Classification of Pulmonary Hypertension

Marc Humbert

Directeur

Centre de Référence de l'Hypertension Pulmonaire Sévère

Hôpitaux Universitaires Paris-Sud – INSERM U999

Université Paris-Sud 11 – Clamart – France

UNIVERSITÉ PARIS SUD

Instituts thématiques

Inserm

Institut national de la santé et de la recherche médicale

LabEx LERMIT

Laboratoire d'Excellence en Recherche sur le Médicament et l'Innovation Thérapeutique

TORINO

DHU Thorax Innovation

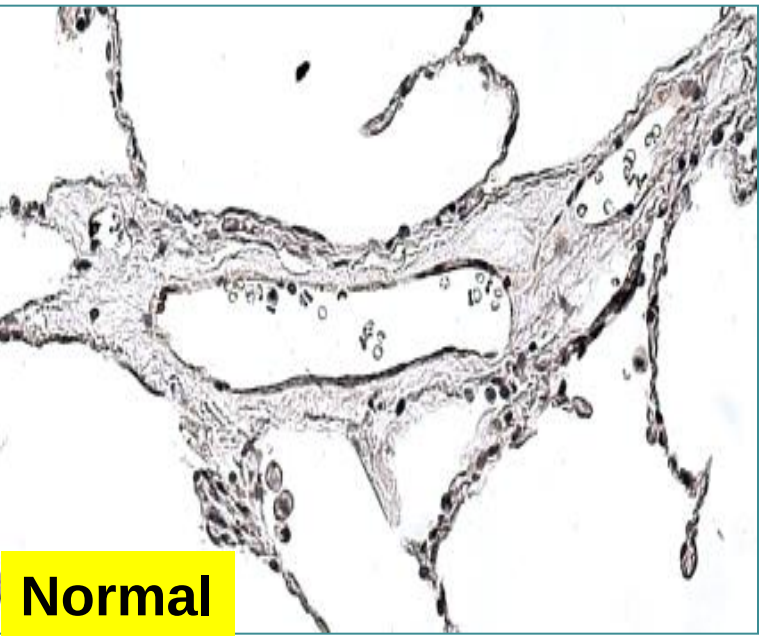
Disclosures

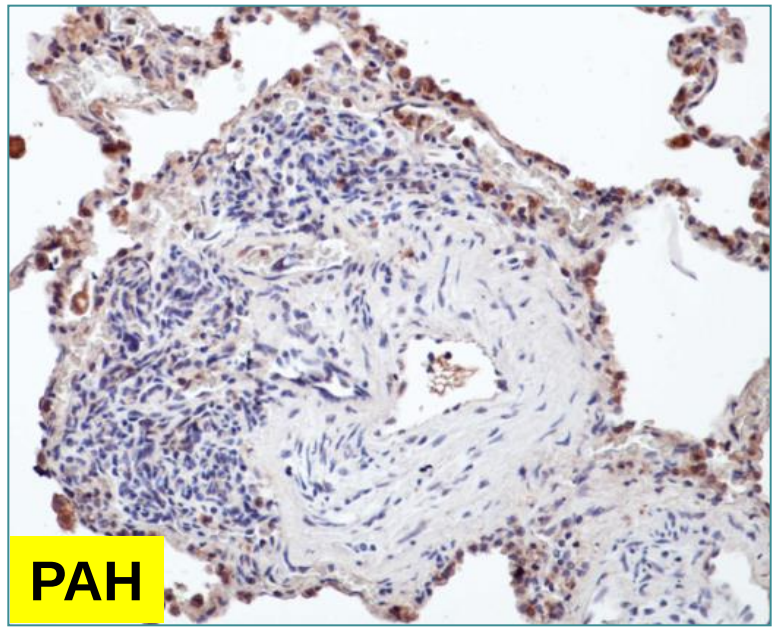
- Consultancy, board or advisory committee, speaker (current):
  - Actelion, Bayer, GSK, Novartis, Pfizer
- Research support (current):
  - Bayer, GSK
- Research support (past):
  - Pfizer

Introduction: Pulmonary Arterial Hypertension

a severe pulmonary vascular disease

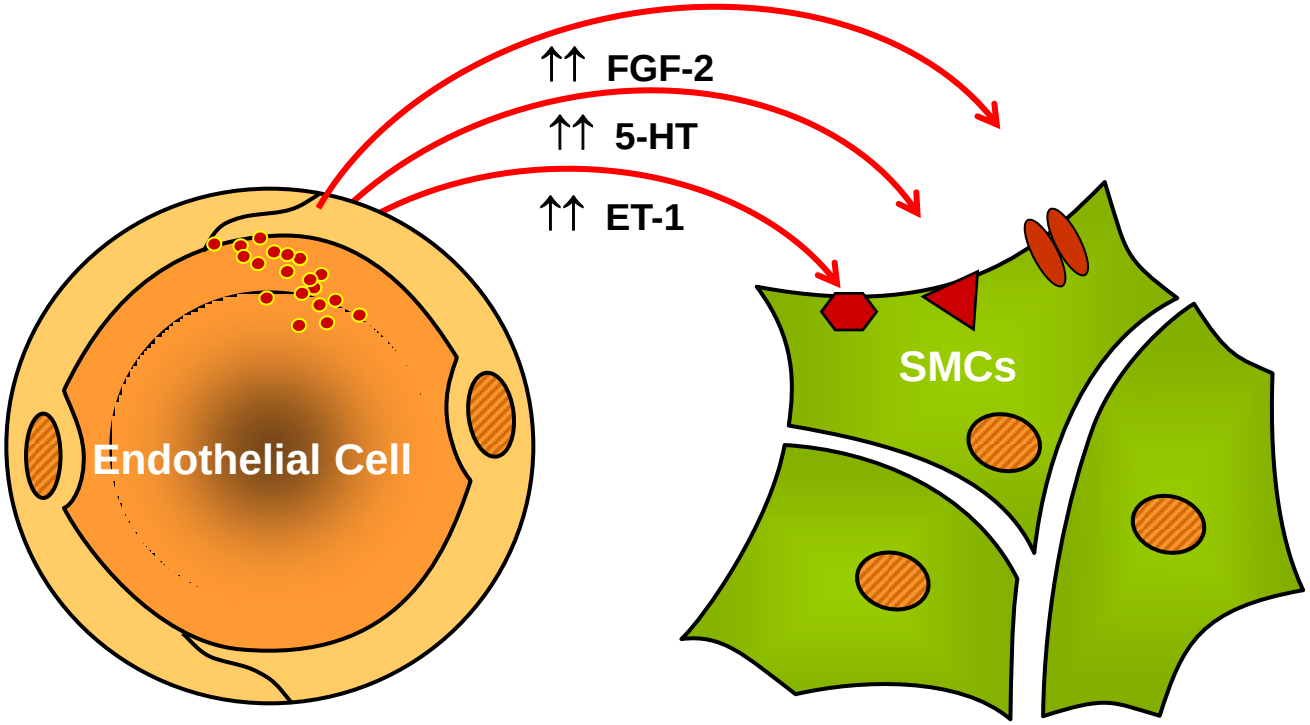
- ***Definition*** **: chronic precapillary pulmonary hypertension**
- ***Cause*** **: progressive structural remodeling of the small pulmonary arteries**
- ***Consequence*** **: right heart failure and death**





Introduction: Pulmonary Arterial Hypertension
a rare, but not an orphan disease

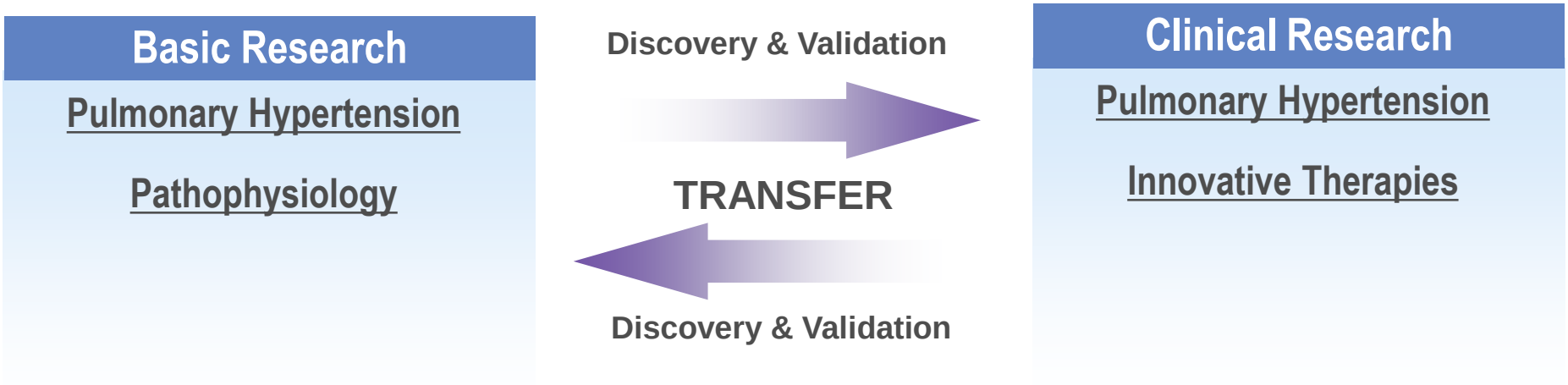
- ***Rare*** **: prevalence 15-25 / million (incidence 6/million/yr)**
- ***Pathophysiology*** **: pulmonary artery endothelial cell dysfunction…**
- ***Drugs*** **: 10 agents approved in the last 15 years (orphan drug status)**
- ***Lung / Heart-Lung transplantation :*** **if refractory to medical therapy**



Inserm

UNIVERSITÉ PARIS SUD
FACULTÉ DE MÉDECINE

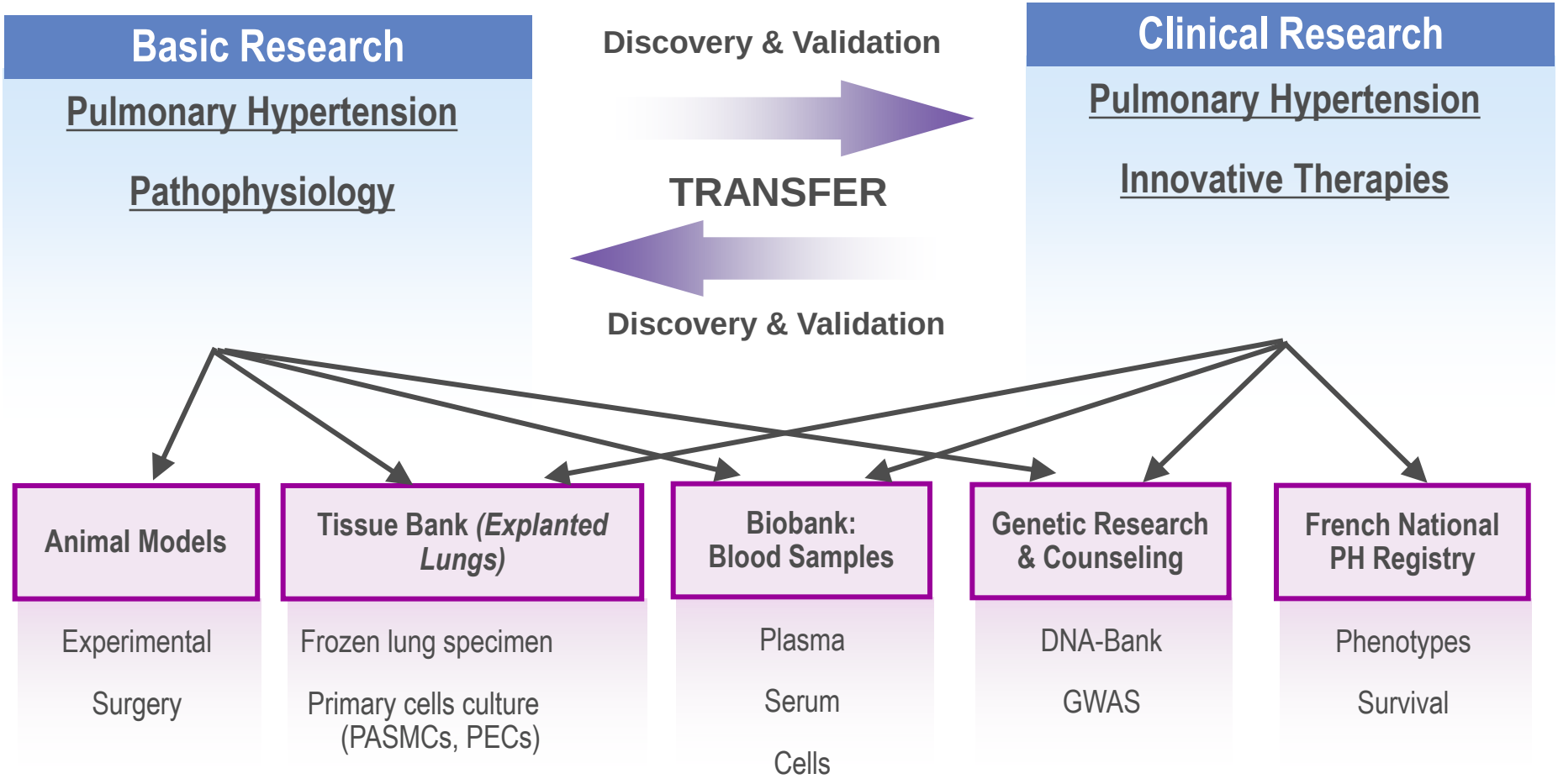
Université Paris-Sud - APHP - CCML – Inserm
UMR_S 999 : HYPERTENSION ARTERIELLE PULMONAIRE
Physiopathologie et Innovation Thérapeutique



Inserm

UNIVERSITÉ PARIS SUD
FACULTÉ DE MÉDECINE

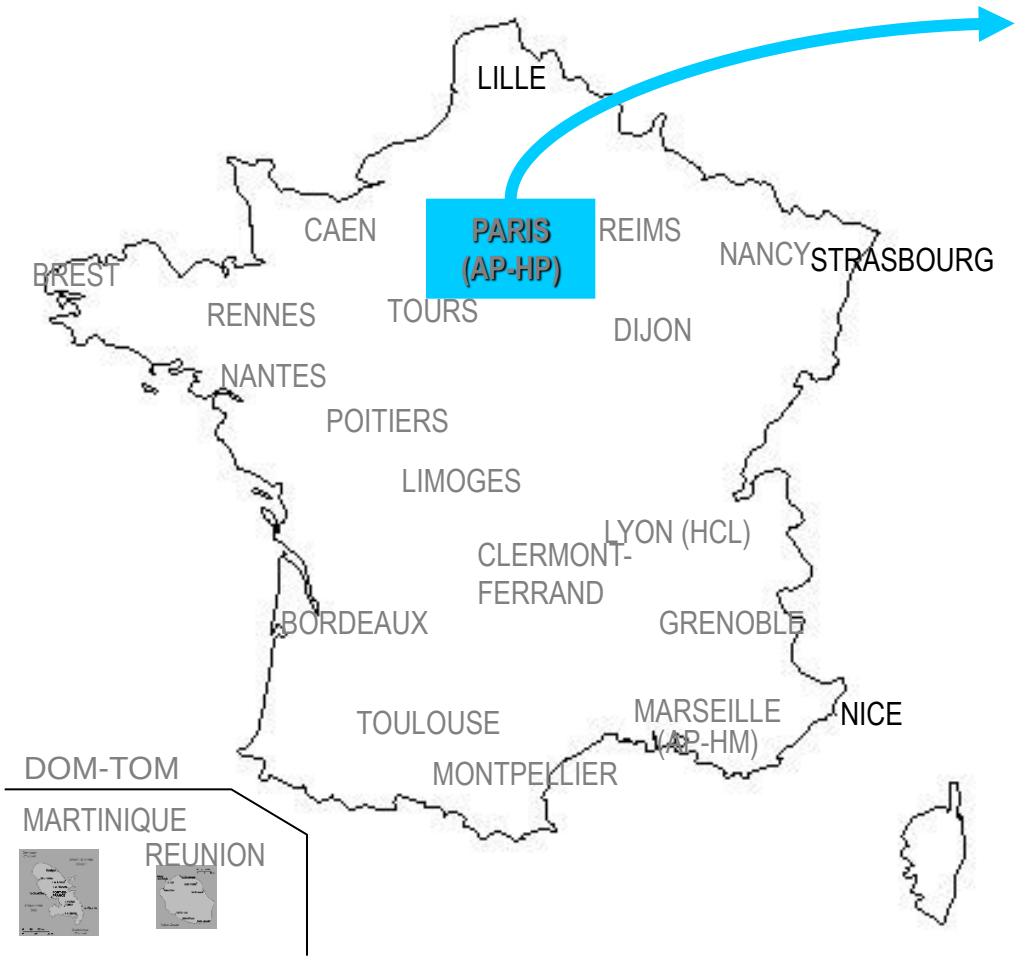
Université Paris-Sud - APHP - CCML – Inserm
UMR_S 999 : HYPERTENSION ARTERIELLE PULMONAIRE
Physiopathologie et Innovation Thérapeutique



Inserm

UNIVERSITÉ PARIS SUD
FACULTÉ DE MÉDECINE

Identify and support pulmonary vascular centers in the country



PARIS (AP-HP)	Centre de Référence
	Hôpital Antoine Béclère
	157 rue de la Porte de Trivaux
	92141 CLAMART Cedex

In Paris:
<u>National Reference Center</u>: AP-HP, Hôpitaux Universitaires Paris-Sud with 2 related constitutive centers: Necker (CHD) & Marie Lannelongue

Outside Paris:
<u>22 Competence Centers</u>, including 2 centers overseas

UNIVERSITÉ PARIS SUD

Haemodynamic definitions of pulmonary hypertension

Definition	Characteristics[a]	Clinical group(s)[b]
PH	PAPm ≥25 mmHg	All
Pre-capillary PH	PAPm ≥25 mmHg PAWP ≤15 mmHg	1. Pulmonary arterial hypertension 3. PH due to lung diseases 4. Chronic thromboembolic PH 5. PH with unclear and/or multifactorial mechanisms
Post-capillary PH	PAPm ≥25 mmHg PAWP >15 mmHg	2. PH due to left heart disease 5. PH with unclear and/or multifactorial mechanisms
Isolated post-capillary PH (Ipc-PH)	DPG <7 mmHg and/or PVR ≤3 WU[c]	
Combined post-capillary and pre-capillary PH (Cpc-PH)	DPG ≥7 mmHg and/or PVR >3 WU[c]	

CO = cardiac output; DPG = diastolic pressure gradient (diastolic PAP – mean PAWP); mPAP = mean pulmonary arterial pressure; PAWP = pulmonary arterial wedge pressure; PH = pulmonary hypertension; PVR = pulmonary vascular resistance; WU = Wood units.

[a]All values measured at rest; see also section 7.

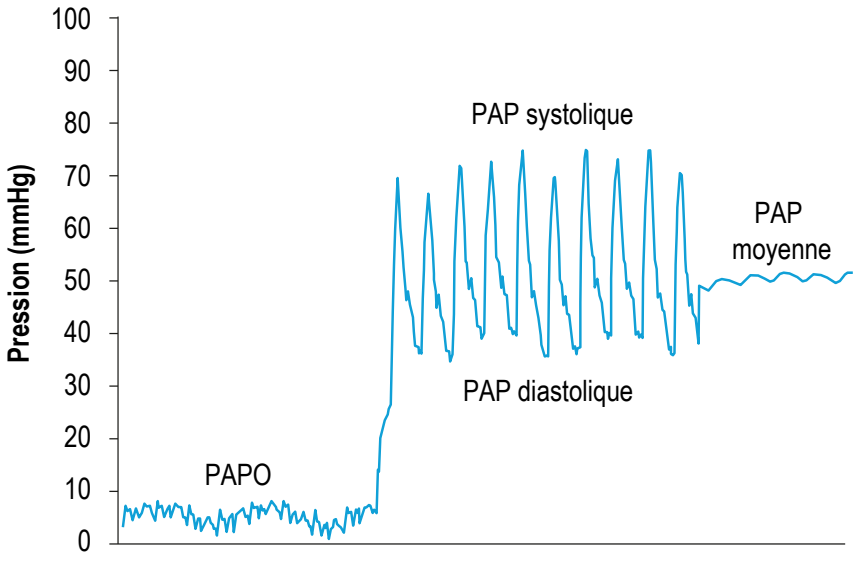
[b]According to Table 4.

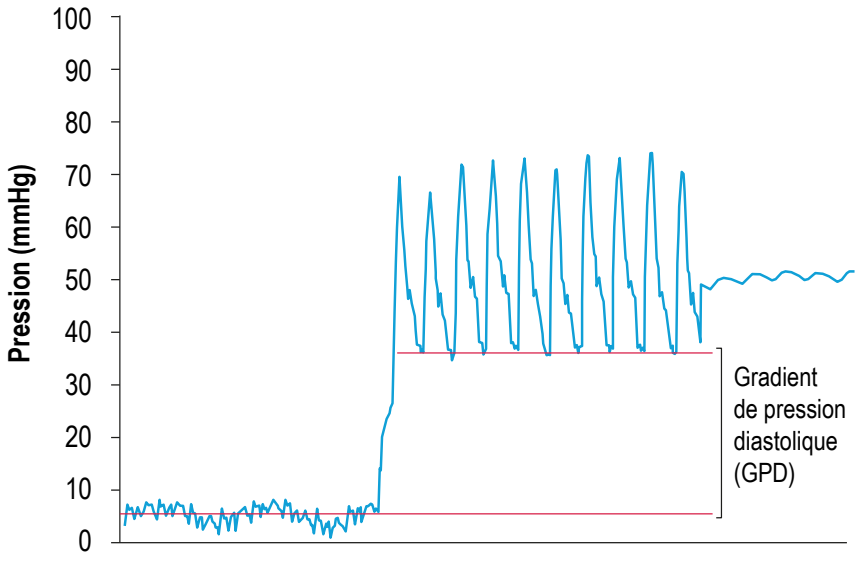
[c]Wood Units are preferred to dynes.s.cm^{-5}.

Eur Respir J 2015; 46: 903-75; Eur Heart J 2016; 37:67-119

Définition de l'hypertension pulmonaire

HTP précapillaire





HTAP

- ✔ PAPm ≥ 25 mmHg
- ✔ PAPO ≤ 15 mmHg
- ✔ RVP > 3 UW

Eur Respir J 2015; 46: 903-75; Eur Heart J 2016; 37:67-119

Classification of Pulmonary Hypertension

A clinical classification was proposed

to individualize different categories of PH sharing

- similar pathophysiological mechanism
- similar histological findings
- similar clinical presentation
- similar management

Rationale for a Clinical Classification of PH

A clinical classification of various forms of pulmonary hypertension can be useful:

- in communicating about individual patients
- in standardizing diagnosis and treatment
- in conducting trials with homogeneous groups of patients
- in analyzing novel pathobiological abnormalities in well-characterized patient populations

CLASSIFICATION

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'.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)[a]

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

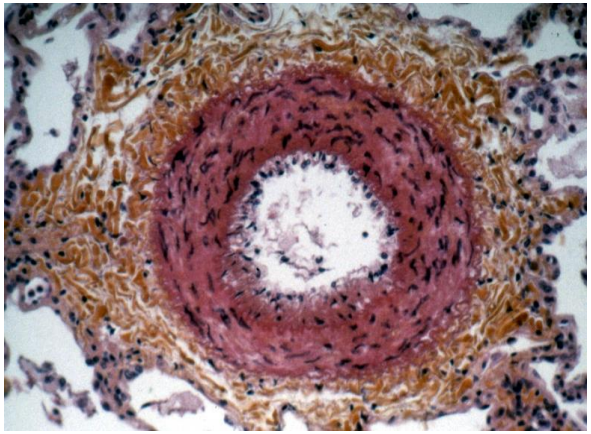
Eur Respir J 2015; 46: 903-75; Eur Heart J 2016; 37:67-119

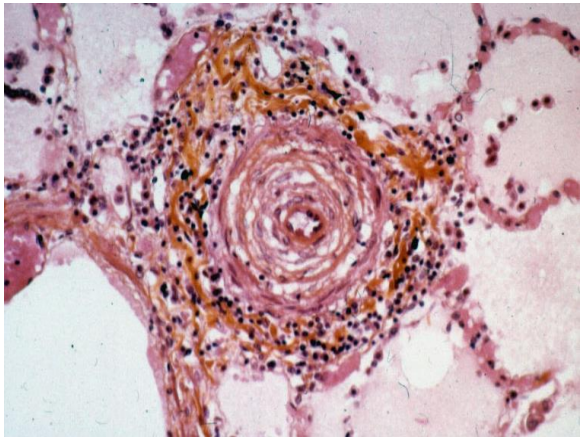
Clinical classification of Pulmonary Hypertension

CATEGORY	TREATMENT
Group 1 **Pulmonary Arterial Hypertension**	**Prostanoids, ERA, PDE5i…**
Group 2 **PH due to Left Heart Disease**	**ACE inhibitors, ß-blockers…**
Group 3 **PH with Lung Diseases/Hypoxemia**	**Oxygen**
Group 4 **Chronic Thromboembolic PH**	**Pulmonary endarterectomy/BPA...**
Group 5 **PH with unclear or multifactorial mechanisms**	**?**

1. Pulmonary Arterial Hypertension

- Idiopathic
- Heritable
- Drugs and toxins
- Associated with other diseases
  - Connective tissue diseases
    - Scleroderma
    - Other CTDs
  - HIV infection
  - Portal hypertension
  - Systemic-to-pulmonary shunts
  - Schistosomiasis

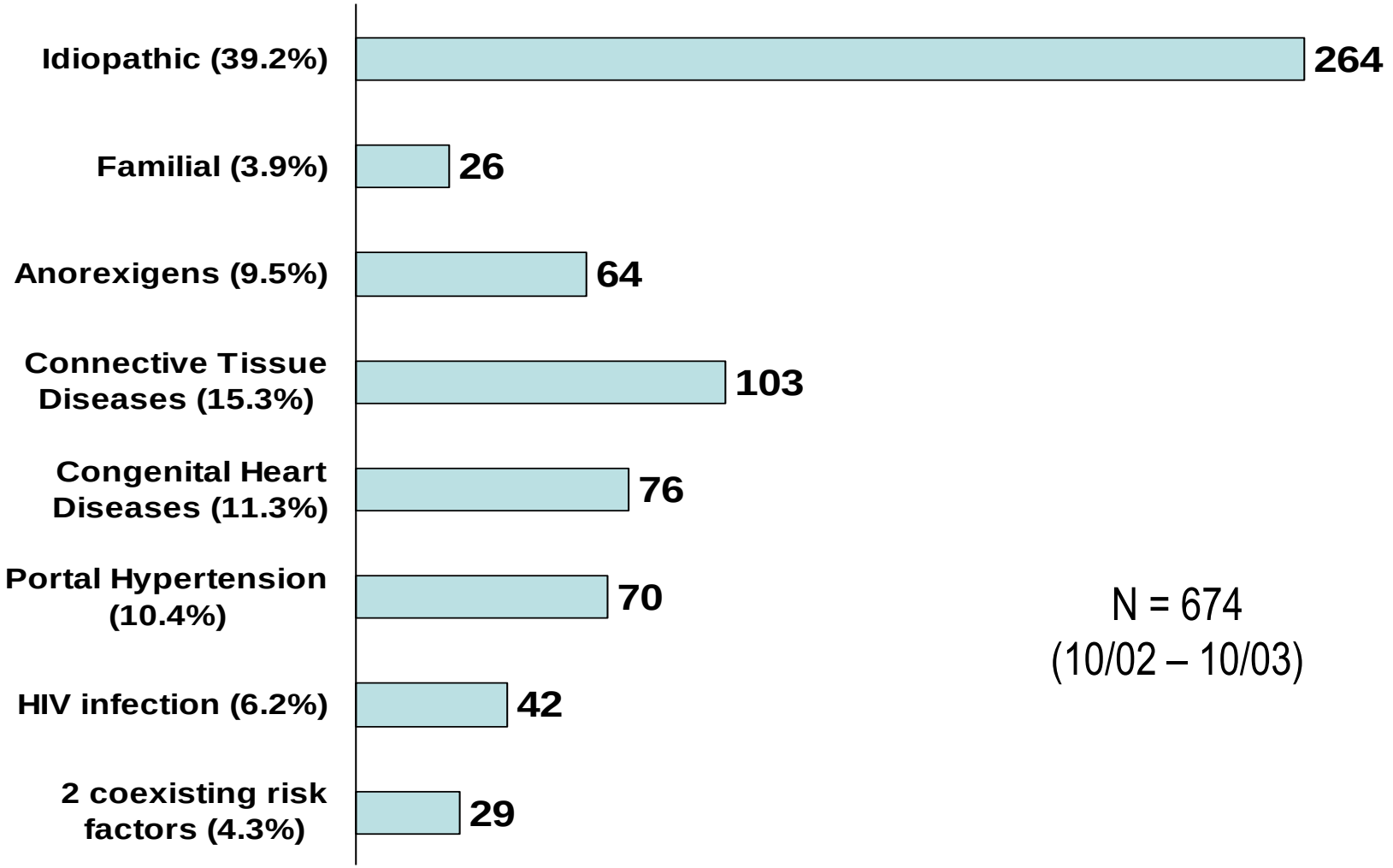




Pulmonary Arterial Hypertension in France

Results from a National Registry

Marc Humbert, Olivier Sitbon, Ari Chaouat, Michèle Bertocchi, Gilbert Habib, Virginie Gressin, Azzedine Yaici, Emmanuel Weitzenblum, Jean-François Cordier, François Chabot, Claire Dromer, Christophe Pison, Martine Reynaud-Gaubert, Alain Haloun, Marcel Laurent, Eric Hachulla, and Gérald Simonneau



Am J Respir Crit Care Med 2006;173:1023–30.

FAMILIAL/HERITABLE PAH

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'.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

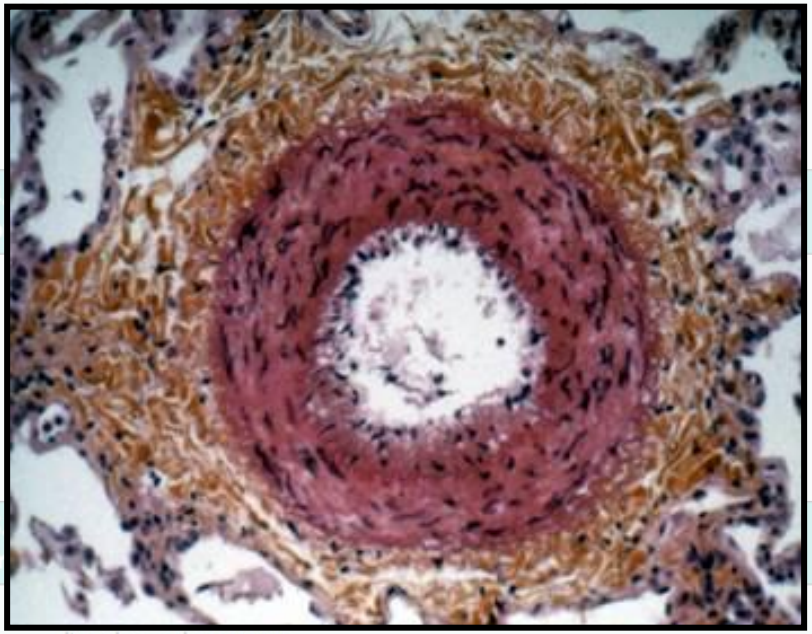
1''. Persistent pulmonary hypertension of the newborn

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



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 thrombotic microangiopathy, fibrosing mediastinitis, chronic renal failure (with/without dialysis), segmental pulmonary hypertension

Eur Heart J 2015, Eur Respir J 2015

FAMILIAL/HERITABLE PAH

2014 — **Bi-allelic mutations of *EIF2AK4*** gene involved in the development of PVOD

2013 — ***KCNK3 and TBX4*** genes involved in the development of PAH

2012 — ***Caveolin-1*** gene involved in the development of PAH

2011 — ***Smad1*** (one case) and ***Smad5*** (one case) genes involved in the development of PAH

2009 — ***Smad8*** gene involved in the development of PAH : (2 cases)

2003 — - ***Endogline*** gene involved in the development of PAH

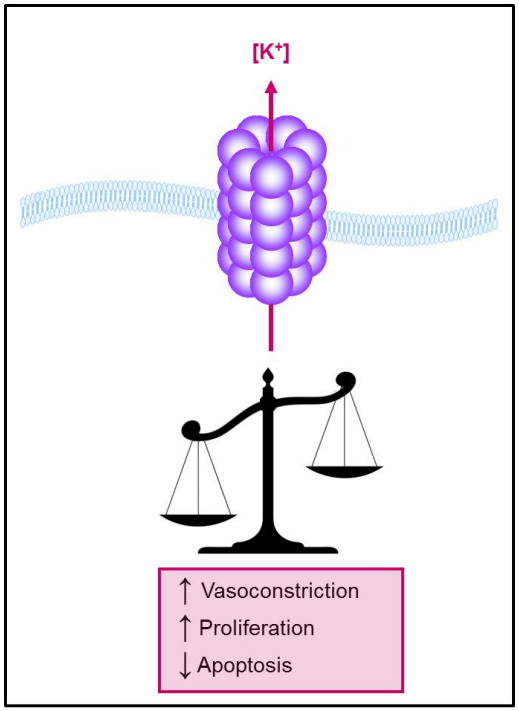
- **Begining of genetic counseling in France**

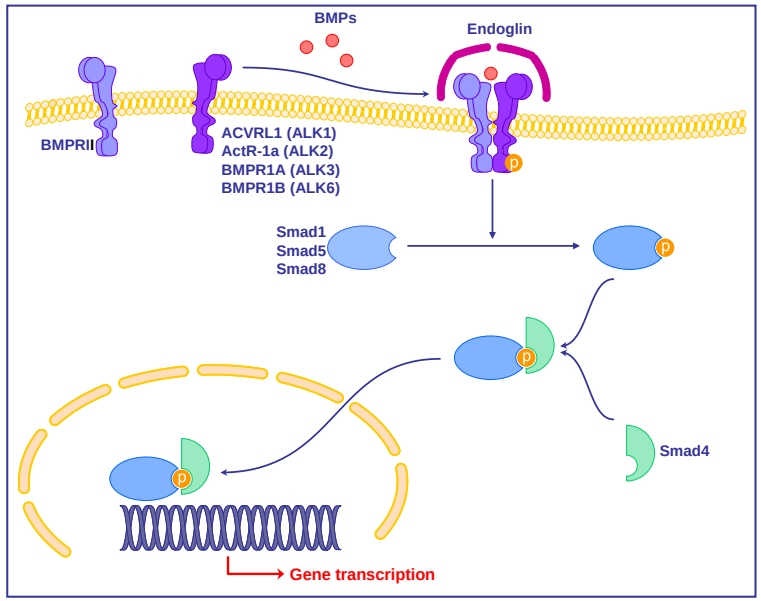
2001 — ***ALK1 (ACVRL1)*** gene involved in the development of PAH

2000 — *BMPR2* gene involved in the development of PAH

1997 — Locus implicated in PAH development localised on chromosome 2

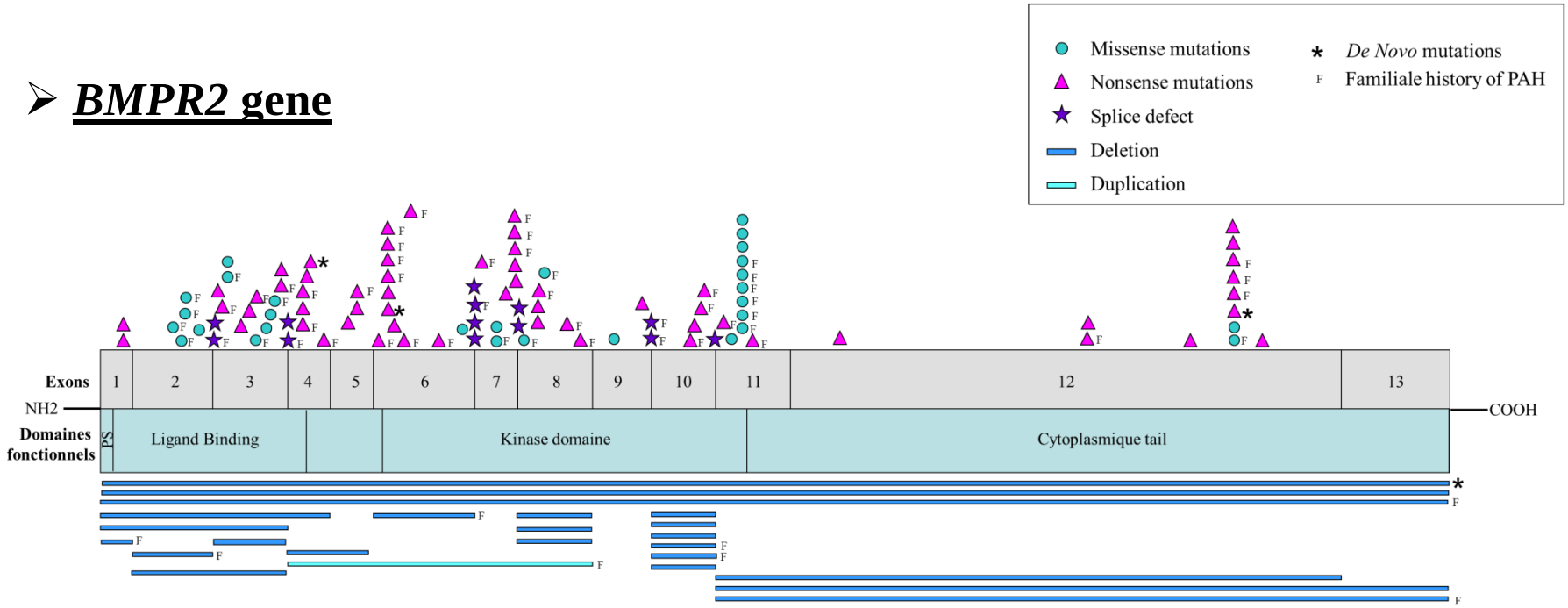
1954 — First familial Pulmonary Hypertension described





BMPR2 MUTATIONS IDENTIFIED

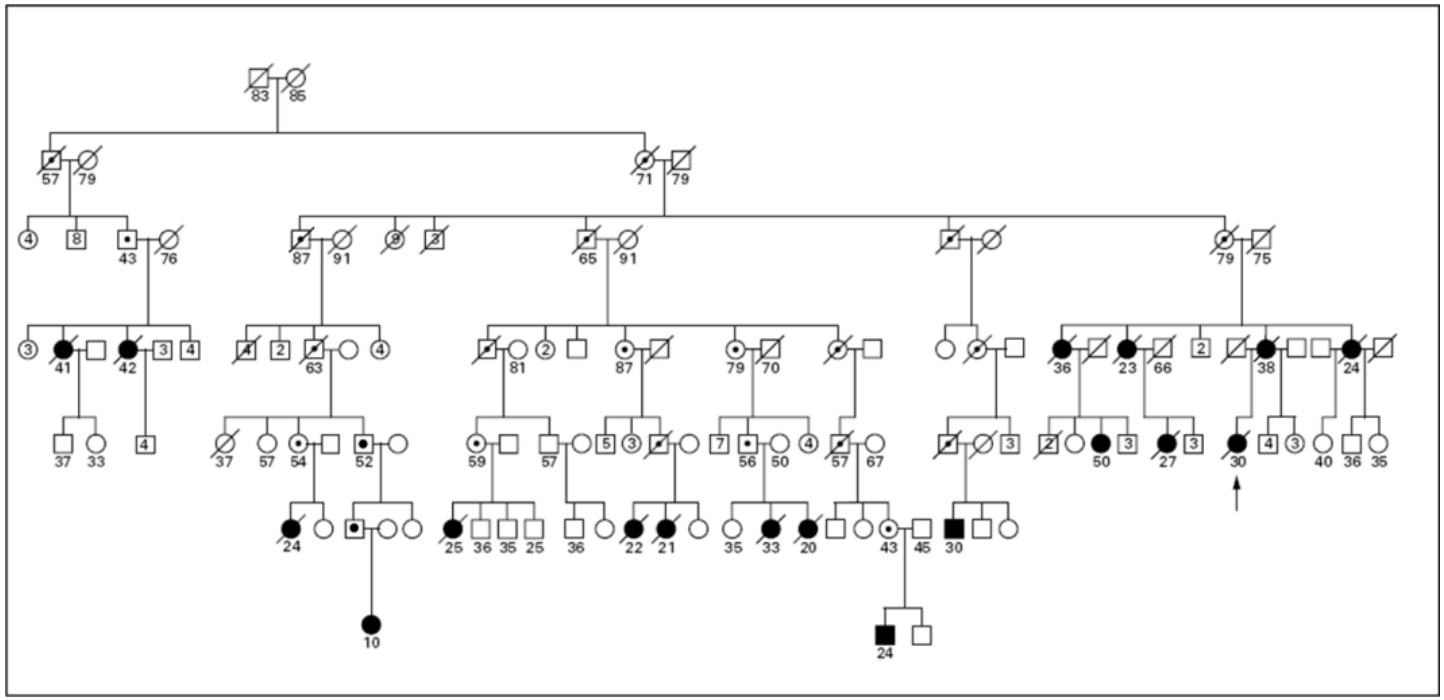
➢ ***BMPR2* gene**



Girerd B. Eur Respir J 2016

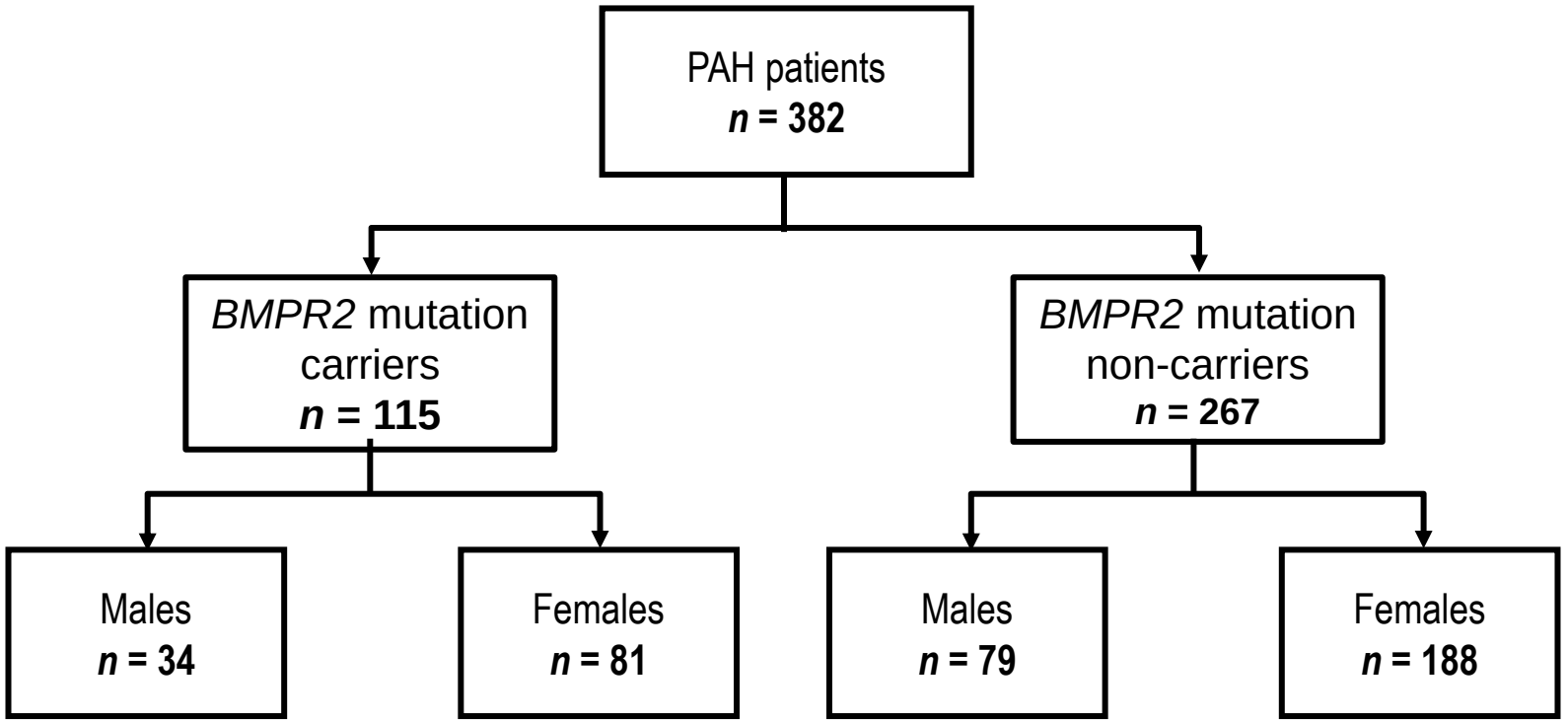
➢ Heritable PAH :

- ***BMPR2***
- **Autosomal dominant**
- **Incomplete penetrance (14% in males , 42% in females)**



Female predominance

- A similar female predominance (sex ratio 2.4/1) is observed in PAH patients carrying or not carrying a *BMPR2* mutation

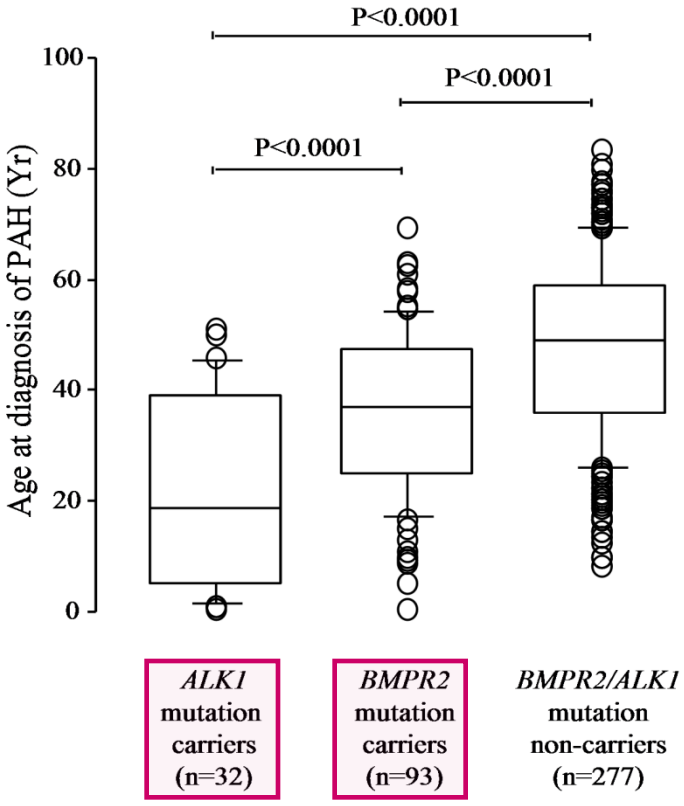


Girerd B, *et al. Respir Res*.2010; 11: 73.

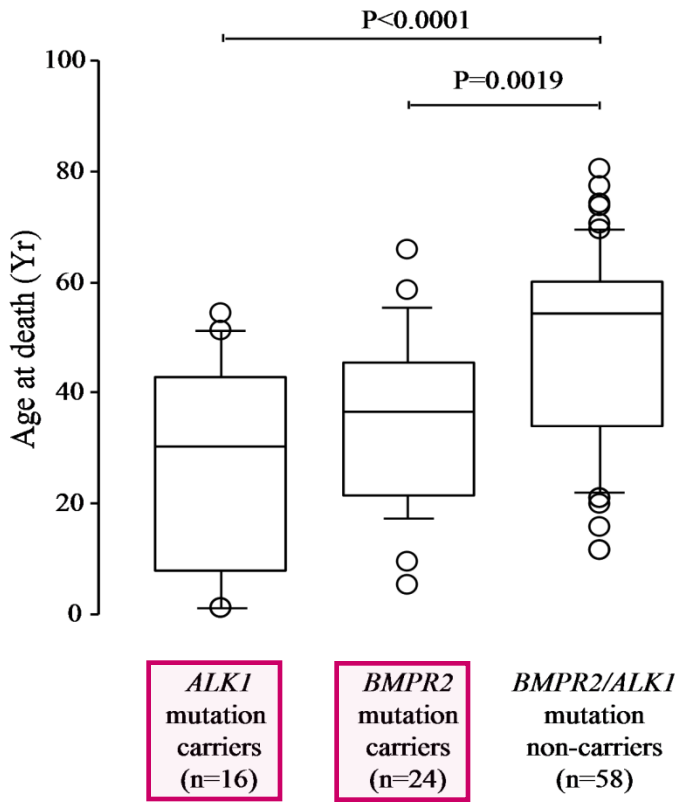
AGE AT DIAGNOSIS AND DEATH

PAH patients carrying *BMPR2* (or *ALK1/ACVRL1)* mutations were younger at diagnosis and at death compared to non carriers

Age at diagnosis



Age at death



Girerd, B, Am J Respir Crit Care Med 2010

BMPR2 mutations and survival in pulmonary arterial hypertension: an individual participant data meta-analysis

Jonathan D W Evans, Barbara Girerd, David Montani, Xiao-Jian Wang, Nazzareno Galiè, Eric D Austin, Greg Elliott, Koichiro Asano, Ekkehard Grünig, Yi Yan, Zhi-Cheng Jing, Alessandra Manes, Massimiliano Palazzini, Lisa A Wheeler, Ikue Nakayama, Toru Satoh, Christina Eichstaedt, Katrin Hinderhofer, Matthias Wolf, Erika B Rosenzweig, Wendy K Chung, Florent Soubrier, Gérald Simonneau, Olivier Sitbon, Stefan Gräf, Stephen Kaptoge, Emanuele Di Angelantonio, Marc Humbert*, Nicholas W Morrell**

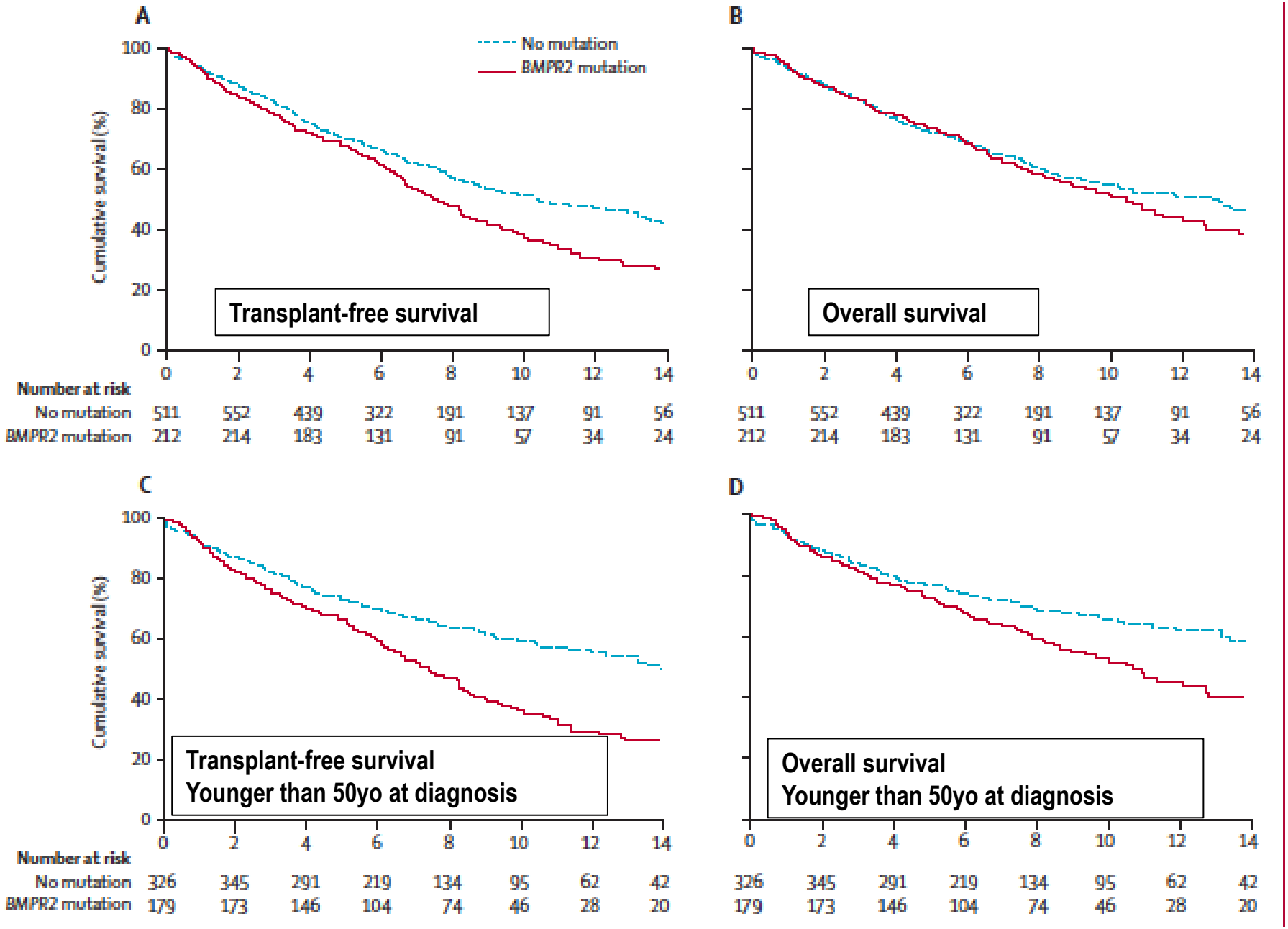
- Patients with PAH and *BMPR2* mutations present at younger age with more severe disease, and are at increased risk of death and transplantation, compared with those without *BMPR2* mutations

- Mutation carriers are less likely to respond to acute vasodilatator testing

Sztrymf B, Am J Respir Crit Care Med 2008
Girerd, B, Am J Respir Crit Care Med 2010
Evans JDW, Lancet Resp Med 2016

	All patients	BMPR2 mutation status		
		Non-carriers (N=1102)	Carriers (N=448)	pvalue
Age at diagnosis (N=1447), years	40·1 (17·2)	42·0 (17·8)	35·4 (14·8)	<0·0001
Male sex	440/1545 (28%)	302/1097 (28%)	138/448 (31%)	0·20
Family history of PAH	202/1376 (15%)	--	202/402 (50%)	--
Body-mass index (N=1206), kg/m²	24·9 (9·1)	24·9 (10·6)	24·9 (5·9)	0·99
6-min walk distance (N=1072), m	378 (124)	374 (128)	388 (113)	0·088
NYHA functional class				0·38
I–II	423/1426 (30%)	313/1031 (30%)	110/394 (28%)	
III	896/1426 (63%)	647/1031 (63%)	249/394 (63%)	
IV	107/1426 (8%)	72/1031 (7%)	35/394 (9%)	
Mean pulmonary artery pressure (N=1503), mm Hg	57·6 (15·0)	56·4 (15·3)	60·5 (13·8)	<0·0001
Pulmonary vascular resistance (N=1300), Wood units	14·0 (8·4)	12·9 (8·3)	16·6 (8·3)	<0·0001
Right atrial pressure (N=1253), mm Hg	8·2 (5·5)	8·0 (5·7)	8·6 (5·2)	0·065
Cardiac output (N=1202), L/min	3·98 (1·44)	4·20 (1·50)	3·50 (1·17)	<0·0001
Cardiac index (N=1358), L/min per m²	2·40 (0·88)	2·51 (0·92)	2·11 (0·69)	<0·0001
Vasodilator responder	157/1287 (12%)	147/907 (16%)	10/380 (3%)	<0·0001

Evans JDW, Lancet Resp Med 2016



Evans JDW, Lancet Resp Med 2016

ORIGINAL ARTICLE
PULMONARY VASCULAR DISEASES

Genetic counselling in a national referral centre for pulmonary hypertension

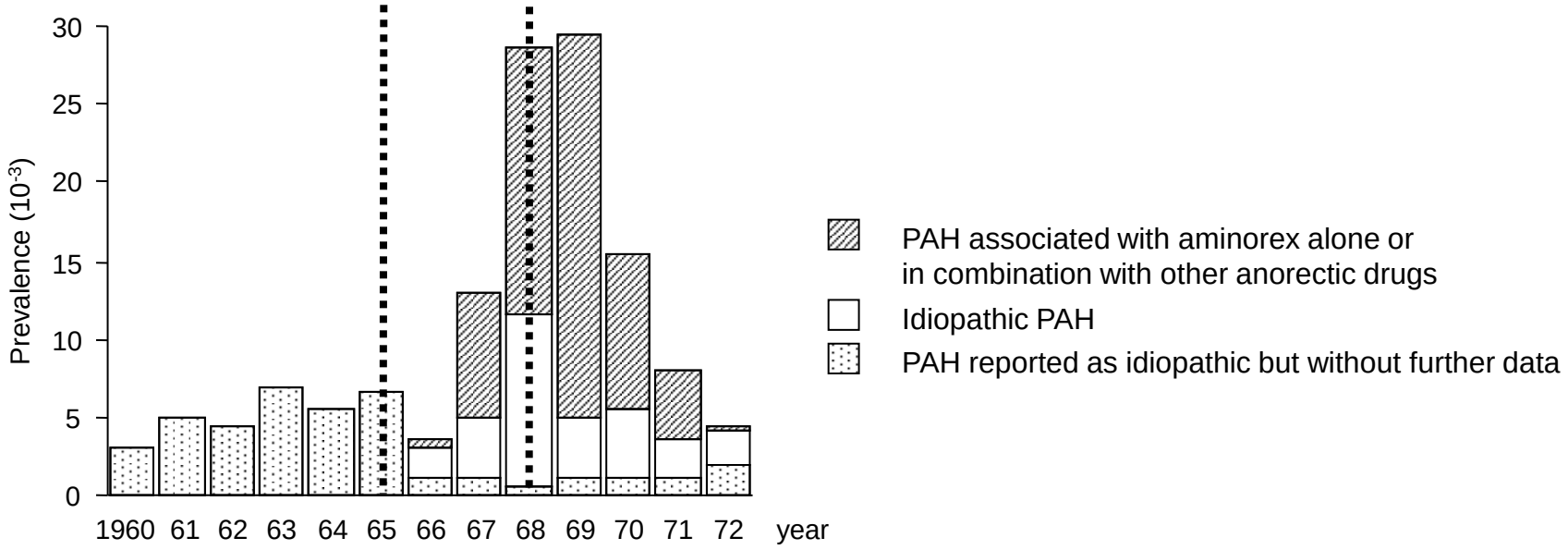
Barbara Girerd[1,2,3,6], David Montani[1,2,3,6], Xavier Jaïs[1,2,3], Mélanie Eyries[4], Azzedine Yaici[1,2,3], Benjamin Sztrymf[1,2,3], Laurent Savale[1,2,3], Florence Parent[1,2,3], Florence Coulet[4], Laurent Godinas[1,2,3], Edmund M. Lau[1,2,5], Yuichi Tamura[1,2,3], Olivier Sitbon[1,2,3], Florent Soubrier[4], Gérald Simonneau[1,2,3] and Marc Humbert[1,2,3]

Girerd B. Eur Respir J 2016

Appetite suppressant-induced PAH

1967-1970

- Epidemic in Austria, Germany and Switzerland
- Geographic and temporal relation to Aminorex
- 75% of patients with PAH exposed to Aminorex
  - Amphetamine like drug
  - Potent appetite suppressor



Gurtner HP. *Cor Vasa* 1985;27:160-71.

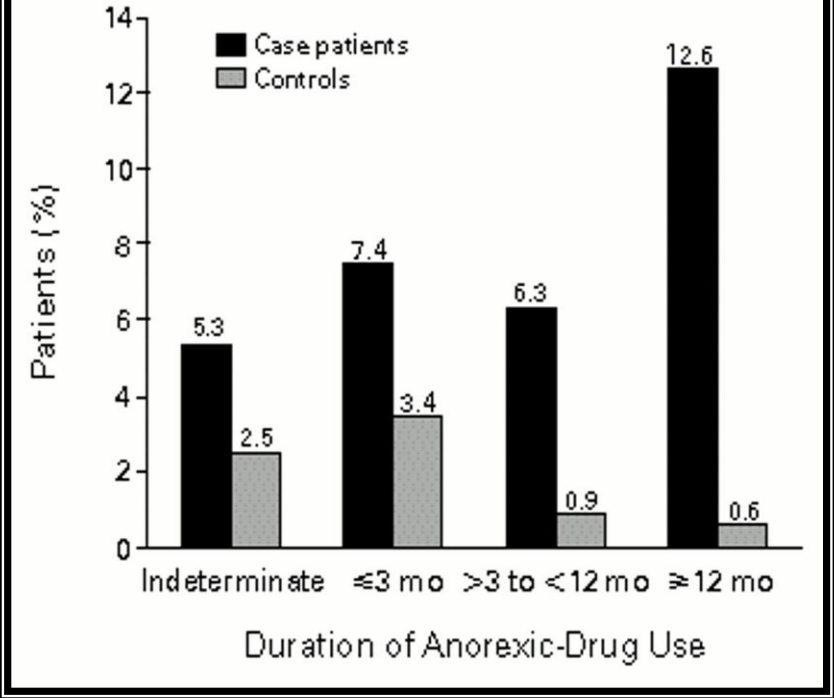
The New England
Journal of Medicine

VOLUME 335 AUGUST 29, 1996 NUMBER 9

APPETITE-SUPPRESSANT DRUGS AND THE RISK OF PRIMARY PULMONARY HYPERTENSION

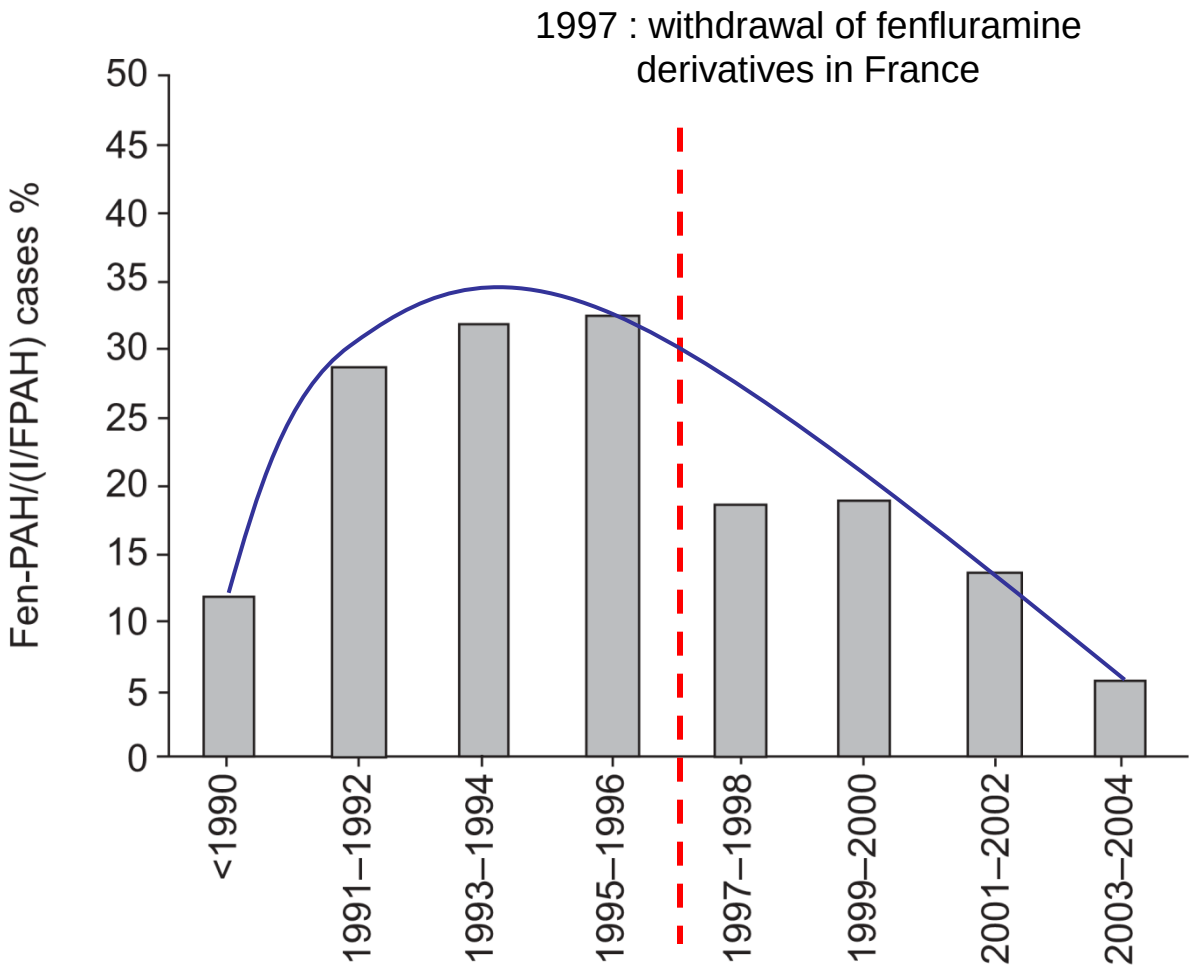
LUCIEN ABENHAIM, M.D., YOLA MORIDE, PH.D., FRANÇOIS BRENOT, M.D.,* STUART RICH, M.D., JACQUES BENICHOU, M.D., XAVIER KURZ, M.D., TIM HIGENBOTTAM, M.D., CELIA OAKLEY, M.D., EMIL WOUTERS, M.D., MICHEL AUBIER, M.D., GÉRALD SIMONNEAU, M.D., AND BERNARD BÉGAUD, M.D.,
FOR THE INTERNATIONAL PRIMARY PULMONARY HYPERTENSION STUDY GROUP†

VARIABLE	CASE PATIENTS (N=95)	CONTROLS (N=355)	ADJUSTED ODDS RATIO (95% CI)*
	no. (%)		
Definite use of appetite suppressants	30 (31.6)	26 (7.3)	6.3 (3.0–13.2)
Duration of use			
≤3 mo	7 (7.4)	12 (3.4)	1.8 (0.5–5.7)
>3 mo	18 (19.0)	5 (1.4)	23.1 (6.9–77.7)
Indeterminate	5 (5.3)	9 (2.5)	2.6 (0.5–12.6)
Products reported as used†			
Dexfenfluramine	18 (18.9)	22 (6.2)	—
Fenfluramine	6 (6.3)	4 (1.1)	—
Diethylpropion	3 (3.2)	2 (0.6)	—
Clobenzorex	3 (3.2)	6 (1.7)	—
Fenproporex	2 (2.1)	1 (0.3)	—
Phenmetrazine	2 (2.1)	0	—
Compounds	7 (7.4)	0	—



Fenfluramine-induced PAH

% of newly-diagnosed Fen-PAH compared to idiopathic or heritable PAH in the French PAH Network



Souza R, *Eur Respir J 2008*.

Benfluorex-induced PAH

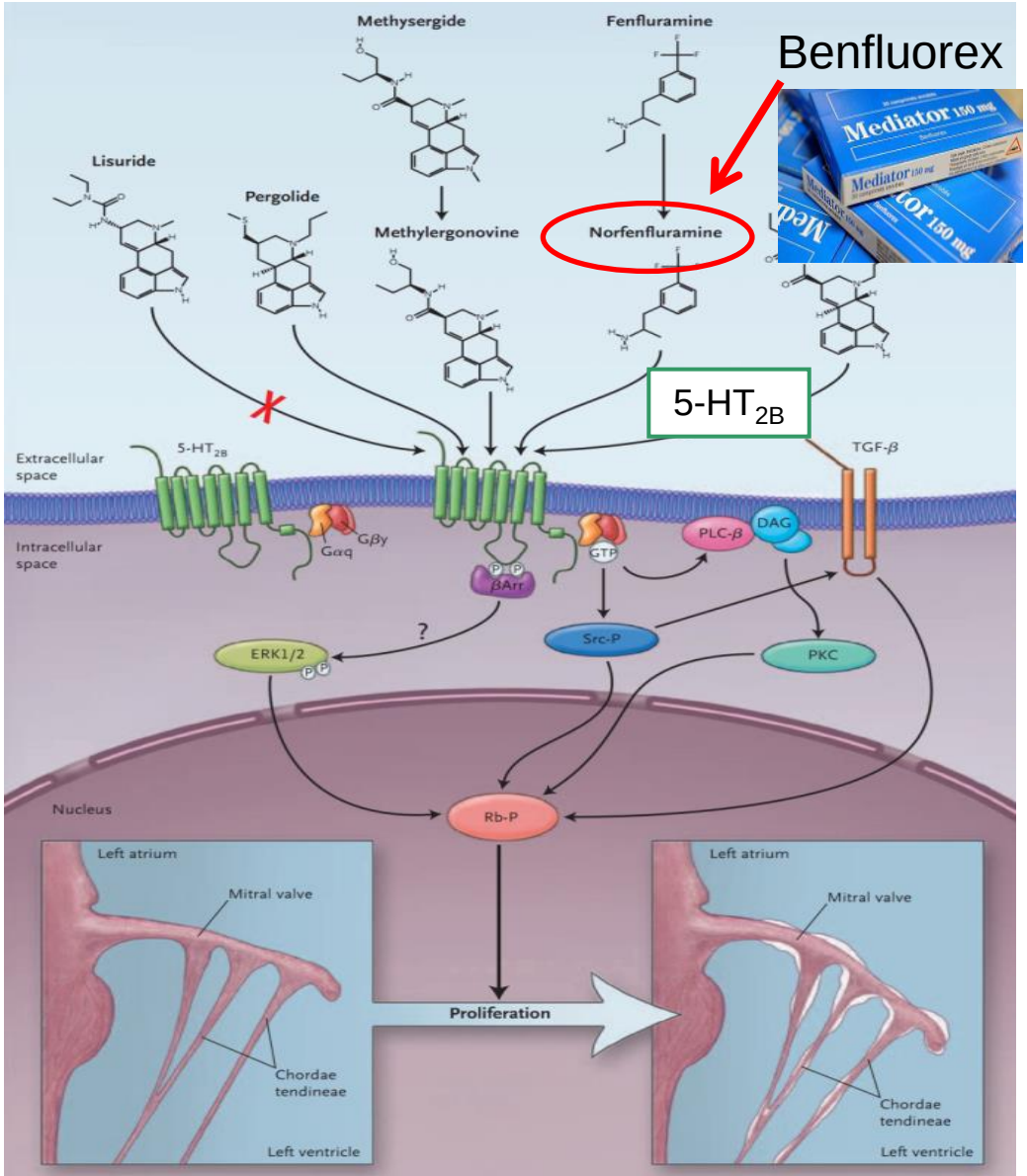
N Eng J Med 2007

FOCUS ON RESEARCH

Drugs and Valvular Heart Disease

Bryan L. Roth, M.D., Ph.D.

- Fenfluramine is metabolized into norfenfluramine.
- Norfenfluramine is an agonist of serotonin receptor 5-HT_{2B}
- Activation of 5-HT_{2B} receptor is a key step in initiating valvular heart disease and PAH



Pulmonary hypertension associated with benfluorex exposure

Laurent Savale[1,2,3], Marie-Camille Chaumais[1,3,4], Vincent Cottin[5], Emmanuel Bergot[6], Irène Frachon[7], Grégoire Prevot[8], Christophe Pison[9], Claire Dromer[10], Patrice Poubeau[11], Nicolas Lamblin[12], Gilbert Habib[13], Martine Reynaud-Gaubert[14], Arnaud Bourdin[15], Olivier Sanchez[16], Pascale Tubert-Bitter[17,18], Xavier Jaïs[1,2,3], David Montani[1,2,3], Olivier Sitbon[1,2,3], Gérald Simonneau[1,2,3] and Marc Humbert[1,2,3]

Eur Respir J 2012

Figure 1. Number of newly-diagnosed benfluorex-associated PH patients per year between 1999 and march 2011.

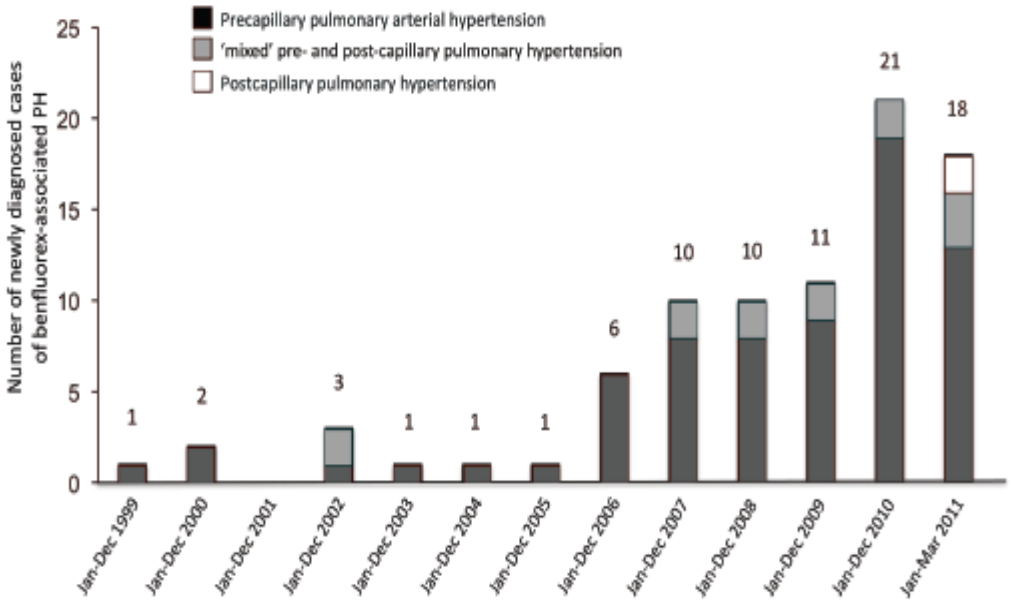
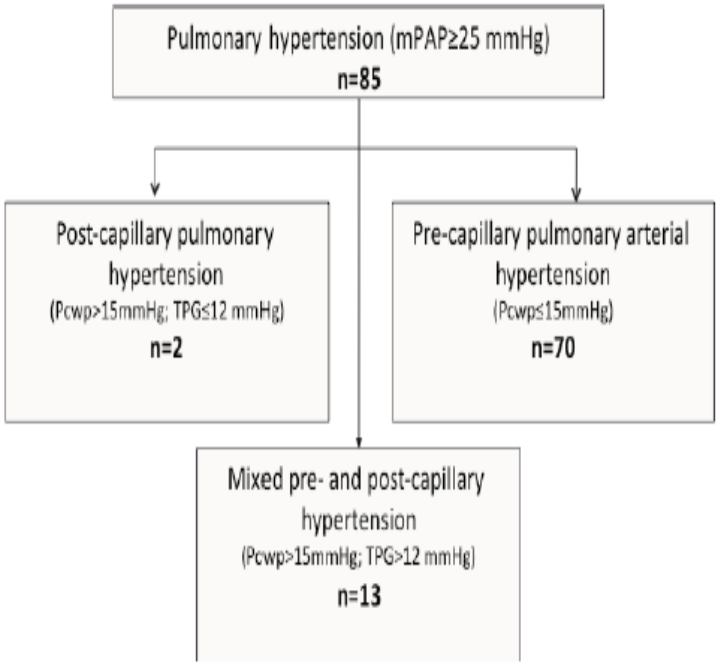


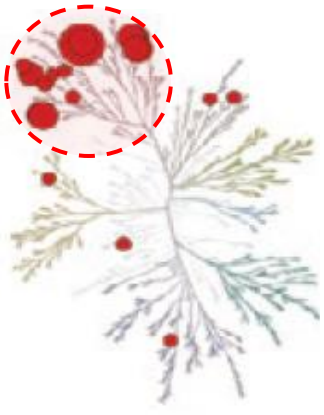
Figure 2. Type of benfluorex-associated pulmonary hypertension identified between 1999 and march 2011.



TYROSINE KINASE INHIBITORS

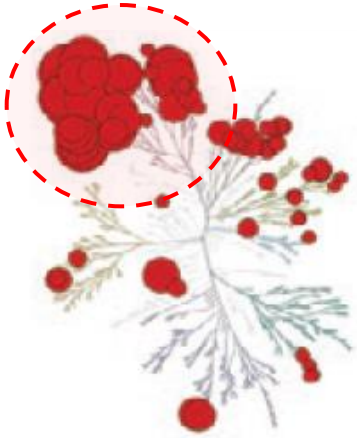
Tyrosine kinase inhibitors

Imatinib



PDGFR
c-kit
Bcr-Abl

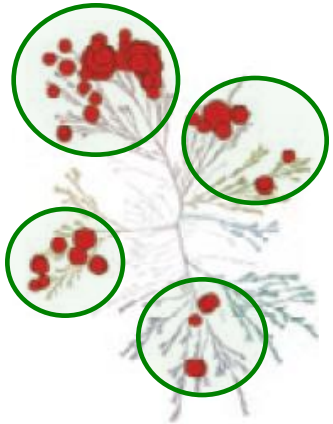
Dasatinib



PDGFR
c-kit
Bcr-Abl
Src

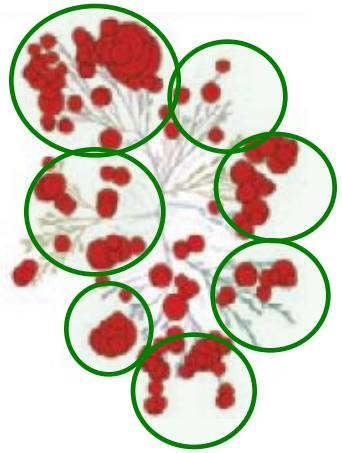
Multikinase inhibitors

Sorafenib



PDGFR
c-kit
VEGFR
Raf-1

Sunitinib



PDGFR
VEGFR
c-kit
FLT3
RET

Pulmonary Arterial Hypertension in Patients Treated by Dasatinib

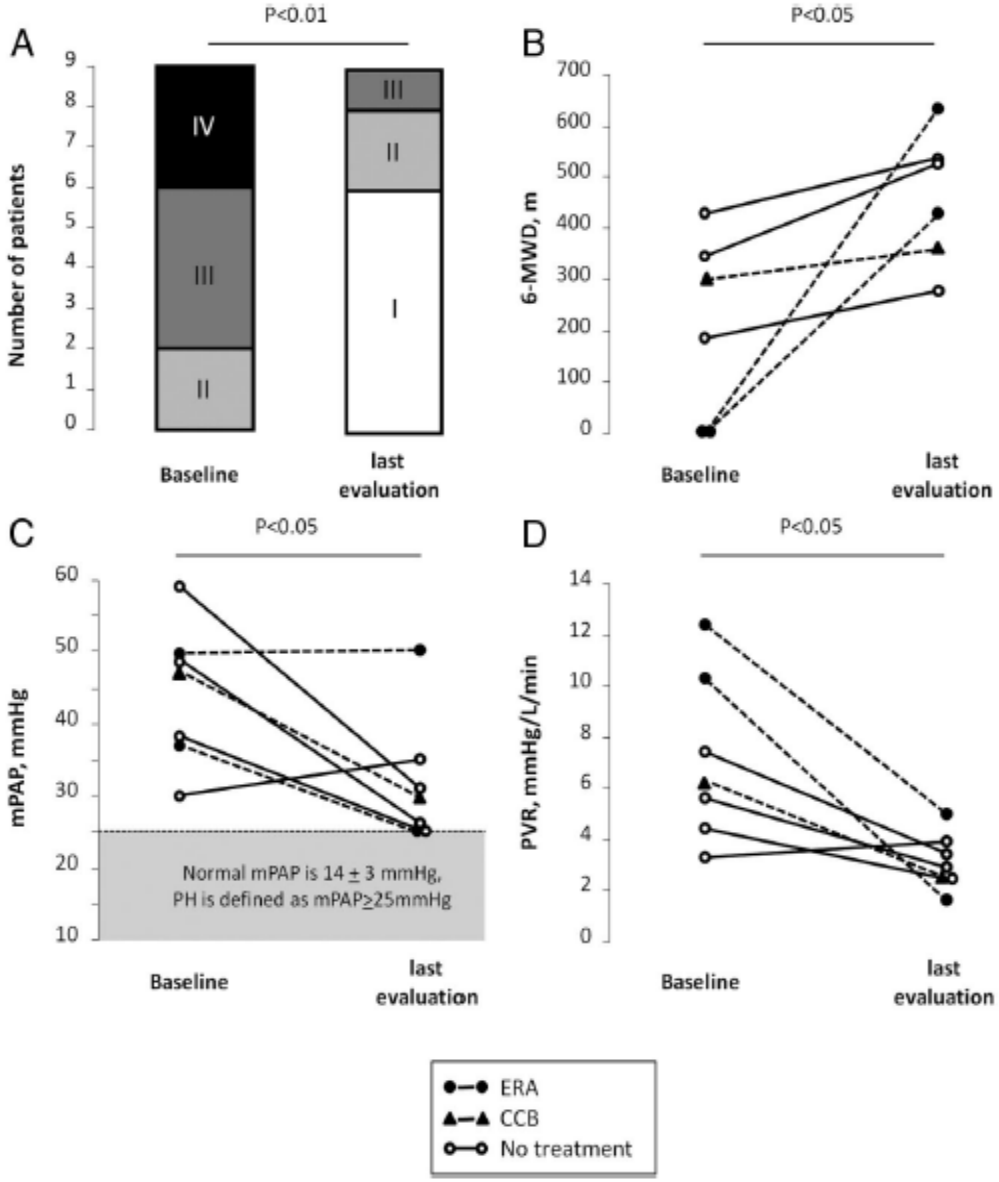
David Montani, MD, PhD; Emmanuel Bergot, MD; Sven Günther, MD; Laurent Savale, MD, PhD; Anne Bergeron, MD, PhD; Arnaud Bourdin, MD, PhD; Helene Bouvaist, MD; Matthieu Canuet, MD; Christophe Pison, MD, PhD; Margareth Macro, MD; Pascal Poubeau, MD; Barbara Girerd; Delphine Natali, MD; Christophe Guignabert, PhD; Frédéric Perros, PhD; Dermot S. O'Callaghan, MD; Xavier Jaïs, MD; Pascale Tubert-Bitter, PhD; Gerard Zalcman, MD, PhD; Olivier Sitbon, MD, PhD; Gérald Simonneau, MD; Marc Humbert, MD, PhD

Background—The French pulmonary hypertension (PH) registry allows the survey of epidemiological trends. Isolated cases of precapillary PH have been reported in patients who have chronic myelogenous leukemia treated with the tyrosine kinase inhibitor dasatinib.

Methods and Results—To describe incident cases of dasatinib-associated PH reported in the French PH registry. From the approval of dasatinib (November 2006) to September 30, 2010, 9 incident cases treated by dasatinib at the time of PH diagnosis were identified. At diagnosis, patients had moderate to severe precapillary PH with functional and hemodynamic impairment. No other incident PH cases were exposed to other tyrosine kinase inhibitors at the time of PH diagnosis. Clinical, functional, or hemodynamic improvements were observed within 4 months of dasatinib discontinuation in all but 1 patient. Three patients required PH treatment with endothelin receptor antagonist (n=2) or calcium channel blocker (n=1). After a median follow-up of 9 months (min-max 3–36), the majority of patients did not demonstrate complete clinical and hemodynamic recovery, and no patients reached a normal value of mean pulmonary artery pressure (≤20 mm Hg). Two patients (22%) died at follow-up (1 of unexplained sudden death and 1 of cardiac failure in the context of septicemia, respectively, 8 and 12 months after dasatinib withdrawal). The lowest estimate of incident PH occurring in patients exposed to dasatinib in France was 0.45%.

Conclusions—Dasatinib may induce severe precapillary PH, suggesting a direct and specific effect of dasatinib on pulmonary vessels. Improvement is usually observed after withdrawal of dasatinib. (***Circulation.* 2012;125:00-00.**)

Montani et al Circulation 2012



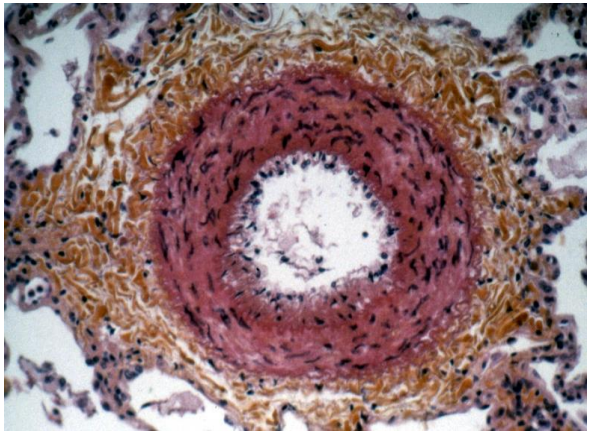
Montani et al Circulation 2012

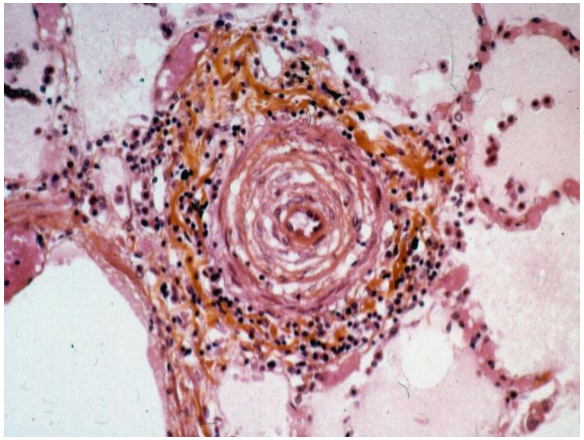
Updated Risks Factors for PAH

Definite	Possible
Aminorex	Cocaine
Fenfluramine	Phenylpropanolamine
Dexfenfluramine	St. John's Wort
Toxic rapeseed oil	Chemotherapeutic agents
Benfluorex **Serotonine Reuptake Inhibitors**	**Interferon type I** **Amphetamines-like**
Likely	**Unlikely**
Amphetamines	Oral contraceptives
Tryptophan	Estrogen
Methamphetamines	Cigarette smoking
Dasatinib	

1. Pulmonary Arterial Hypertension

- Idiopathic
- Heritable
- Drugs and toxins
- **Associated with other diseases**
  - Connective tissue diseases
    - Scleroderma
    - Other CTDs
  - HIV infection
  - Portal hypertension
  - Systemic-to-pulmonary shunts





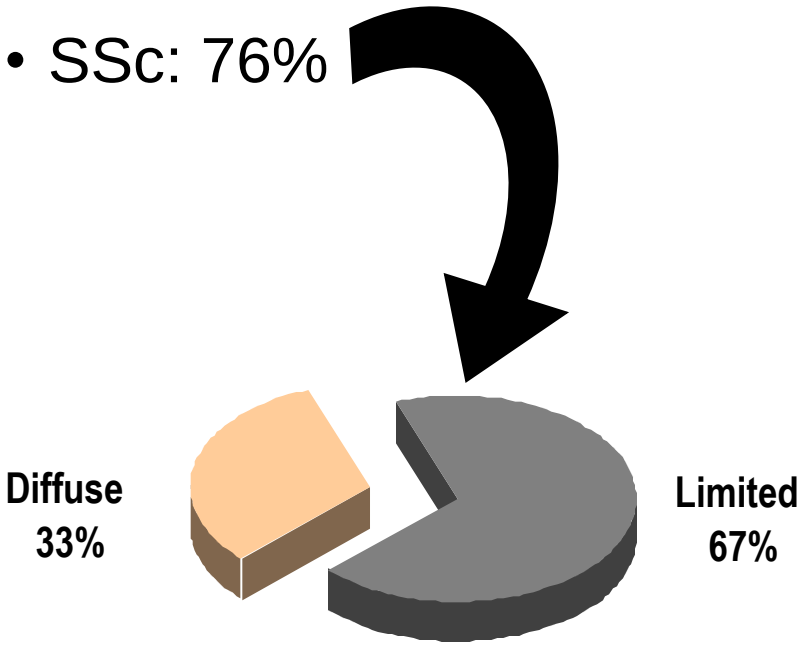
Pulmonary Arterial Hypertension in France

Results from a National Registry

Marc Humbert, Olivier Sitbon, Ari Chaouat, Michèle Bertocchi, Gilbert Habib, Virginie Gressin, Azzedine Yaici, Emmanuel Weitzenblum, Jean-François Cordier, François Chabot, Claire Dromer, Christophe Pison, Martine Reynaud-Gaubert, Alain Haloun, Marcel Laurent, Eric Hachulla, and Gérald Simonneau

SSc is the leading cause of CTD-associated PAH

- SLE: 15%
- SSc: 76%
- Other: ~ 10%
  - MCTD
  - Sjögren's syndrome
  - Polymyositis
  - (Rheumatoid arthritis)



Am J Respir Crit Care Med 2006;173:1023–30.

PAH associated with SSc: Prevalence

Reference	Methodology	Patients (N)	SSc profile	PAH definition	PAH prevalence
Ungerer 1983 USA	Prospective Monocentric 1973 to 1979	49	Proximal SSc and CREST	Mean PAP $\geq$ 20 mmHg and mean PCWP $\leq$ 12 mmHg (right heart catheterization)	16%
Murata 1992 Japan	Prospective Monocentric 1988 to 1991	71	SSc and MCTD	$V_{IT} \geq$ 2.5 m/s Doppler Echo	17%
Battle 1996 USA	Prospective Monocentric	34	**Diffuse or limited c SSc**	sPAP $\geq$ 30 mmHg Doppler Echo	35%
Koh 1996 Canada	Prospective Monocentric 1978 to 1994	344	**Diffuse or limited cutaneous SSc**	RHC: PAPm $\geq$ 25 and PCWP $\leq$ 12 mmHg , OR Echo: PsVD > 35 mmHg or RV dilatation, P or T insufficiency, or paradoxical septum motion	4.9%
MacGregor 2001 UK	Prospective Monocentric 1992 to 1997	152	**Diffuse or limited c SSc**	PAPs > 30 mmHg Doppler Echo	13%
Mukerjee 2003 UK	**Prospective Monocentric 1998 to 2002**	**722**	**Diffuse or limited c SSc**	**RHC: mPAP > 25 mmHg at rest or > 30 on exercise, PCWP < 15 mmHg**	**12 %**
Hachulla 2005 France	**Prospective Multicentric 2002-3**	**599**	**Diffuse or limited c SSc**	**RHC: mPAP > 25 mmHg at rest or > 30 on exercise, PCWP < 15 mmHg**	**7.85%**

Connective tissue diseases

Recommendations	Class[a]	Level[b]
In patients with PAH associated with CTD the same treatment algorithm as for patients with IPAH is recommended.	I	C
Resting echocardiography is recommended as a screening test in asymptomatic SSc patients with systemic sclerosis, followed by annual screening with echocardiography, DLCO and biomarkers.	I	C
RHC is recommended in all cases of suspected PAH associated with CTD.	I	C
Oral anticoagulation may be considered on an individual basis and in the presence of thrombophilic predisposition.	IIb	C

CTD = connective tissue disease; IPAH = idiopathic pulmonary arterial hypertension; PAH = pulmonary arterial hypertension; RHC = right heart catheterization.
[a]Class of recommendation. [b]Level of evidence.

Eur Respir J 2015; 46: 903-75; Eur Heart J 2016; 37:67-119

PAH associated with HIV: Prevalence

Ref.	Country	Study	HIV patients (n)	PAH-HIV patients (n)	Prevalence
Himelman *(1989)*	USA	Retrospective	1200	6	0.50%
Speich *(1991)*	Switzerland	Prospective	1200	6	0.50%
Opravil *(1997)*	Switzerland	Retrospective	3349	19	0.57%
Sitbon *(2007)*	France	Prospective	7648	35	0.46%

Himelman RB, *et al*. *Am J Cardiol* 1989; 64: 1396-9.
Speich R, *et al*. *Chest* 1991; 100: 1268-71.
Opravil M, *et al*. *Am J Respir Crit Care Med* 1997; 155: 990-5.
Sitbon O, *et al*. *Am J Respir Crit Care Med* 2008; 177: 108-13.

HIV infection

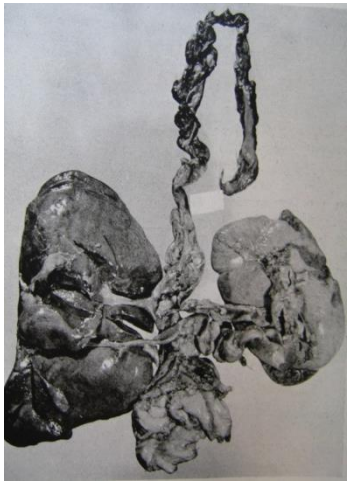
Recommendations	Class[a]	Level[b]
Echocardiographic screening in asymptomatic HIV patients to detect PH is not recommended.	III	C
In patients with PAH associated with HIV infection, the same treatment algorithm as for patients with PAH should be considered, taking into consideration comorbidities and drug–drug interactions.	IIa	C
Anticoagulation is not recommendend for lack of data on the efficacy to risk ratio.	III	C

Eur Respir J 2015; 46: 903-75; Eur Heart J 2016; 37:67-119

Portopulmonary Hypertension (PoPH)

- First described in 1951 by Mantz and Craige

  "*Portal thrombosis with portocaval shunt an resultant cor pulmonale*"



- Portal hypertension rather than hepatic disorder by itself is the main determining risk factor for developing portopulmonary hypertension
  - Po-PH is independent of cause and severity of liver disease
  - Extrahepatic portal hypertension in 10 % of cases

Prevalence of portopulmonary hypertension

- Patients with cirrhosis
  - Retrospective autopsy study (17 901 patients)[1]: 0.73% in cirrhotics
  - Clinical series of 2,459 patients with biopsy proven cirrhosis[1]: 0.61%
- Patients with portal hypertension
  - Prospective hemodynamic study in 507 consecutive patients with cirrhosis[2]: 2%
- Liver transplant candidates
  - 3 hemodynamic studies in patients undergoing OLT[3-5]: 3.5% to 6%

1. Mc Donnell *et al* - *Am Rev Resp Dis* - 1983

2. Hadengue *et al* - *Gastroenterology* - 1991

3. Castro *et al* - *Mayo Clin Proc* - 1996

4. Tamara *et al* - *Anaesth Analg* - 1996

5. Colle I, *et al*. *Hepatology* - 2003

Portopulmonary Hypertension

Recommendations	Class[a]	Level[b]
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
It is recommended that patients affected by PAH associated with portal hypertension are referred to centres with expertise in managing both conditions.	I	C
It is recommended that the treatment algorithm for patients with other forms of PAH is applied to patients with PAH associated with portal hypertension taking into account the severity of liver disease.	I	C
Anticoagulation is not recommended in patients with pulmonary hypertension associated with portal hypertension.	III	C
Liver transplantation may be considered in selected patients responding well to PAH therapy.	IIb	C
Liver transplantation is contraindicated in patients with severe and uncontrolled PAH.	III	C

Eur Respir J 2015; 46: 903-75; Eur Heart J 2016; 37:67-119

Congenital heart diseases

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

Eur Respir J 2015; 46: 903-75; Eur Heart J 2016; 37:67-119

Congenital heart diseases

Recommendations	Class[a]	Level[b]
Bosentan is recommended in WHO-FC III patients with Eisenmenger's syndrome.	I	B
Other ERAs, PDE-5i, and prostanoids should be considered in patients with Eisenmenger's syndrome.	IIa	C
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 oxygen saturation and reduces symptoms.	IIa	C
If symptoms of hyperviscosity are present, phlebotomy with isovolumic replacement should be considered usually when the haematocrit is >65%.	IIa	C
The use of supplemental iron treatment may be considered in patients with low ferritin plasma levels.	IIb	C
Combination drug therapy may be considered in patients with Eisenmenger's syndrome.	IIb	C
The use of CCBs is not recommended in patients with Eisenmenger's syndrome.	III	C

Eur Respir J 2015; 46: 903-75; Eur Heart J 2016; 37:67-119

CLASSIFICATION OF PH

ESC/ERS GUIDELINES

2015

1. Pulmonary arterial hypertension

1.1 Idiopathic
1.2 Heritable
1.2.1 BM
1.2.2 O
1.3 Drugs
1.4 Assoc
1.4.1 C
1.4.2 H
1.4.3 P
1.4.4 C
1.4.5 Sc

1'. Pulmona
haemangion

1'.1 Idiop
1'.2 Herit
1'.2.1 E
1'.2.2 C
1'.3 Drug
1'.4 Assoc
1'.4.1 C
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

ttern

her

al

ative

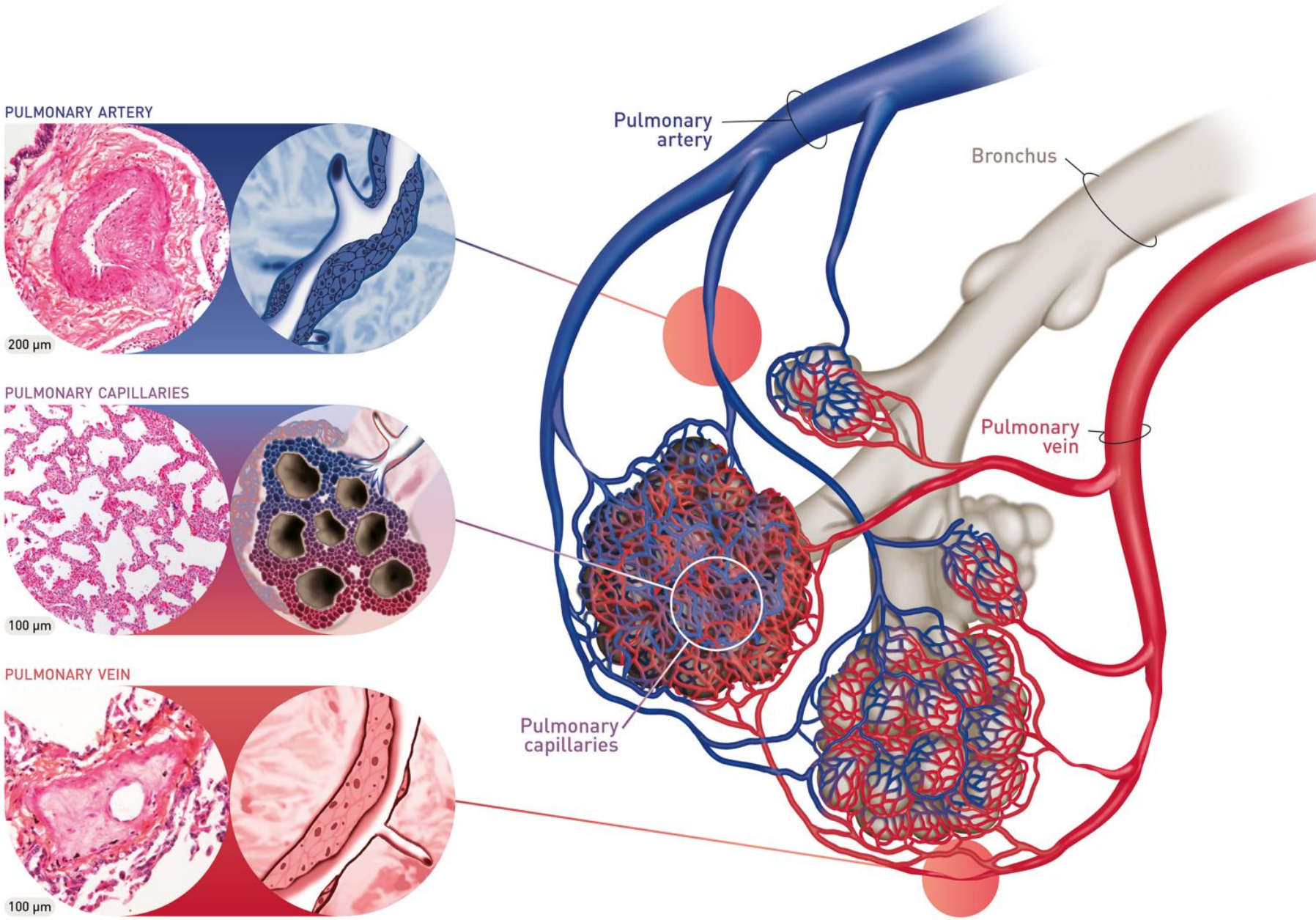
disorders, splenectomy.
5.2 Systemic disorders, sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis
5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
5.4 Others: pulmonary tumoral thrombotic microangiopathy, fibrosing mediastinitis, chronic renal failure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

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
  - 1'.4.2 HIV infection

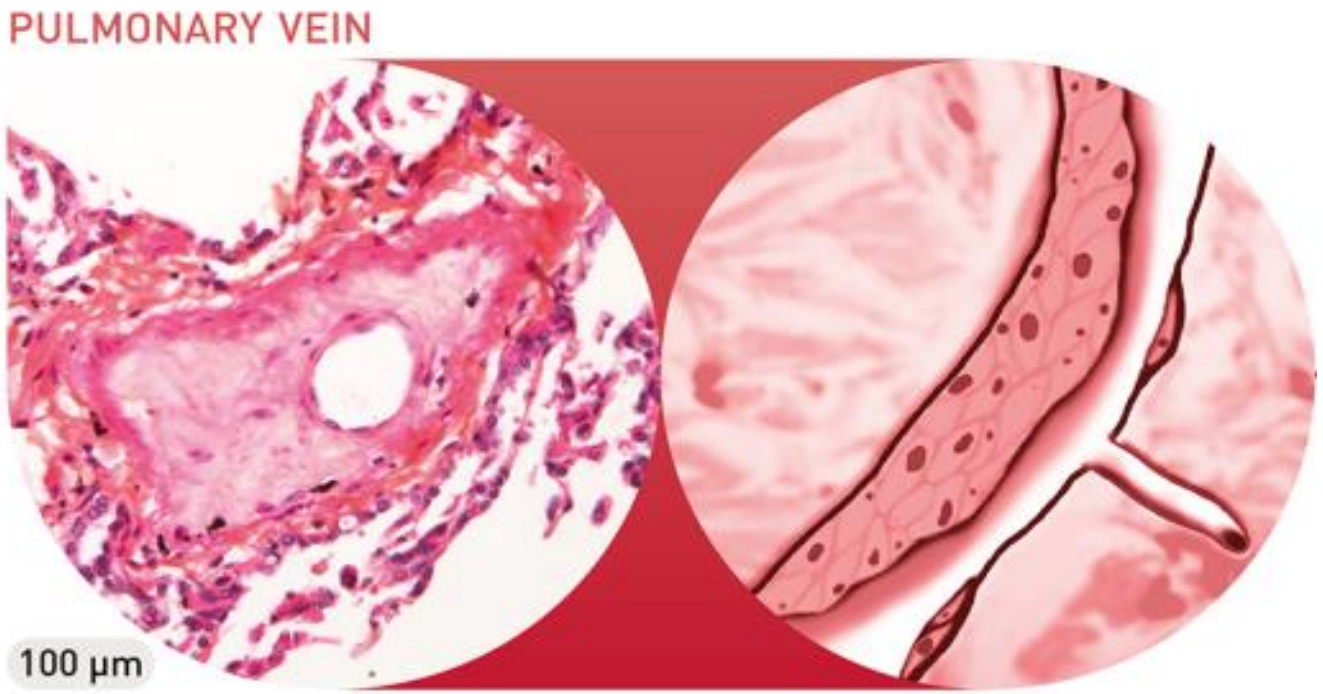
Eur Heart J 2015, Eur Respir J, 2015

Pathologic assesment



Montani D *et al. Eur Respir J 2016*

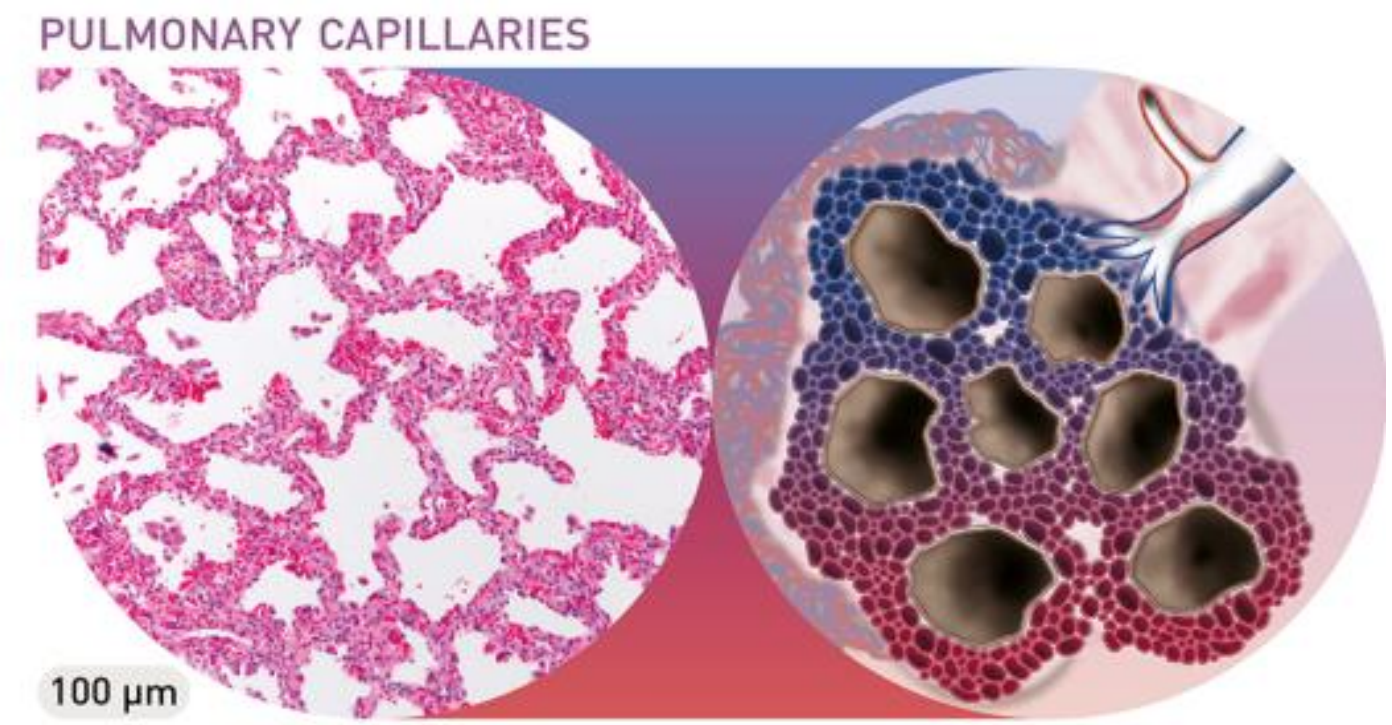
Pathologic assesment



Occlusive intimal fibrosis of septal veins and small veins

Montani D *et al. Eur Respir J 2016*

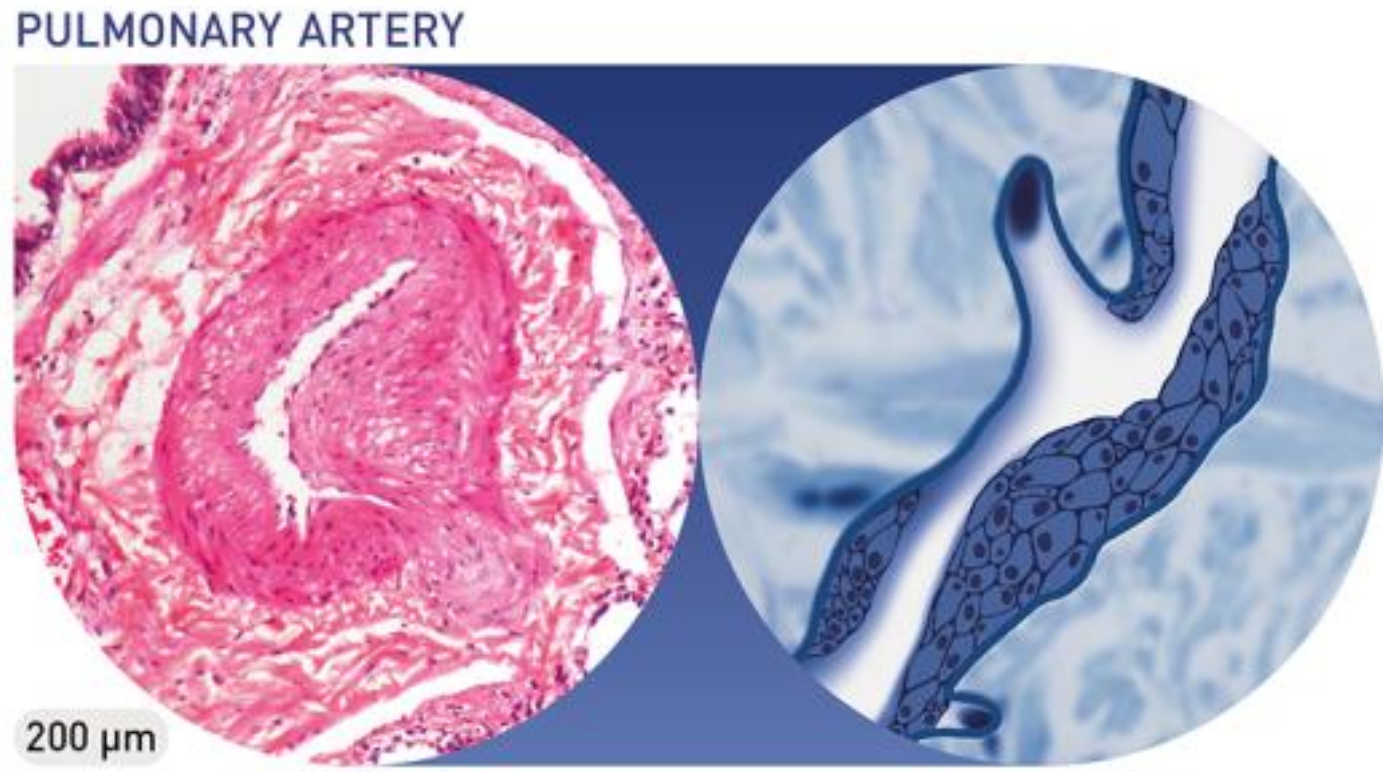
Pathologic assesment



Patchy capillary proliferation

Montani D *et al. Eur Respir J 2016*

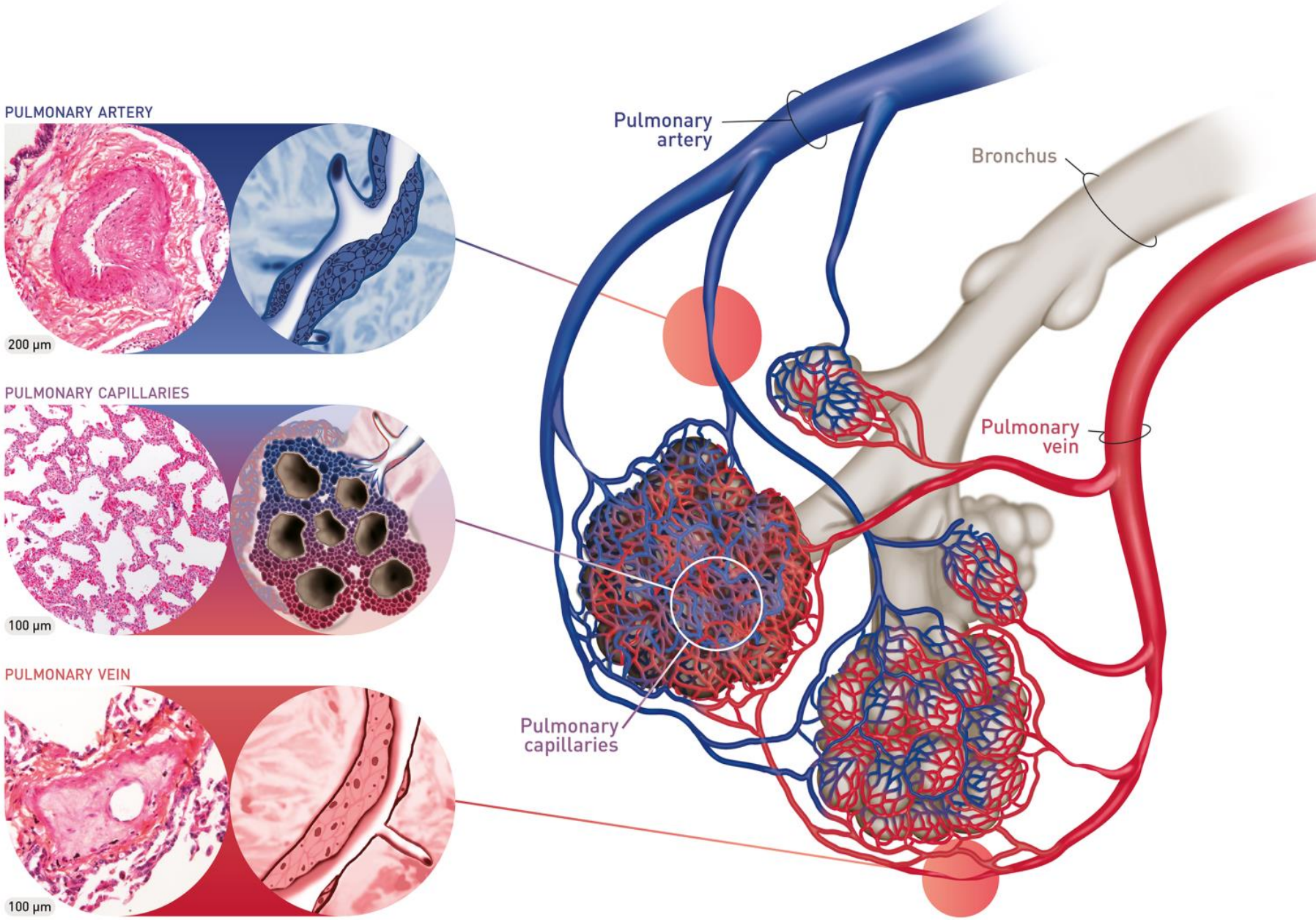
Pathologic assesment



Arterial remodeling without any plexiform lesions

Montani D *et al. Eur Respir J 2016*

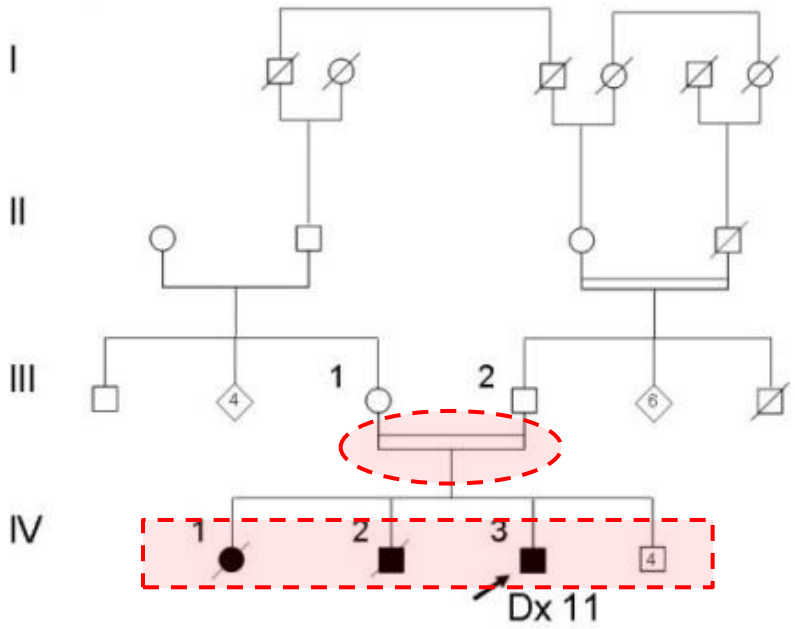
Pathologic assesment

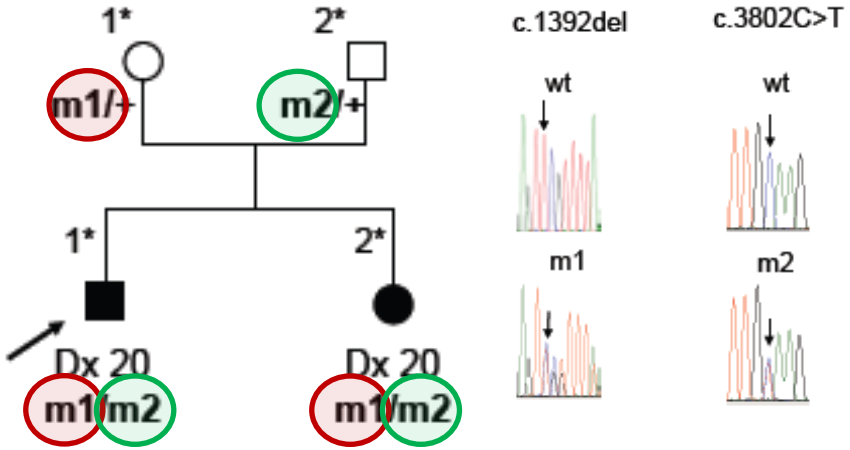


Montani D *et al. Eur Respir J 2016*

GENETIC IN PVOD

PVOD or PCH family





Autosomal recessive transmission

All heritable PVOD patients and 10-15% of sporadic form of PVOD had biallelic mutations in ***EIF2AK4*** **gene** (chr 15)

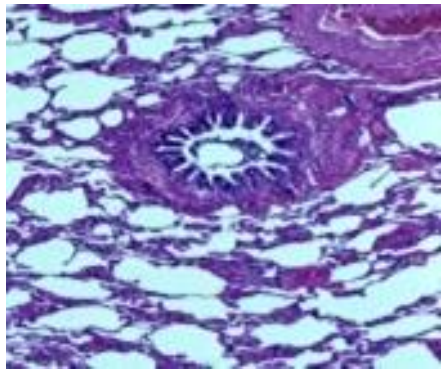
Eyries et al, *Nature Genetics* 2014

Pulmonary veno-occlusive disease

Recommendations	Class[a]	Level[b]
A combination of clinical findings, physical examination, bronchoscopy and radiological findings is recommended to diagnose PVOD/PCH.	I	C
Identification of a bi-allelic *EIF2AK4* mutation is recommended to confirm a diagnosis of heritable PVOD/PCH without histological confirmation.	I	B
Referral of eligible patients with PVOD/PCH to a transplant centre for evaluation is indicated as soon as the diagnosis is established.	I	C
Patients with PVOD/PCH should be managed only in centres with extensive experience in PH due to the risk of lung oedema after the initiation of PAH therapy.	IIa	C

Eur Respir J 2015; 46: 903-75; Eur Heart J 2016; 37:67-119

2. PH due to left heart diseases



Systolic dysfunction

Diastolic dysfunction

Valvular diseases

- Probably the most frequent group
- Lack of epidemiological data
- 2 categories
  - Passive post-capillary PH
    (no gradient between mPAP and PWP)
  - Mixed pre and post-capillary PH
    (gradient between mPAP and PWP >12 mmHg)

Haemodynamic definitions of pulmonary hypertension

Definition	Characteristics[a]	Clinical group(s)[b]
PH	PAPm ≥25 mmHg	All
Pre-capillary PH	PAPm ≥25 mmHg PAWP ≤15 mmHg	1. Pulmonary arterial hypertension 3. PH due to lung diseases 4. Chronic thromboembolic PH 5. PH with unclear and/or multifactorial mechanisms
Post-capillary PH	PAPm ≥25 mmHg PAWP >15 mmHg	2. PH due to left heart disease 5. PH with unclear and/or multifactorial mechanisms
Isolated post-capillary PH (Ipc-PH)	DPG <7 mmHg and/or PVR ≤3 WU[c]	
Combined post-capillary and pre-capillary PH (Cpc-PH)	DPG ≥7 mmHg and/or PVR >3 WU[c]	

CO = cardiac output; DPG = diastolic pressure gradient (diastolic PAP – mean PAWP); mPAP = mean pulmonary arterial pressure; PAWP = pulmonary arterial wedge pressure; PH = pulmonary hypertension; PVR = pulmonary vascular resistance; WU = Wood units.

[a]All values measured at rest; see also section 7.

[b]According to Table 4.

[c]Wood Units are preferred to dynes.s.cm^{-5}.

Eur Heart J 2015, Eur Respir J 2015

2. PH due to left heart diseases

Clinical presentation	Echocardiography	Other features
Age >65 years	Structural left heart abnormality • Disease of left heart valves • LA enlargement (>4.2 cm) • Bowing of the IAS to the right • LV dysfunction • Concentric LV hypertrophy and/or increased LV mass	ECG • LVH and/or LAH • AF/Afib • LBBB • Presence of Q waves
Symptoms of left heart failure	Doppler indices of increased filling pressures • Increased E/e' • >Type 2–3 mitral flow abnormality	Other imaging • Kerley B lines • Pleural effusion • Pulmonary oedema • LA enlargement
Features of metabolic syndrome	Absence of • RV dysfunction • Mid systolic notching of the PA flow • Pericardial effusion	
History of heart disease (past or current)		
Persistent atrial fibrillation		

AF = atrial flutter; Afib = atrial fibrillation; ECG = electrocardiogram; IAS = inter-atrial septum; LA = left atrium; LAH = left anterior hemiblock; LBBB = left bundle branch block; LV = left ventricle; LVH = left ventricular hypertrophy; PA = pulmonary artery; RV = right ventricle.

Eur Respir J 2015; 46: 903-75; Eur Heart J 2016; 37:67-119

2. PH due to left heart diseases

Recommendations	Class[a]	Level[b]
Optimization of the treatment of the underlying condition is recommended before considering assessment of PH-LHD (i.e. treating structural heart disease).	I	C
It is recommended to identify other causes of PH (i.e. COPD, SAS, PE, CTEPH) and to treat them when appropriate before considering assessment of PH-LHD.	I	C
It is recommended to perform invasive assessment of PH in patients on optimized volume status.	I	C
Patients with PH-LHD and a severe pre-capillary component as indicated by a high DPG and/or high PVR should be referred to an expert PH center for a complete diagnostic work-up and an individual treatment decision.	IIa	C
The importance and role of vasoreactivity testing is not established in PH-LHD, except in patients who are candidates for heart transplantation and/or LV assist device implantation.	III	C
The use of PAH approved therapies is not recommended in PH-LHD.	III	C

Eur Respir J 2015; 46: 903-75; Eur Heart J 2016; 37:67-119

Group 3: Chronic respiratory diseases / Hypoxia

Terminology	Haemodynamics (right heart catheterization)
COPD/IPF/CPFE without PH	PAPm <25 mmHg
COPD/IPF/CPFE with PH	PAPm ≥25 mmHg
COPD/IPF/CPFE with severe PH	PAPm >35 mmHg, or PAPm ≥25 mmHg in the presence of a low cardiac output (CI <2.5 L/min, not explained by other causes)

CI = cardiac index; COPD = chronic obstructive pulmonary disease; CPFE = combined pulmonary fibrosis and emphysema; IPF = idiopathic pulmonary fibrosis; PAP = pulmonary artery pressure; PAPm = mean pulmonary arterial pressure; PH = pulmonary hypertension.

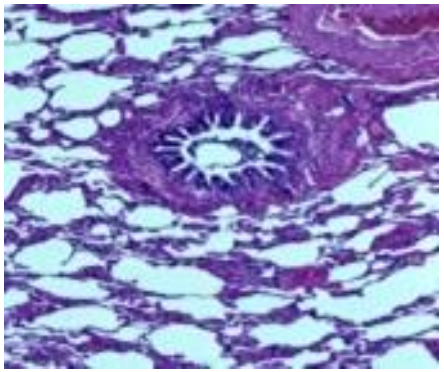
Eur Respir J 2015; 46: 903-75; Eur Heart J 2016; 37:67-119

Group 3: Chronic respiratory diseases / Hypoxia

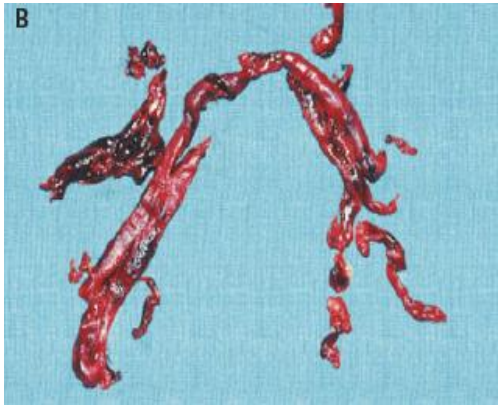
Recommendations	Class[a]	Level[b]
Echocardiography is recommended for the non-invasive diagnostic assessment of suspected PH in patients with lung disease.	I	C
In patients with echocardiographic signs of severe PH and/or severe right ventricular dysfunction referral to an expert center is recommended.[c]	I	C
The optimal treatment of the underlying lung disease including long-term O_2 therapy in patients with chronic hypoxaemia is recommended in patients with PH due to lung diseases.	I	C
Referral to PH expert center should be considered for patients with signs of severe PH/severe RV failure for individual-based treatment.	IIa	C
RHC is not recommended for suspected PH in patients with lung disease, unless therapeutic consequences are to be expected (e.g. lung transplantation, alternative diagnoses such as PAH or CTEPH, potential enrolment in a clinical trial).	III	C
The use of drugs approved for PAH is not recommended in patients with PH due to lung diseases.	III	C

Eur Respir J 2015; 46: 903-75; Eur Heart J 2016; 37:67-119

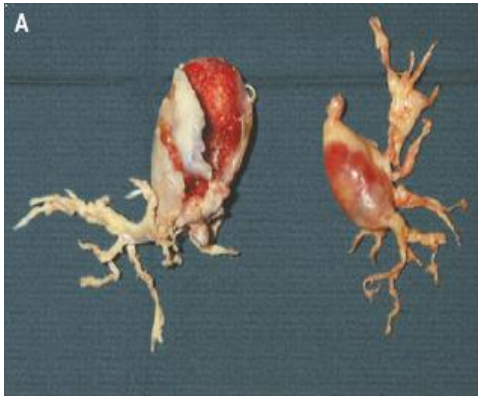
4. Chronic Thromboembolic PH (CTEPH)



Acute PE



Chronic PE

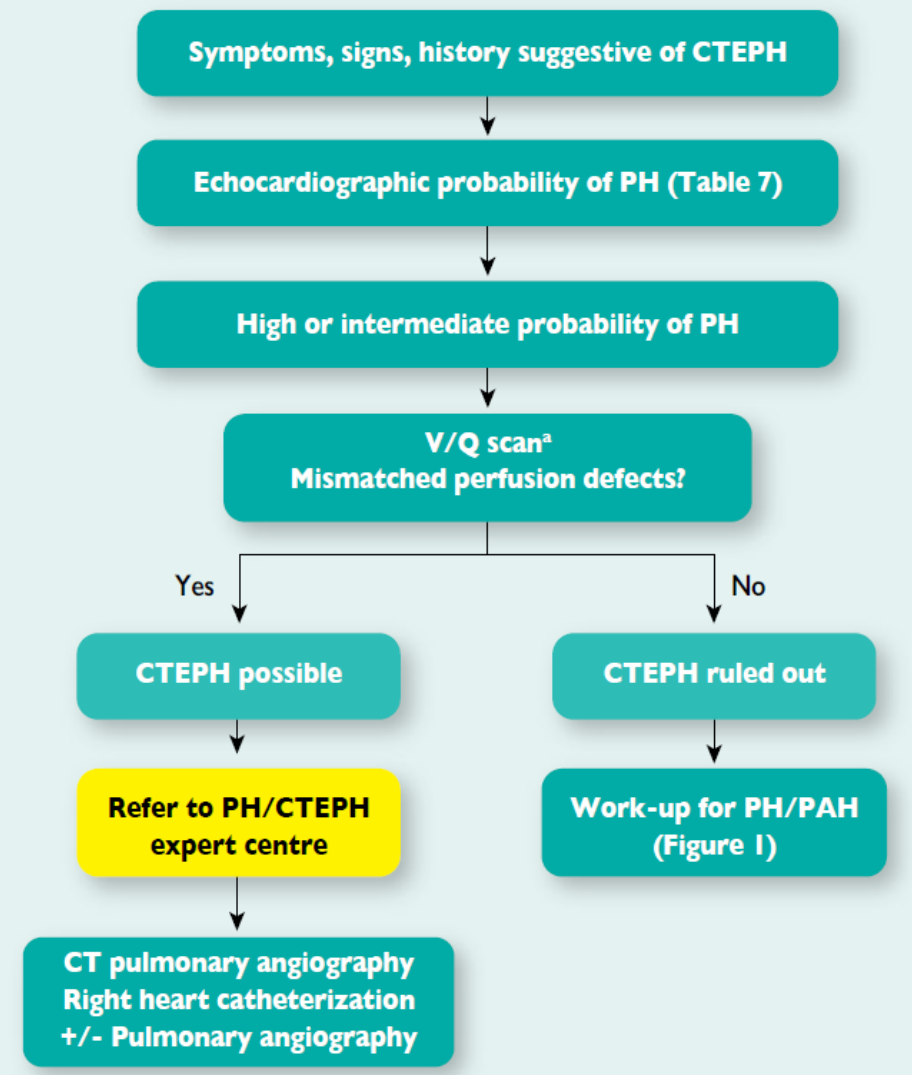


Represents a frequent form of PH:

- 0.1% to 3% after acute PE
- 500 to 2000 new cases / year in the US
- >250 new cases / year in the French reference center (GH Paris-Sud & CCML)
- >120 pulmonary endarterectomies/year (CCML)

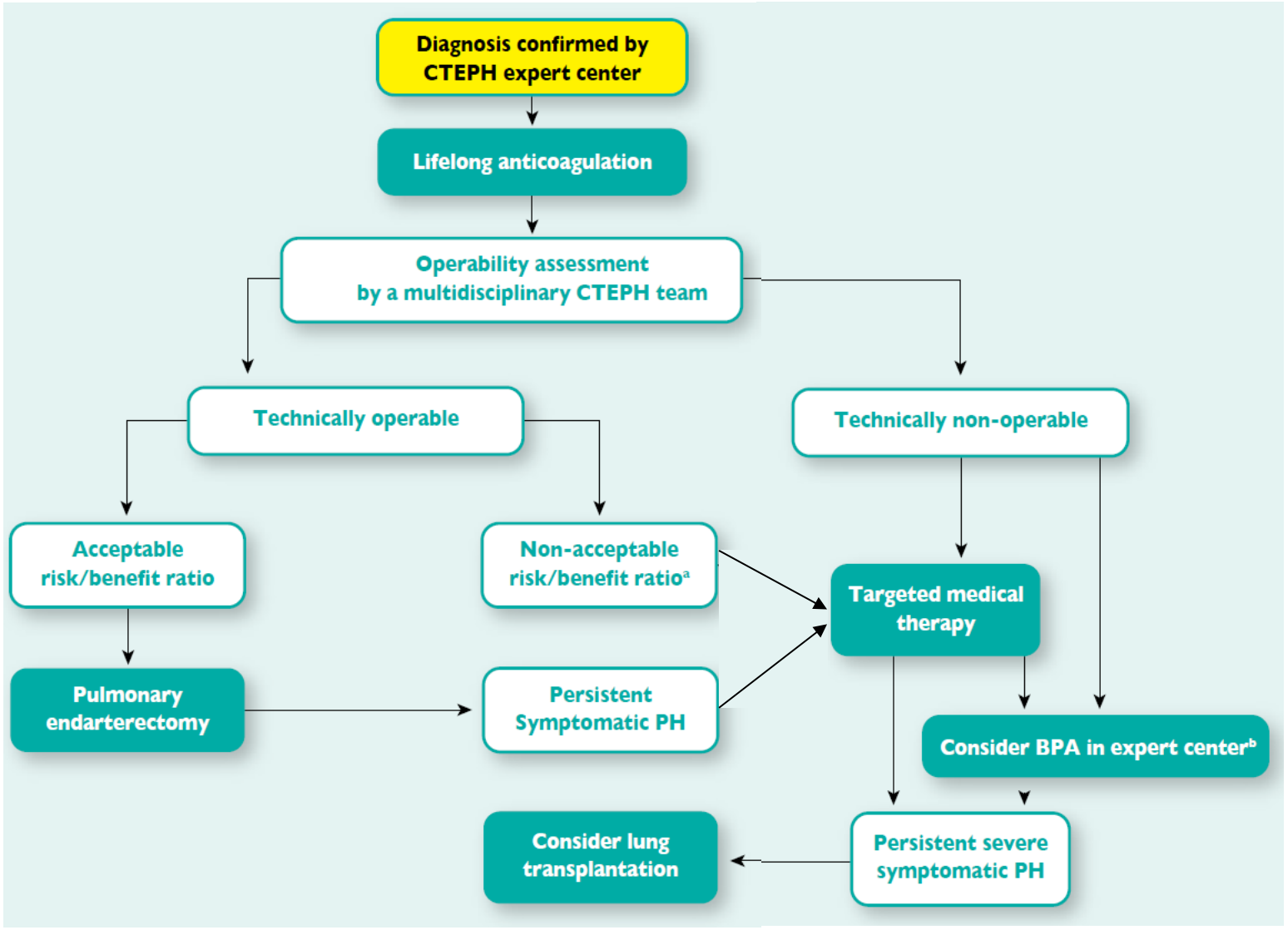
Fedullo PF, *et al*. *N Engl J Med* 2001.
Pengo, *et al*. *N Engl J Med* 2003.

4. Chronic Thromboembolic PH (CTEPH)



Eur Respir J 2015; 46: 903-75; Eur Heart J 2016; 37:67-119

4. Chronic Thromboembolic PH (CTEPH)



Eur Respir J 2015; 46: 903-75; Eur Heart J 2016; 37:67-119

4. Chronic Thromboembolic PH (CTEPH)

Recommendations	Class[a]	Level[b]
In PE survivors with exercise dyspnoea, CTEPH should be considered.	IIa	C
Life-long anticoagulation is recommended in all patients with CTEPH.	I	C
It is recommended that in all patients with CTEPH the assessment of operability and decisions regarding other treatment strategies be made by a multidisciplinary team of experts.	I	C
Surgical PEA in deep hypothermia circulatory arrest is recommended for patients with CTEPH.	I	C
Riociguat is recommended in symptomatic patients who have been classified as having persistent/recurrent CTEPH after surgical treatment, or inoperable CTEPH, by a CTEPH team including at least one experienced PEA surgeon.	I	B
Off-label use of drugs approved for PAH may be considered in symptomatic patients who have been classified as having persistent/ recurrent CTEPH after surgical treatment, or inoperable CTEPH by a CTEPH team including at least one experienced PEA surgeon.	IIb	B
Interventional BPA may be considered in patients who are technically non-operable, or carry an unfavourable risk-benefit ratio for PEA.	IIb	C
Screening for CTEPH in asymptomatic survivors of PE is currently not recommended.	III	C

Eur Respir J 2015; 46: 903-75; Eur Heart J 2016; 37:67-119

CONCLUSION

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'.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)[a]

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