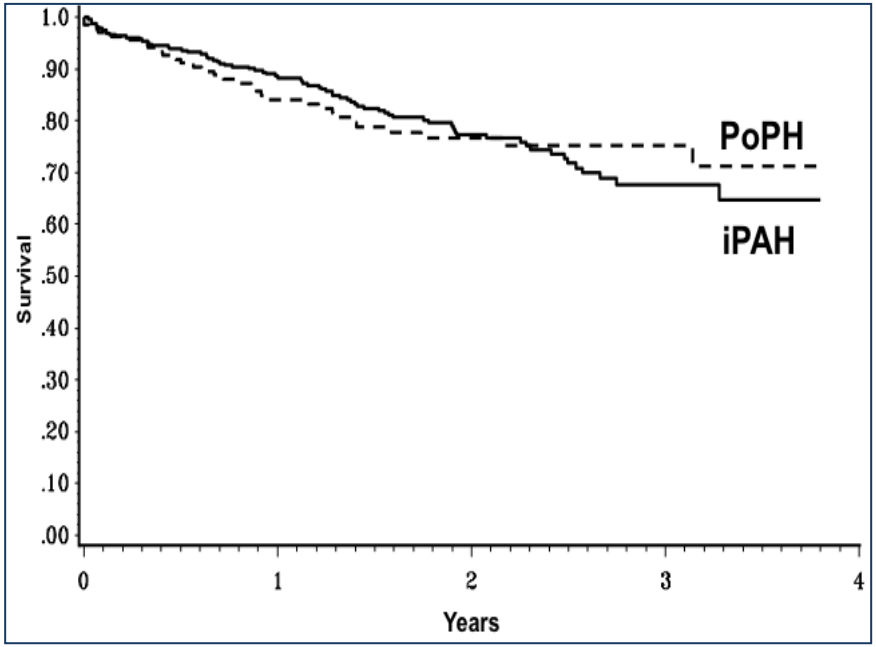
Hervé P, *et al*. *Eur Respir J* 1998; 11: 1153–66.
Galiè N, Humbert M, *et al.* 2015 ESC/ERS Guidelines. *Eur Respir J 2015 & Eur Heart J* 2016.

Why survival of patients with PoPH is so different in the US and in France?

US cohort



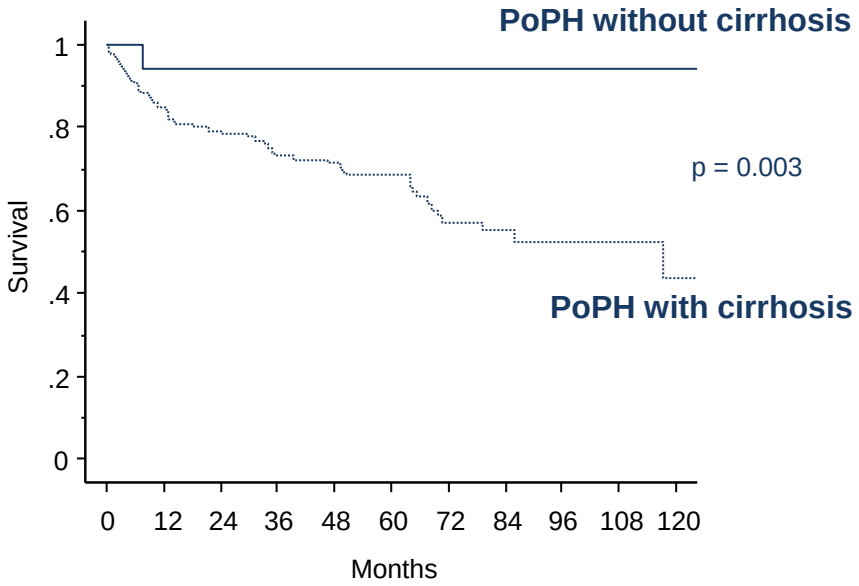
French cohort

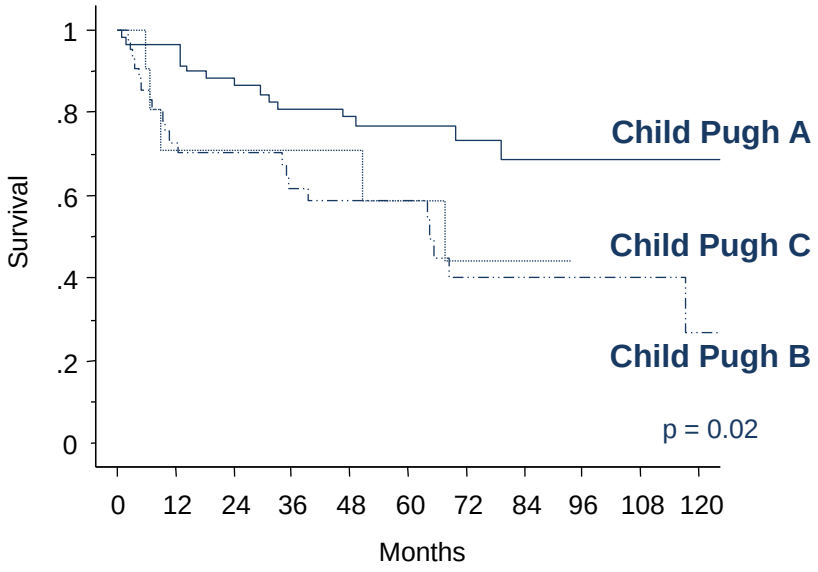


50% ⟵ 3-year survival ⟶ 75%

Krowka M, *et al. Chest* 2012; 141: 906–15.
Le Pavec J, *et al. Am J Respir Crit Care Med* 2008; 178: 637–43.

Survival of patients with PoPH in mainly due to the severity of liver disease

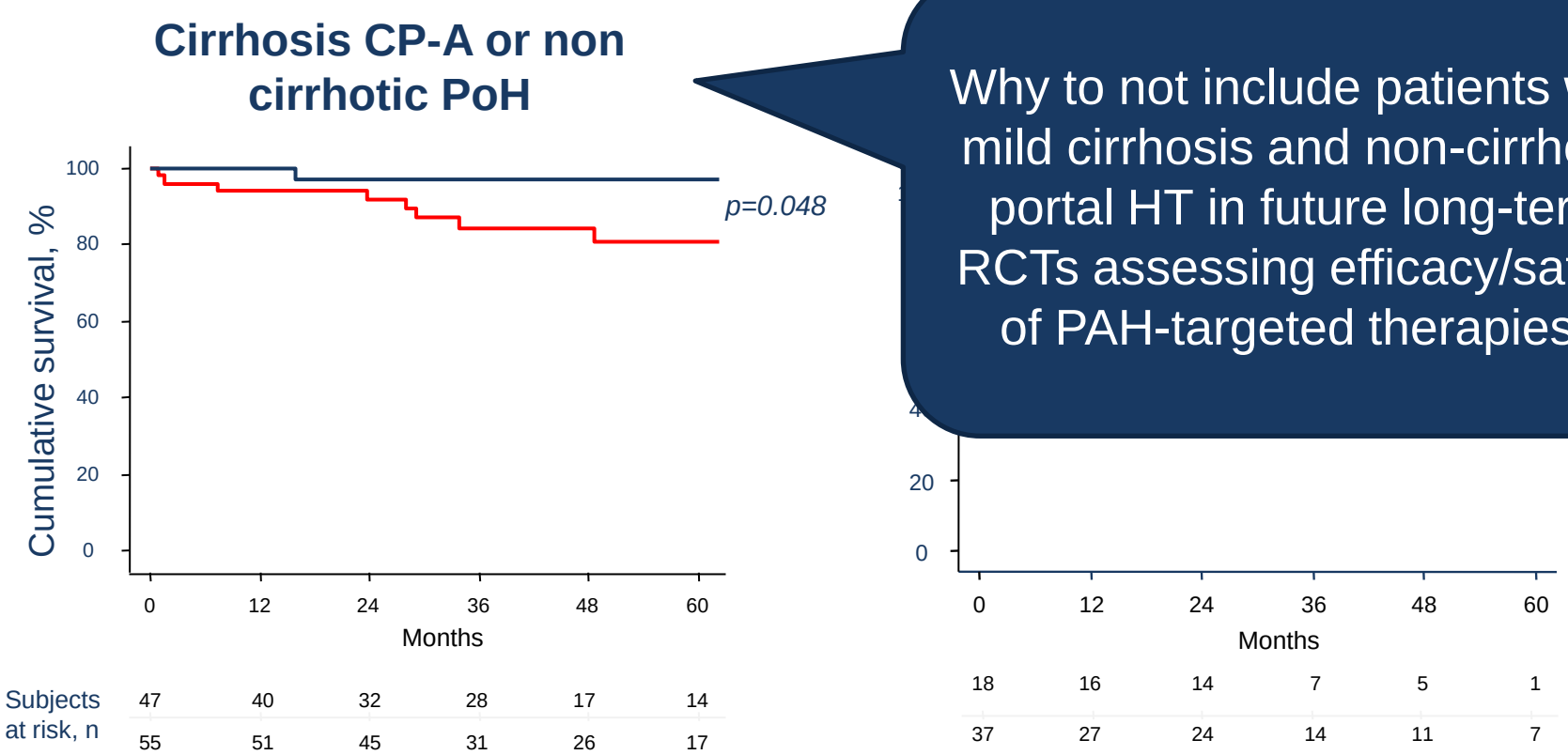




Variables	Hazard Ratio	95% Confidence Interval	P-value
Absence of cirrhosis	0.20	0.07 – 0.59	0.003
Cirrhosis Child Pugh B	2.05	1.22 – 3.43	0.007
Cirrhosis Child Pugh C	2.42	1.26 – 4.65	0.008
Cardiac index	0.56	0.38 - 0.83	0.004

Le Pavec J, *et al. Am J Respir Crit Care Med* 2008; 178: 637–43.

PAH-targeted therapy may improve survival of PoPH patients with mild cirrhosis or non-cirrhotic portal HT



Why to not include patients with mild cirrhosis and non-cirrhotic portal HT in future long-term RCTs assessing efficacy/safety of PAH-targeted therapies?

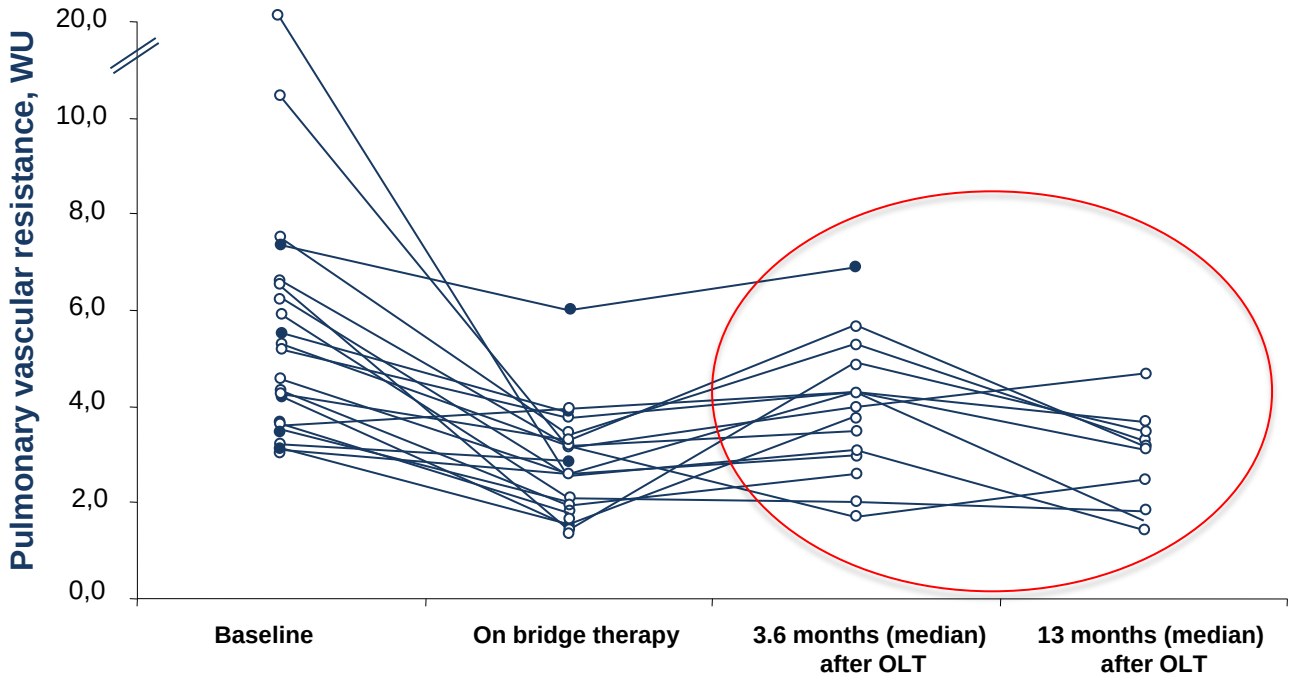
Patients treated with PAH-targeted medications

Untreated patients

Savale L, *et al.* Presented at ATS Conference 2010.

Combination of PAH-targeted therapy and liver transplantation in patients with PoPH

- 6 deaths including 3 PAH-related (D7, M2, M6 post-op.)
- Epoprostenol weaning off in all survivors, 6 months after LT

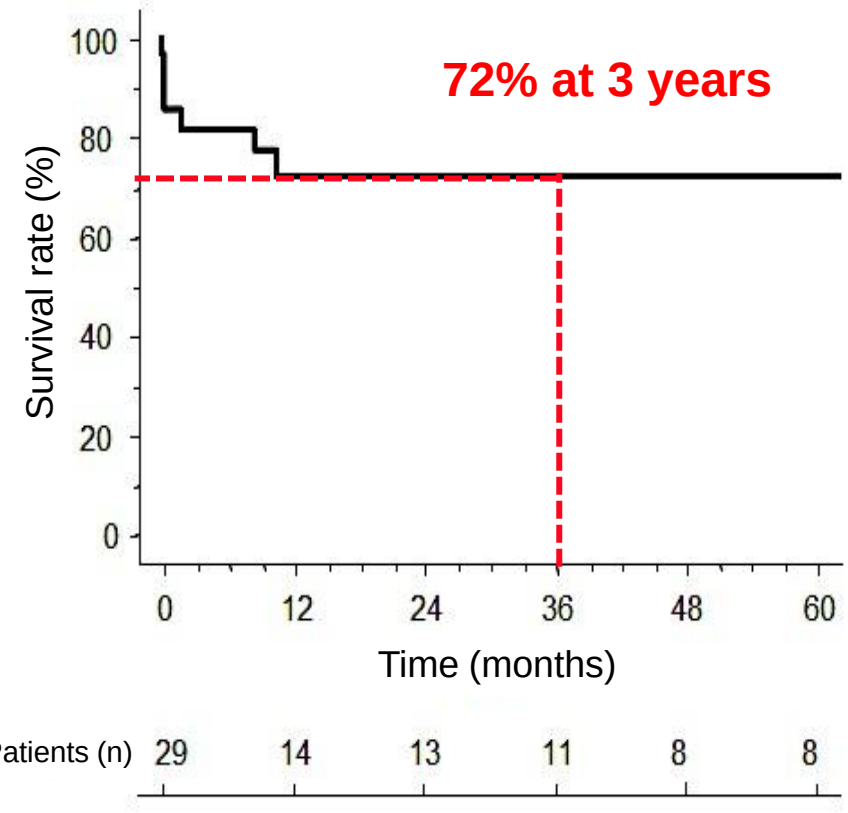


mPAP<25 mmHg
N=7/19 (37%)

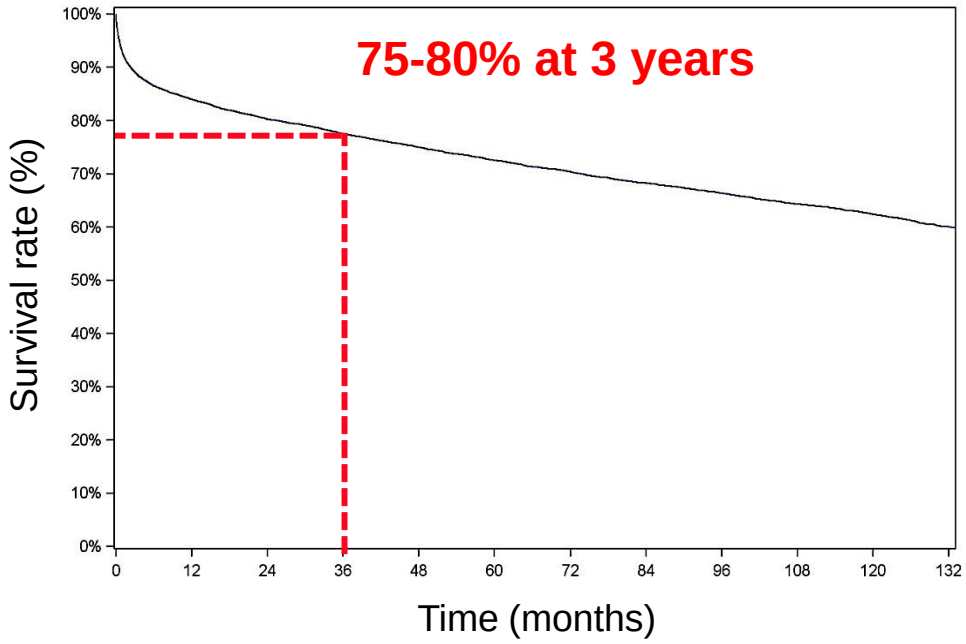
Savale L, *et al. Hepatology. In revision*.

PoPH: Survival after liver transplantation

Liver transplant PoPH

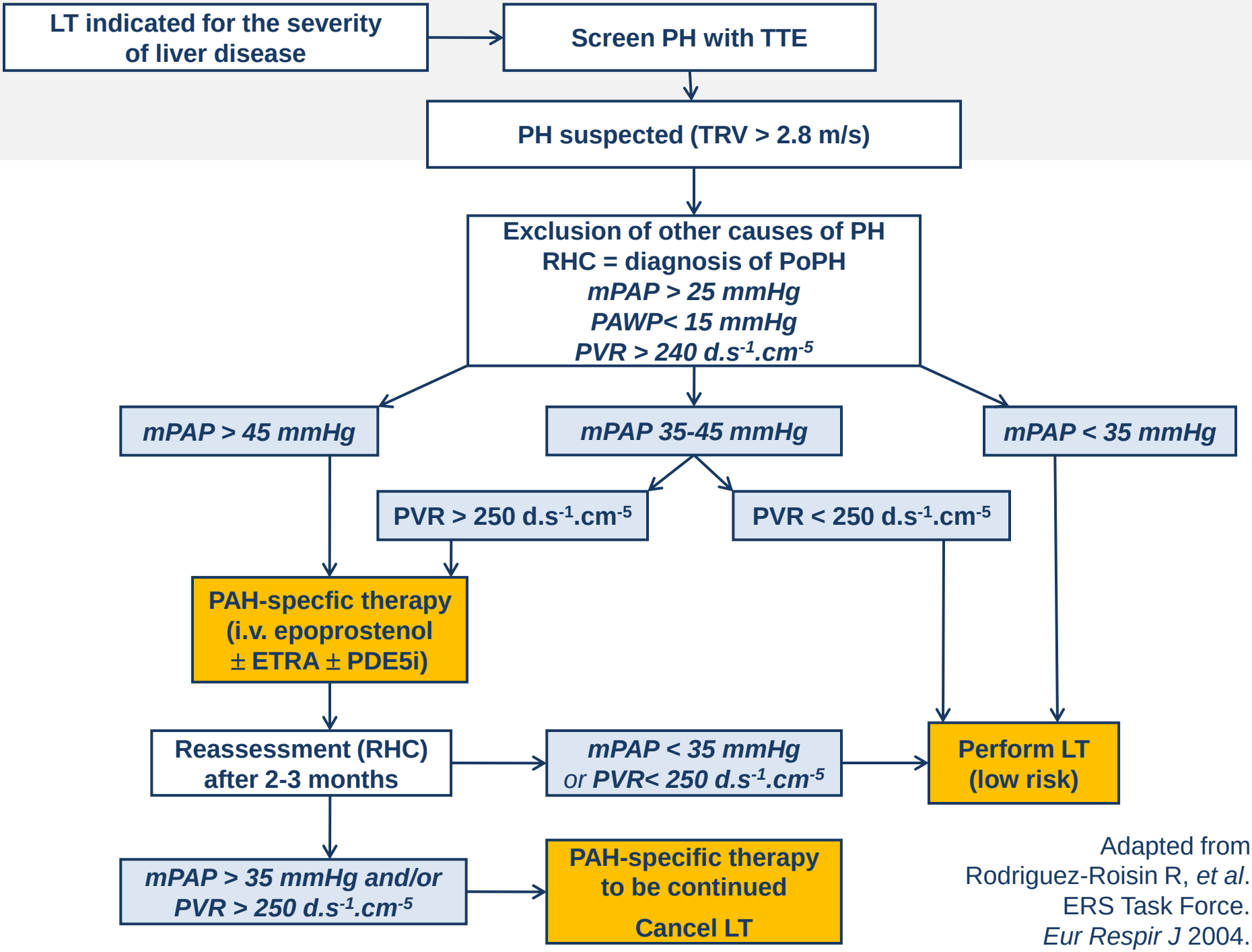


Overall LT in France



Data from French
“Biomedicine Agency”

Savale L, *et al. Hepatology. In revision*.



Adapted from
Rodriguez-Roisin R, *et al*.
ERS Task Force.
Eur Respir J 2004.

Comprehensive clinical classification of pulmonary hypertension Group 1

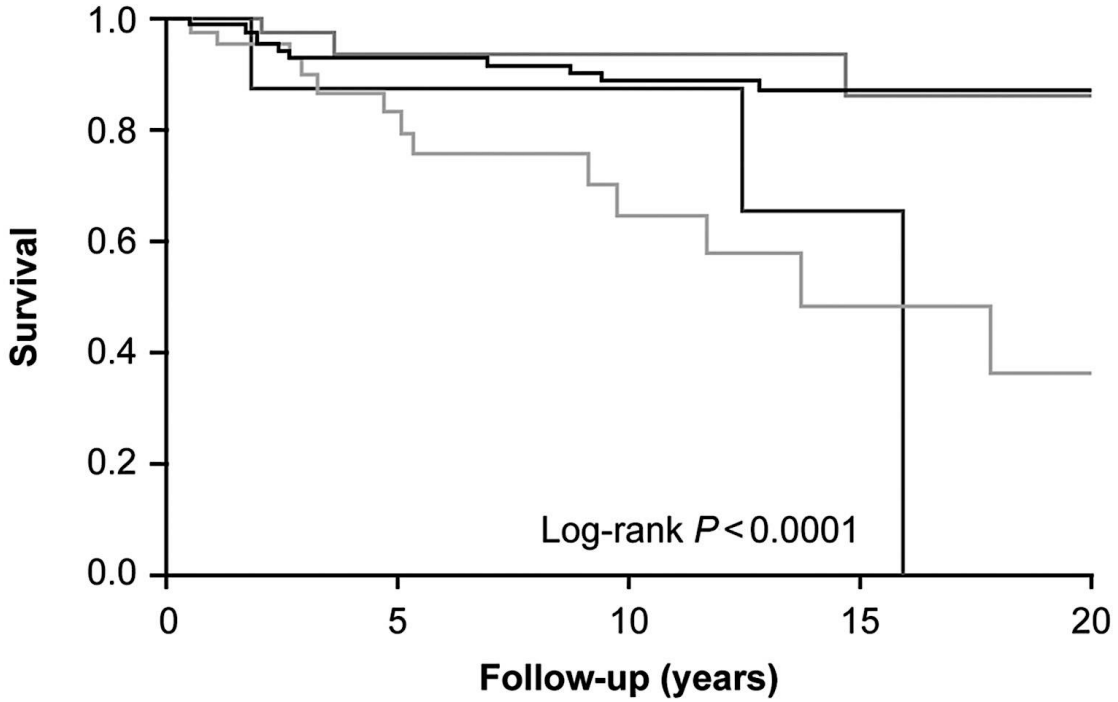
1. Pulmonary arterial hypertension
1.1 Idiopathic
1.2 Heritable
1.2.1 BMPR2 mutation
1.2.2 Other mutations
1.3 Drugs and toxins induced
1.4 Associated with:
1.4.1 Connective tissue disease
1.4.2 Human immunodeficiency virus (HIV) infection
1.4.3 Portal hypertension
1.4.4 Congenital heart diseases (Table 5)
1.4.5 Schistosomiasis
1'. Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis
1''. Persistent pulmonary hypertension of the newborn

- Eisenmenger's syndrome
- PAH associated with prevalent S to P shunt
- PAH with small/coincidental findings
- PAH after defect correction

Galiè N, Humbert M, Vachiéry JL et al. Eur Heart J, 2016; Eur Respir J 2015; 46: 903-75.

Survival of patients with PAH associated with CHD according to clinical subgroups

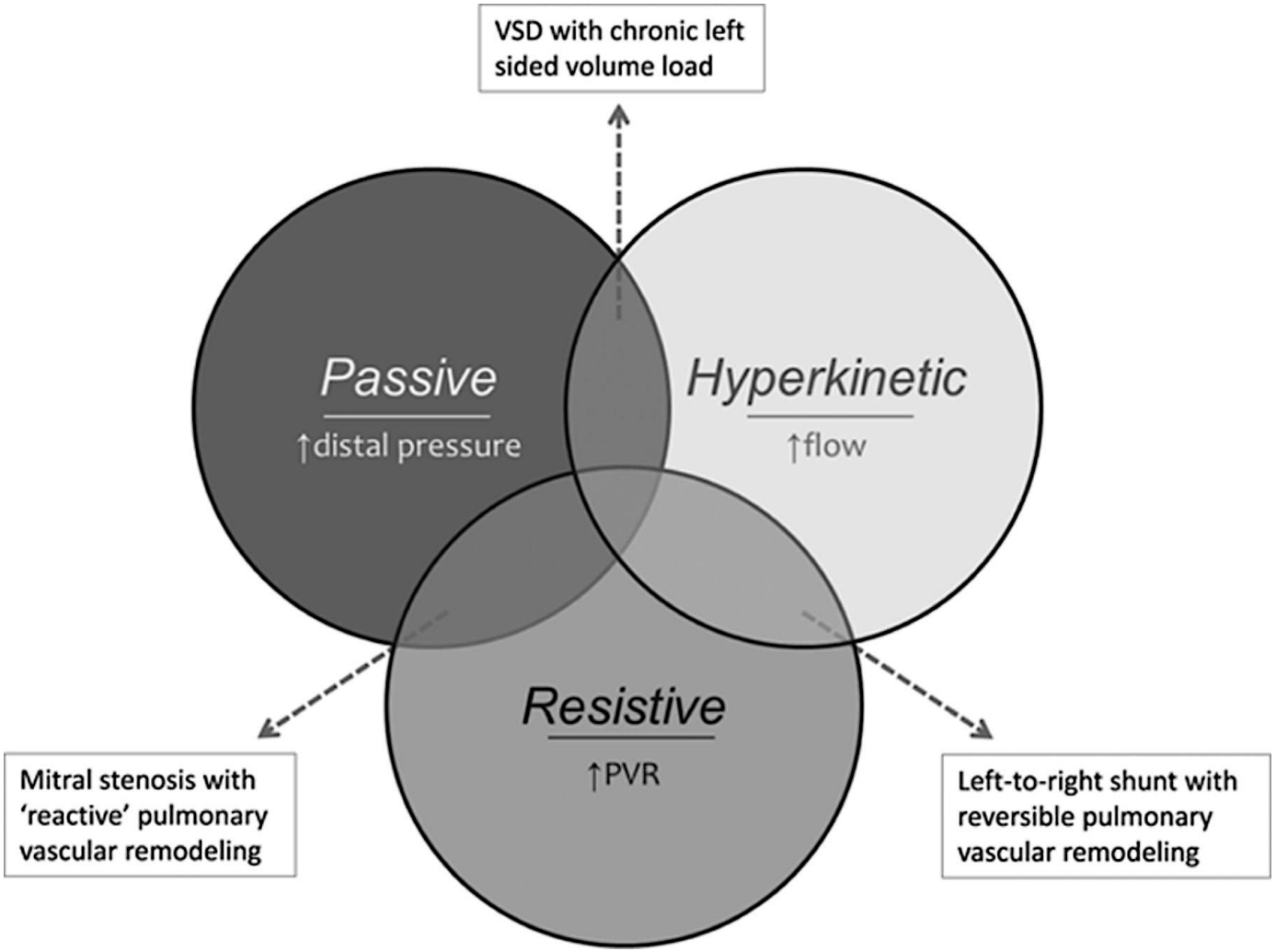
Single-center retrospective analysis in N= 192 patients



Patients at risk					
Eisenmenger	90	71	59	52	48
PAH-CHD with L-to-R shunts	48	22	18	11	10
PAH-CHD with small defects	10	4	4	2	0
PAH after defect correction	44	22	12	4	3

Manes A, *et al. Eur Heart J 2014*;35:716-24.

The three major hemodynamic causes of PH and their intersections in patients with CHD



Examples of overlap in patients with CHD

Opotowsky AR, *et al. Circulation* 2015;131:200-10.

Recommendations for correction of CHD with prevalent systemic-to-pulmonary shunts

PVRi (WU • m²)	PVR (WU)	Correctable[c]	Class[a]	Level[b]
<4	<2.3	Yes	IIa	C
>8	>4.6	No	IIa	C
4–8	2.3–4.6	Individual patient evaluation in tertiary centres	IIa	C

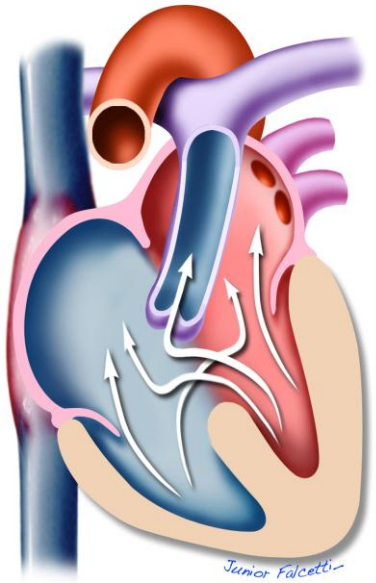
PVR = pulmonary vascular resistance; PVRi = PVR index; WU= Wood units.
[a] Class of recommendation. [b] Level of evidence
[c] With surgery of intravascular percutaneous procedure

- Long-term impact of defect closure in the presence of PAH with already increased PVR is unknown.
- Presence of exercise-induced and resting desaturation is concerning
- There is no evidence that a « treat-and-repair » approach in patients with PAH and high PVR is associated with long-term benefit

Galiè N, Humbert M, *et al.* 2015 ESC/ERS Guidelines. *Eur Respir J 2015 & Eur Heart J* 2016.

Short and long-term outcomes depend on several issues ...

- Nutritional status
- Extracardiac syndromes and comorbidities
  - Airway and lung disease
- Complexity of the anomaly
  - Possibility of significant residual lesions
- Pulmonary vascular disease
- Postoperative support
- Assistance after hospital discharge
  - Social / Economic issues



Recommendations for PAH associated with congenital heart diseases (CHD)

PAH-targeted therapy in Eisenmenger syndrome

Anticoagulant issue

Oxygen therapy issue

Recommendations	Class[a]	Level[b]	Ref.[c]
Bosentan WHO			22
Other EI prostano in patien syndrome			14, 24
In the absence of significant haemoptysis, oral anticoagulant treatment may be considered in patients with PA thrombosis or signs of heart failure	IIb	C	
The use of supplemental O_2 therapy should be considered in cases in which it produces a consistent increase in arterial O_2 saturation and reduces symptoms	IIa	C	179

Only one RCT with bosentan.
Another one ongoing (Maestro)

No RCT with other drugs in monotherapy

Galiè N, Humbert M, *et al.* 2015 ESC/ERS Guidelines. *Eur Respir J 2015 & Eur Heart J* 2016.

Recommendations for PAH associated with congenital heart diseases (CHD)

Hyperviscosity issue

Supplemental iron treatment issue

Combination therapy in ES

CCBs not recommended

Recommendations	Class[a]	Level[b]	Ref.[c]
If symptoms of hyperviscosity are present, phlebotomy with isovolumic replacement should be considered, usually when the haematocrit is >65%	IIa	C	183
The use of supplemental iron treatment m… patients w… levels			
Combinat… considere…			4
The use o… recommende… Eisenmenger syndrome	III	C	189

PAH-CHD: <10% of patients in RCTs with combination therapy

Vast majority of CHD with corrected shunts

Galiè N, Humbert M, *et al.* 2015 ESC/ERS Guidelines. *Eur Respir J 2015 & Eur Heart J* 2016.

Proposal for goals in PAH – CHD

Determinant of prognosis	Better prognosis	Worse prognosis
Right ventricular failure	Not applicable	Yes, guarded
Syncope	No	Uncertain
WHO FC	I/II	III/IV
6MWD	Longer (>350 m)	Shorter (<300 m)
Oxygen saturation	> 85%	$\leq$ 85% or drop $\geq$ 2% per year
Iron deficiency	Transferrin saturation $\geq$ 20%	Transferrin saturation < 20%
BNP levels	Normal or near-normal	> 30 pmol/L
Echocardiography	TAPSE > 1.5 cm, RA area < 25 cm^2, RA/LA < 1.5	TAPSE $\leq$ 1.5 cm, RA area $\geq$ 25 cm^2, RA/LA $\leq$ 1.5
Haemodynamics	RAP < 8 mmHg and CI $\geq$ 2.5 L/min/m^2	RAP > 15 mmHg and CI $\leq$ 2.0 L/min/m^2

Gatzoulis, Beghetti, Galie, et al. *Int J Cardiol* 2014.

PAH-CHD: Summary

- Guidelines provide guidance for Eisenmenger syndrome treatment in adults
- PAH-targeted therapies show benefit in Eisenmenger syndrome
- Treat-to-target strategy is necessary in Eisenmenger syndrome as patients seem not to be as stable as previously reported. However there is a need for defining specific targets for this population
- Guidelines and classification need to be implemented to include children and other forms of CHD-PAH