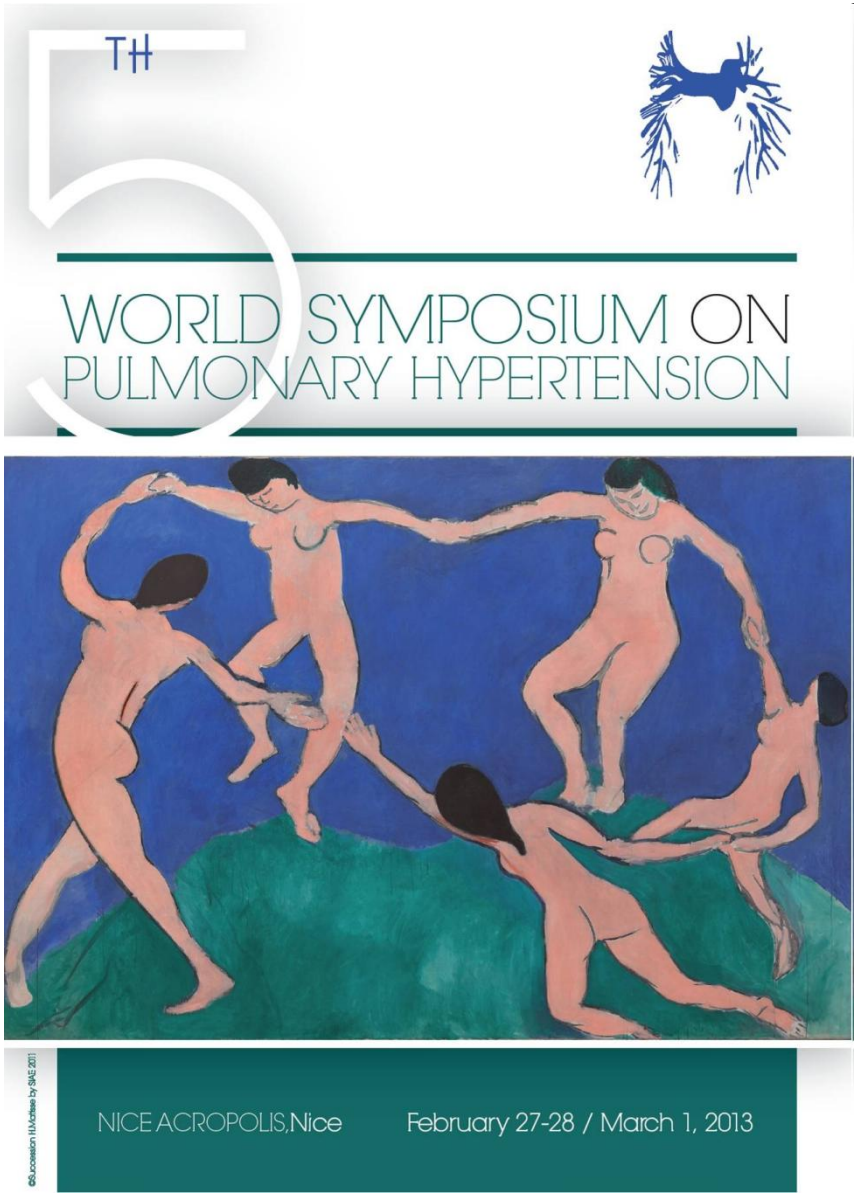
TASK FORCE 3:

Gerald Simonneau, Rogerio Souza



3 Definitions and Classifications and Particularities of Different PAH Subgroups

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10.	Michael Landzberg	Boston MA	USA	Mike.Landzberg@CARDIOTHEBOSTON.ORG	
11.	Roberto Machado	Chicago IL	USA	machador@uic.edu	
12.	Horst Olschewski	Graz	AUSTRIA	Horst.Olschewski@klinikum-graz.at; horst.olschewski@medunigraz.at	
13.	Ivan Robbins	Nashville TN	USA	ivan.robbins@Vanderbilt.Edu	

TASK FORCE 3

Gerald Simonneau Kremlin Bicetre (Fr) CH
Rogerio Souza Sao Paulo (Br) CoCH

- **A .Should we include rest PVR in the definition of PH?**
  how do we define and handle "borderline" PH?
  Should PVR & PAP on exercise be reintroduced in the definition?

- **B. PAH associated with CHD in adults**

- **C. Are there novel drugs and toxins inducing PAH?**

- **D.Which changes in group 5?**
  New groups identified or previous one to shift to another PH?
  group? Should we maintain sickle cell disease PAH in group 1?

- A .Should we include rest PVR in the definition of PH?
- how do we define and handle “borderline” PH?
- Should PVR & PAP on exercise be reintroduced in the definition?

A 1 .Should we include rest PVR in the definition of PH?

4th WS R. Barst et al (JACC 2004)

Definition of PAH : mean PAP ≥ 25 mmHg at rest

or > 30 mm Hg with exercise

PCWP ≤ 15 mmHg PVR > 3 WU (240 dyn.sec.cm^{-5})

5th WS D. Badesch et al (JACC 2009)

simplification of PH definition as follows:

- Exercise and PVR criteria should be eliminated
- PH is defined as resting m PAP ≥25 mmHg
- mPAP <20 mmHgshould be considered normal
- Further studies are needed to determine the natural history of patients with m PAP 21 to 24 mm Hg

- **A 1 .Should we include rest PVR in the definition of PH?**

Table 3 Haemodynamic definitions of pulmonary hypertension[a]

Definition	Characteristics	Clinical group(s)[b]
Pulmonary hypertension (PH)	Mean PAP ≥ 25 mmHg	All
Pre-capillary PH	Mean PAP ≥ 25 mmHg PWP ≤15 mmHg CO normal or reduced[f]	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	Mean PAP ≥ 25 mmHg PWP >15 mmHg CO normal or reduced[f]	2. PH due to left heart disease
Passive	TPG ≤12 mmHg	
Reactive (out of proportion)	TPG >12 mmHg	

[a]All values measured at rest.

ESC & ERS Guidelines 2009

A1. Should we include PVR at rest in the definition of PH

- The definition of PH should be a simple and pragmatic and should be changed only for very important reasons

- Due to the lack of new pertinent informations, it seems reasonable to keep the Dana Point definition of PH unchanged (PAPm ≥25 mmHg at rest)and to not include rest PVR in the definition of PH

  in agreement with the TF 6 (Marius Hoeper, Chair)

On Pulmonary Vascular Resistance: The Need For More Precise Definition

MAURICE McGREGOR, MD, and ALLAN SNIDERMAN, MD

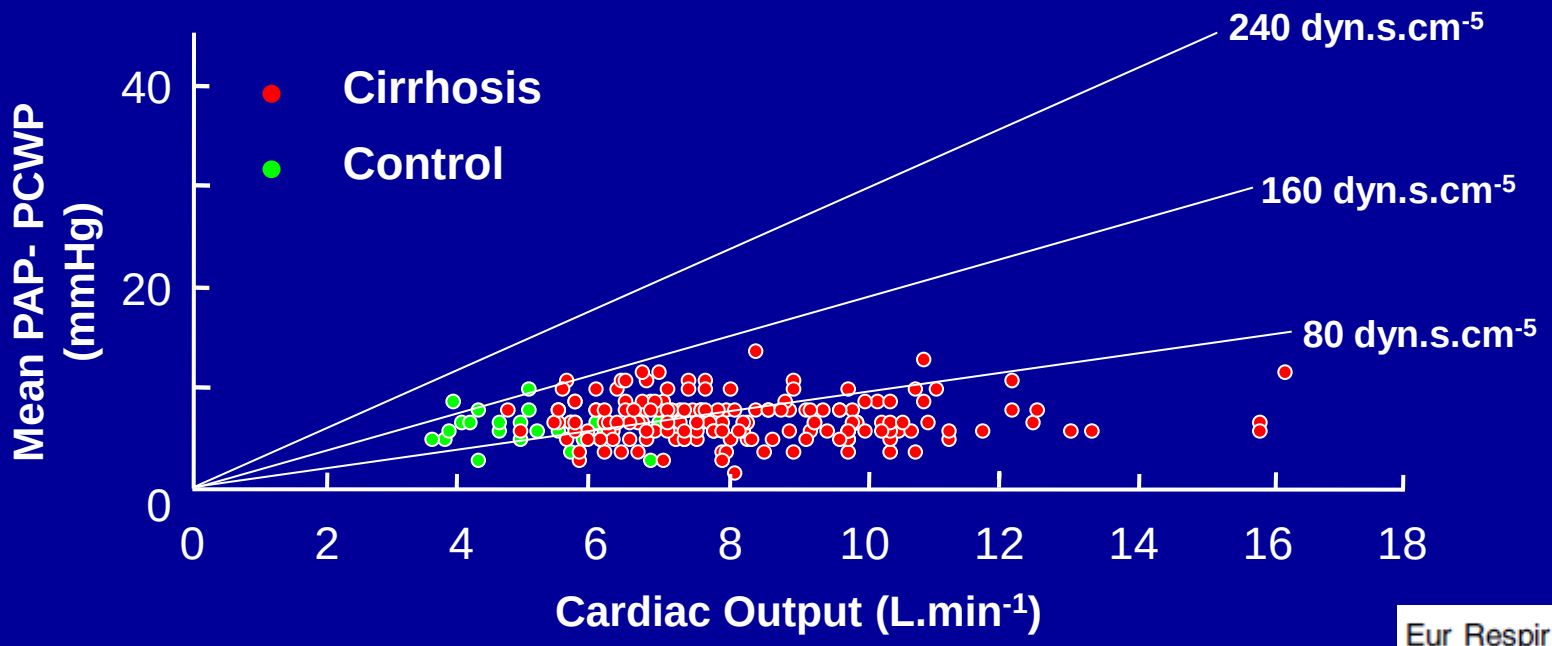
In summary, the ratio of PA pressure with or without subtraction of LA pressure, divided by flow, has traditionally been understood to indicate resistance. This is misleading because this ratio will change with changes in flow, without there being any change in the forces opposing flow.

January 1, 1985 THE AMERICAN JOURNAL OF CARDIOLOGY

Pulmonary haemodynamics in liver cirrhosis

- N = 178
- M/F = 110/66
- No ß-blocker
- PAPm < 25 mmHg

	Mean	SD	Range
RAP, mmHg	5.7	2.7	[0 – 15]
mPAP, mmHg	15.5	3.4	[6 – 24]
PCWP, mmHg	9.2	3.1	[2 – 17]
CO, L.min^{-1}	8.25	2.13	[4.45 – 16.37]
CI, L.min^{-1}.m^{-2}	4.64	1.11	[2.92 – 9.21]
PVR, dyn.s.cm^{-5}	65	28	[10 – 157]



Eur Respir J 2004;

A Hemodynamic Study of Pulmonary Hypertension in Sickle Cell Disease

Florence Parent, M.D., Dora Bachir, M.D., Jocelyn Inamo, M.D., François Lionnet, M.D., Françoise Driss, M.D., Gylna Loko, M.D., Anoosha Habibi, M.D., Soumiya Bennani, M.D., Laurent Savale, M.D., Serge Adnot, M.D., Bernard Maitre, M.D., Azzedine Yaïci, M.D., Leila Hajji, M.D., Dermot S. O'Callaghan, M.D., Pierre Clerson, M.D., Robert Girot, M.D., Frederic Galacteros, M.D., and Gerald Simonneau, M.D.

	Pre-capillary PAH	Post-capillary PH	No PH on RHC
No of Patients (Percentage)	11 (2.9%)	13 (3.3%)	72 (18.7%)
mPAP (mm Hg)	28±4	32±7	19±3
sPAP (mm Hg)	43±7	45±8	28±4
dPAP (mm Hg)	15±5	22±6	12±3
RAP (mm Hg)	5±2	13±5	7±2
PCWP (mm Hg)	10±3	21±5	11±3
CO (L/min)	8.2±1.6	9.1±2.1	8.4±2.1
PVR (dyn.s.cm^{-5})	178±55	104±26	72±26

New Engl J Med 2011

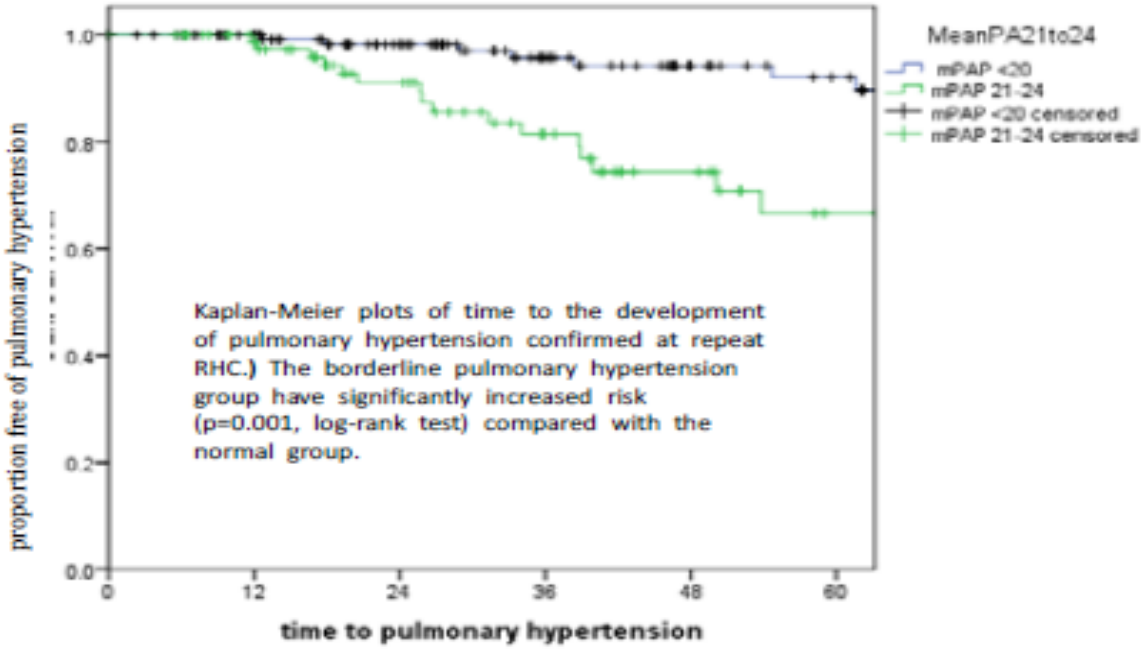
A2 how do we define and handle "borderline" PH?

- The upper limit of a normal PAPm is 20 mmHg.
- PH is defined as mean PAP≥ 25 mmHg
- For patients with a mean PAP between 21 and 24 mm Hg

  who not fulfill the criteria for manifest PH It has been proposed to use the term of **"borderline" PH**
- "borderline PH" is frequently observed in Group 2 and 3, however the clinical meaningful of this observation is unknown and has no therapeutic implications
- "Borderline PH" is also frequently observed in scleroderma patients screened for PH. A substantial number of these patients seem to develop manifest PAH in the follow-up. We recommend today to use the term of **"borderline" PH** only in scleroderma patients

Long-term Follow-up of Borderlin PH in Sleroderma

Royal Free cohort – natural history of borderline PH (mPAP 21-24 mm Hg at first RHC)



(months)		0	12	24	36	48	60
at risk	Normal	142	126	96	68	48	38
	Borderline	86	75	52	35	23	13

Valerio Schreiber, Denton, Coghlan, submitted 2012

A3Should PVR & PAP on exercise be reintroduced in the definition?

- Due to the lack of robust data allowing to define adequately an abnormal response of pulmonary circulation at exercise, PAP and or PVR criteria to define PH on exercise should not be re-introduced at the present time in the definition of PH
- Further studies are needed to define which values of PAPm and PVR on execise could be considered as abnormal predicting subsequently the occurrence of an overt PH and leading to some therapeutic implications.
- A first step should be to define a standardized protocol of exercise for evaluation of hemodynamic on exercise

- **C. Are there novel drugs and toxins inducing PAH?**

-Benfluorex
-Dasatinib
-Interferon
-Methylphenidate

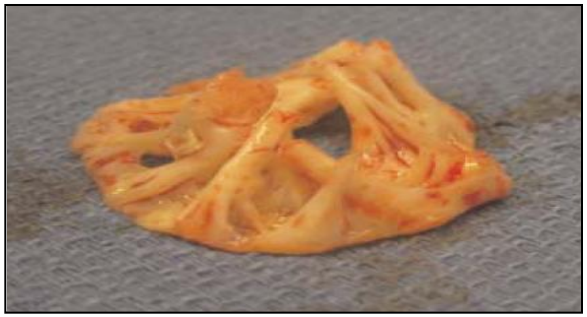
Fenfluramine-like cardiovascular side-effects of benfluorex

ERJ 2009

K. Boutet*, I. Frachon#, Y. Jobic#, C. Gut-Gobert#, C. Leroyer#, D. Carlhant-Kowalski#, O. Sitbon*, G. Simonneau* and M. Humbert*

	Case 1	Case 2	Case 3	Case 4	Case 5
mPAP mmHg	51	40	60	45	28
CI $L \cdot min^{-1} \cdot m^{-2}$	1.37	2.3	3.2	3.3	2.42
Pulmonary artery wedged pressure	9	3	12	12	12
Acute vasoreactivity#	Neg.	Pos.	Neg.	Neg.	NA
6MWD m	265	363	295	132+	218

1 case of valvular heart disease



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 Apr 20. [Epub ahead of print]

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

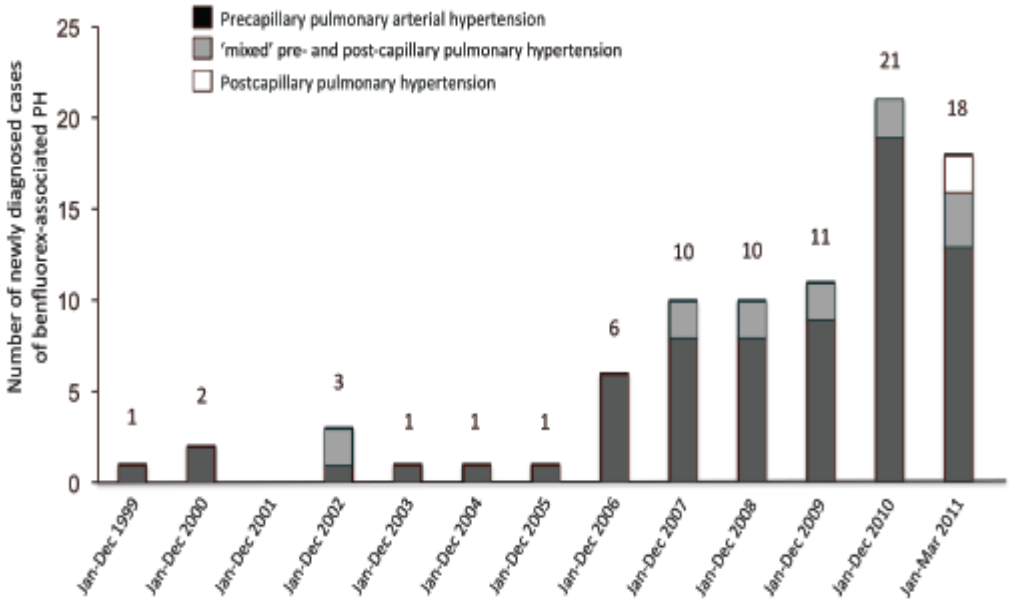
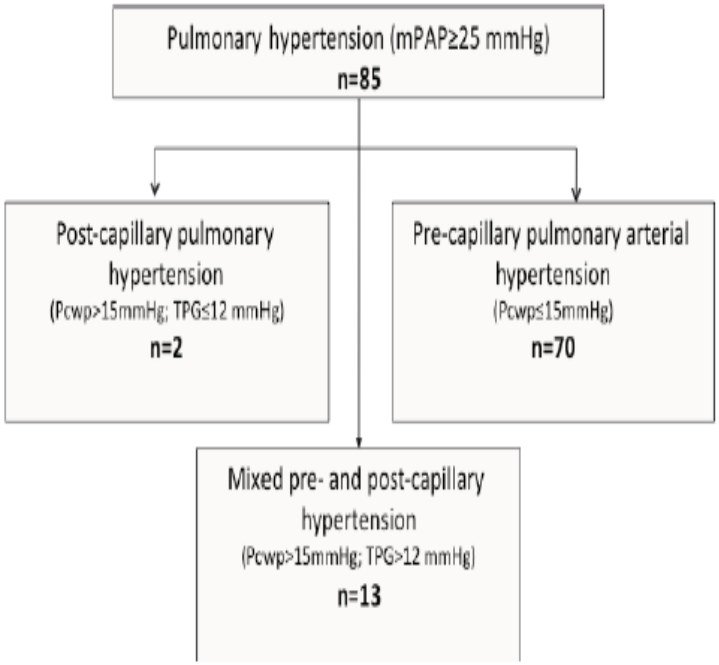


Figure 2. Type of benfluorex-associated pulmonary hypertension identified between 1999 and march 2011.



	Benfluorex	Dexfenfluramine & Fenfluramine	P*
Subjects, n	70	109	
Age, years (median [IQR])	61 [51-71]	52 [44-59]	<0.0001
Gender (Female:Male) ratio	3.1	19	<0.0001
Body mass index, kg/m^2 (median [IQR])	30 (26-34)	27 (24-33)	<0.05
Delay between first anorexigen exposure and PAH diagnosis, months (median [IQR])	108 [60-144]	78 [43-140]	NS
Anorexigen exposure duration, months (median [IQR])	30 [12-70]	6 [3-12]	<0.001
NYHA-FC, n (%)			
II	12 (17%)	15 (14%)	
III	52 (74%)	71 (65%)	NS
IV	6 (9%)	23 (21%)	
6MWD, m (median [IQR])	319 [209-372]	250 [121-355]	<0.01
Hemodynamics (mean±SD):			
RAP, mmHg	9±5	11±6	<0.05
mPAP, mmHg	47±11	60±12	<0.0001
Pcwp, mmHg	10±4	9±3	NS
Cardiac index, L/min/m^2	2.4±0.6	2.2±0.6	NS
PVRi, mmHg /L/min/m^2	17±8	26±11	<0.0001

L Savale et al Eur Respir J. 2012 Apr 20. [Epub ahead of print]

TYROSINE KINASE INHIBITORS

Tyrosine kinase inhibitors

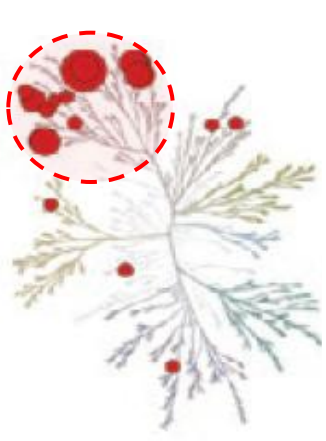
Multikinase inhibitors

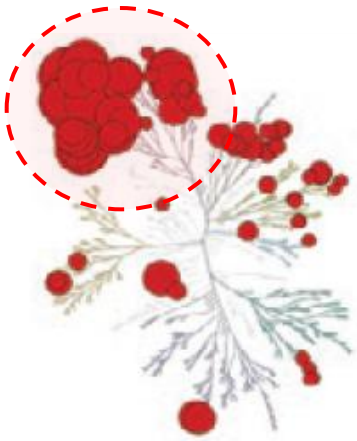
Imatinib

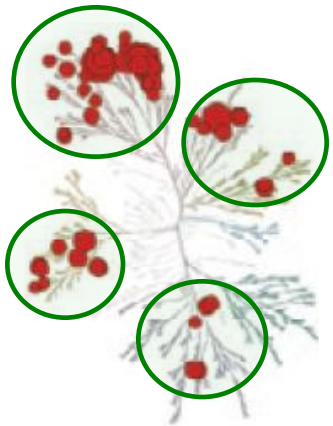
Dasatinib

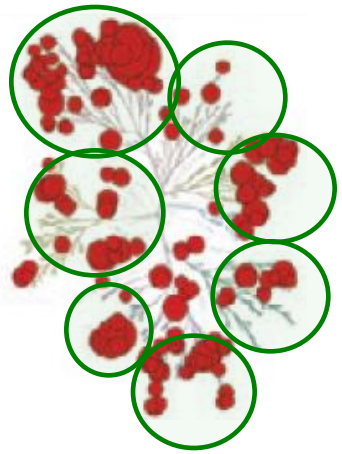
Sorafenib

Sunitinib









PDGFR
c-kit
Bcr-Abl

PDGFR
c-kit
Bcr-Abl
Src

PDGFR
c-kit
VEGFR
Raf-1

PDGFR
VEGFR
c-kit
FLT3
RET

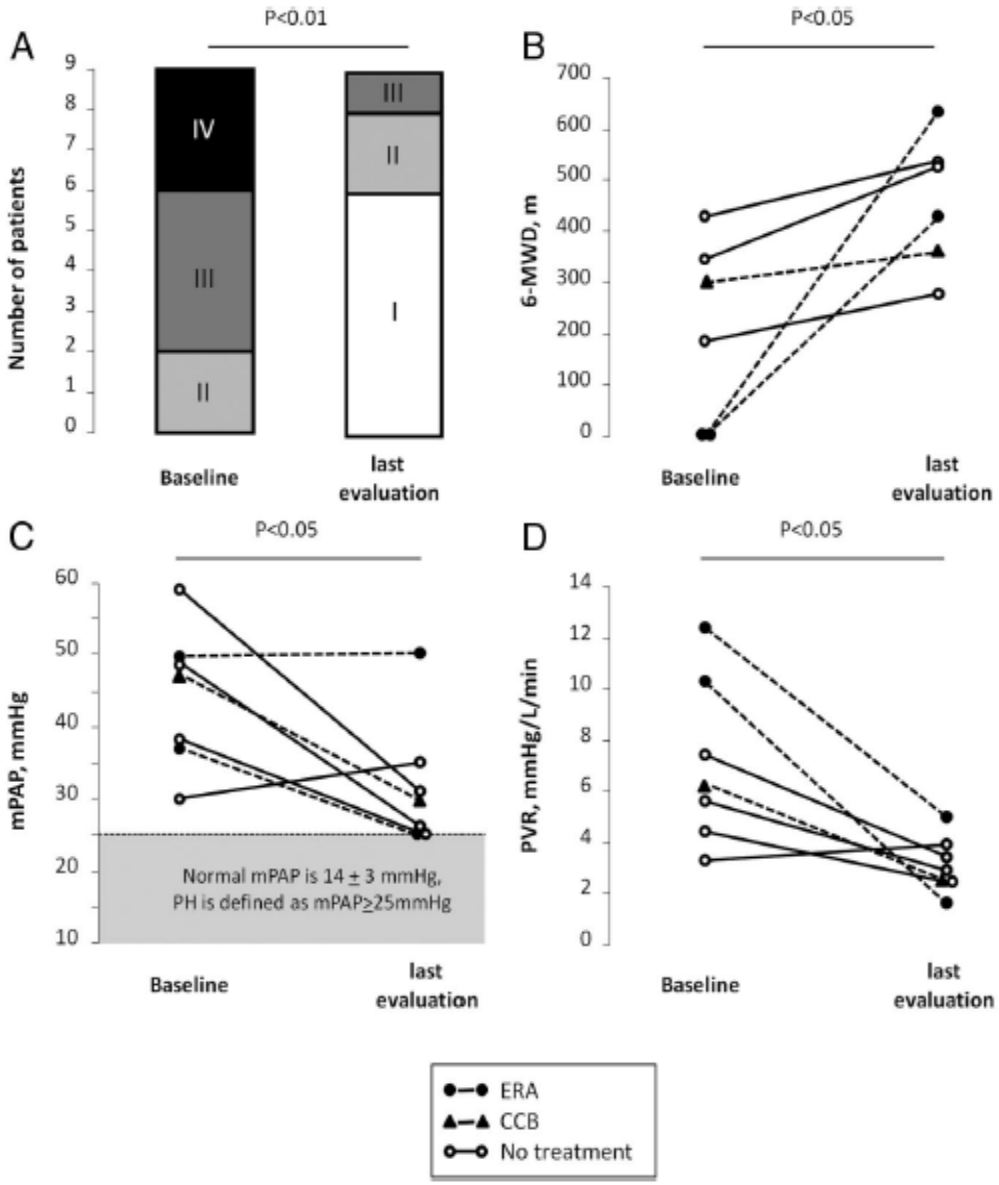
Pulmonary Arterial Hypertension in Patients Treated by Dasatinib

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.**)



D Montani et al Circulation 2012

Pharmacology & Therapeutics 135 (2012) 44–53

Contents lists available at SciVerse ScienceDirect

Pharmacology & Therapeutics

journal homepage: www.elsevier.com/locate/pharmthera

Associate editor: M.G. Belvisi

Pharmacology and therapeutic potential of interferons ☆

Peter M. George [a,*], Rekha Badiger [a], William Alazawi [b], Graham R. Foster [b], Jane A. Mitchell [a]

[a] Cardiothoracic Pharmacology, National Heart and Lung Institute (NHLI), Imperial College, Dovehouse Street, London SW3 6LY, UK
[b] The Liver Unit, The Blizard Institute, Barts & The London School of Medicine, UK

10. Pulmonary hypertension and the link with IFN signalling

we have found that as with type II IFN-γ, type I IFN-α and IFN-β activate pulmonary vascular cells to release ET-1 and that both pegylated and non-pegylated forms of IFN-α activate human pulmonary artery smooth muscle cells (Badiger et al., 2011). We have also demonstrated that direct stimulation of pulmonary artery smooth muscle cells with virus and viral toll like receptor ligands results in activation with IP10 and ET-1 release (Badiger, De Sousa, Wort, Paul-Clark, & Mitchell, 2008; Badiger et al., 2008). This all adds more weight to the growing body of evidence that viruses and/or IFN may be implicated in the development of pulmonary hypertension.

Interferon and Pulmonary Hypertension

Sildenafil therapy for **interferon**-β-1a-induced **pulmonary** arterial **hypertension**: a case report.
Caravita S, Secchi MB, Wu SC, Pierini S, Paggi A.
Cardiology. 2011;120(4):187-9. doi: 10.1159/000335064. Epub 2012 Jan 20

Irreversible **pulmonary hypertension** associated with the use of **interferon** alpha for chronic hepatitis C.
Dhillon S, Kaker A, Dosanjh A, Japra D, Vanthiel DH.
Dig Dis Sci. 2010 Jun;55(6):1785-90. Epub 2010 Apr 22

Today about 10 cases reported in the French registry

Methylphenydate and Pulmonary Hypertension

- Methylphenydate is a drug used in children against hyperactivity disorder
- Inhibiting reuptake of Dopamine and Norepinephrine
- Amphetamine- like effects is also suspected

Pulmonary Arterial Hypertension in an adolescent treated with Methylphenidate Karaman LG et al J Child Adolesc Psychopharmacol. 2010 Jun;20(3):229-31

- D.Which changes in group 5?

  -Should we maintain sickle cell disease PAH in group 1?

  - New subgroups groups identified or previous one to shift to another PH group?

Clinical Classification of PH

Simonneau G, et al. J Am Coll Cardiol 2009.

1 Pulmonary arterial hypertension (PAH)
- 1.1 Idiopathic
- 1.2 Heritable
  - 1.2.1 BMPR2
  - 1.2.2 ALK1, endoglin (with or without hereditary haemorrhagic telangiectasia)
  - 1.2.3 Unknown
- 1.3 Drugs and toxins induced
- 1.4 Associated with (APAH)
  - 1.4.1 Connective tissue diseases
  - 1.4.2 HIV infection
  - 1.4.3 Portal hypertension
  - 1.4.4 Congenital heart disease
  - 1.4.5 Schistosomiasis
  - 1.4.6 Chronic haemolytic anaemia
- 1.5 Persistent pulmonary hypertension of the newborn

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

2 Pulmonary hypertension due to left heart disease
- 2.1 Systolic dysfunction
- 2.2 Diastolic dysfunction
- 2.3 Valvular disease

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 abnormalities

4 Chronic thromboembolic pulmonary hypertension

5 PH with unclear and/or multifactorial mechanisms
- 5.1 Haematological disorders: myeloproliferative disorders, splenectomy.
- 5.2 Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis, lymphangioleiomyomatosis, neurofibromatosis, vasculitis
- 5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
- 5.4 Others: tumoural obstruction, fibrosing mediastinitis, chronic renal failure on dialysis

A Hemodynamic Study of Pulmonary Hypertension in Sickle Cell Disease

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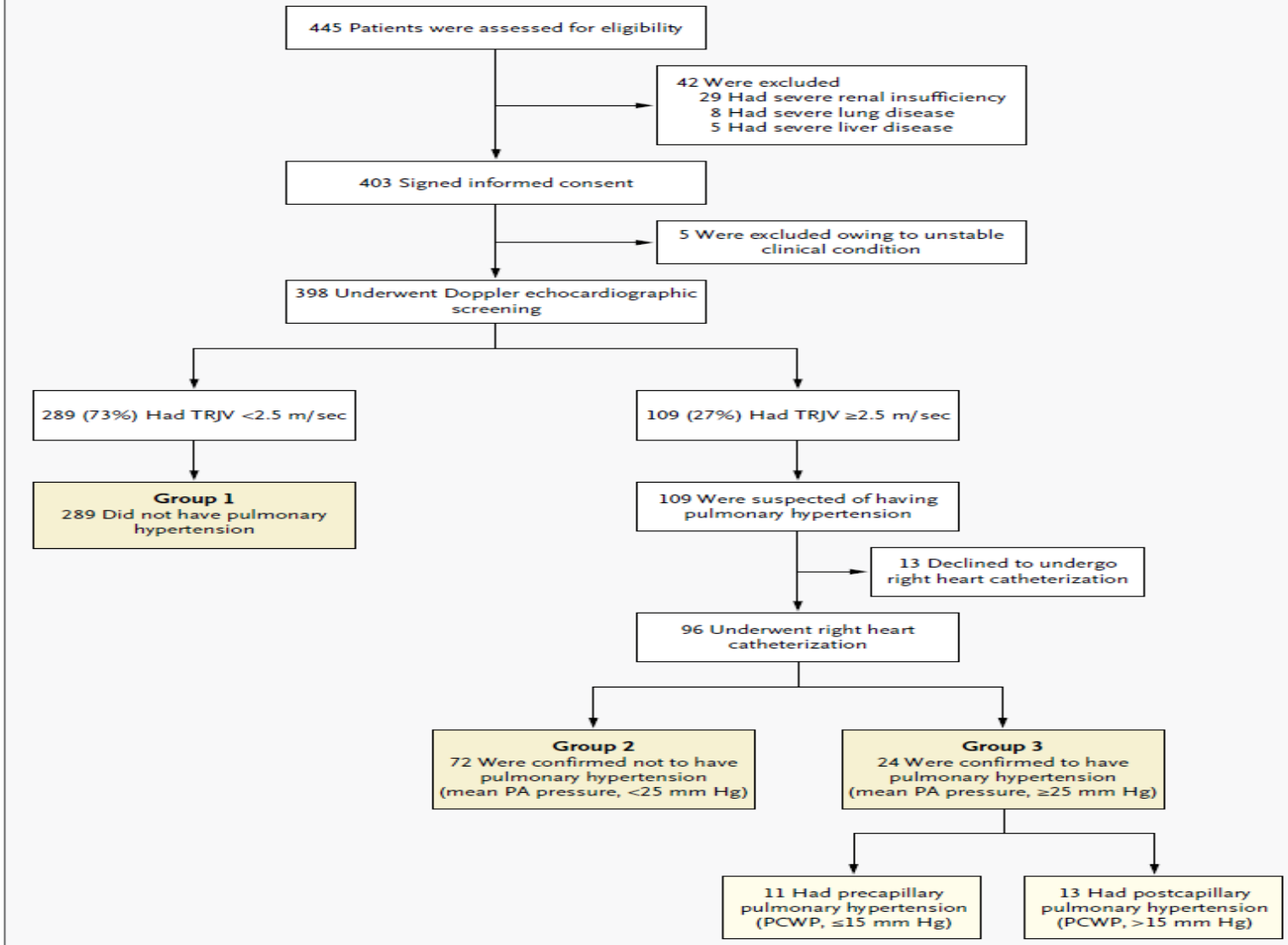
New Engl J Med 2011



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No of Patients (Percentage)	11 (2.9%)	13 (3.3%)	72 (18.7%)
mPAP (mm Hg)	28±4	32±7	19±3
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RAP (mm Hg)	5±2	13±5	7±2
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PVR (dyn.s.cm^{-5})	178±55	104±26	72±26

New Engl J Med 2011

Hemodynamics at Diagnosis in different PAH subgroups

PAH subgroups	IPAH* (n=288)	CTD-PAH* (n=157)	PoPH* (n=127)	CHD-PAH* (n=35)	HIV-PAH** (n=59)	Precap-PH in SCD*** (n=11)
RAP, mmHg	8 ± 5	7 ± 5	8 ± 6	7 ± 5	8 ± 5	5 ± 2
mPAP, mmHg	49 ± 13	41 ± 9	47 ± 12	51 ± 16	49 ± 10	28 ± 4
PCWP, mmHg	9 ± 4	8 ± 4	9 ± 4	8 ± 4	9 ± 5	10 ± 3
Cardiac Index, L/min/m²	2.4 ± 0.8	2.8 ± 0.9	3.0 ± 1.0	3.0 ± 1.0	2.9 ± 0.7	5.8 ± 1.3
PVR, dyn.sec.cm^{-5}	831 ± 461	649 ± 379	611 ± 311	753 ± 370	737 ± 328	178 ± 55

- * Sitbon et al ESC 2011. French registry (incident cases 2007-2009).
- ** Degano et al Eur Respir J 2009 - *** Parent et al New Engl J Med 2011

Eur Respir J 2012; 39: 1–1
DOI: 10.1183/09031936.00119811

EDITORIAL

Pulmonary hypertension in patients with sickle cell disease: not so frequent but so different. The importance of right heart catheterisation

G. Simonneau and F. Parent

Finally, pre-capillary PH associated with sickle cell disease appears quite different from the other forms of PAH in terms of both its haemodynamic profile and response to specific PAH therapies. These observations call into question the rationale for keeping sickle cell disease in group 1 (PAH) of the clinical PH classification system.

Should we maintain sickle cell disease PAH in group 1? (Roberto Machado US)

- Although limited, autopsy studies also provide insight into the presence of pulmonary vascular disease in patients with sickle cell disease.
- In a series of 20 patients with sickle hemogobinopathy, the pulmonary vascular bed of all 20 patients revealed changes considered diagnostic of pulmonary hypertension, ranging from grade I to grade IV.(ref) Reversible hypertensive changes (grade I to grade III) were seen in 8 patients, and irreversible changes (grade IV lesions) were seen in the remaining 12 patients. Plexiform lesions were seen in 12/20 patients.[9]
- In another series of 21 patients who experienced sudden/unexpected death during a hospital admission for an acute illness (vasooclusive crisis n=13, sepsis/infection = 5, acute kidney injury n=2, CNS hemorrhage n=1), 7 patients demonstrated grades I–IV lesions with one reported case with plexiform lesions.[10]

9. Haque AK et al Pulmonary hypertension in sickle cell hemoglobinopathy: a clinicopathologic study of 20 cases.Human pathology 2002;33:1037-43.
10.Graham et al. Sickle cell lung disease and sudden death: a retrospective/prospective study of 21 autopsy cases and literature review. The American journal of forensic medicine and pathology 2007;28:168-72.

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  - 1.2.1 BMPR2
  - 1.2.2 ALK1, endoglin (with or without hereditary haemorrhagic telangiectasia)
  - 1.2.3 Unknown
- 1.3 Drugs and toxins induced
- 1.4 Associated with (APAH)
  - 1.4.1 Connective tissue diseases
  - 1.4.2 HIV infection
  - 1.4.3 Portal hypertension
  - 1.4.4 Congenital heart disease
  - 1.4.5 Schistosomiasis
  - 1.4.6 Chronic haemolytic anaemia
- 1.5 Persistent pulmonary hypertension of the newborn

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

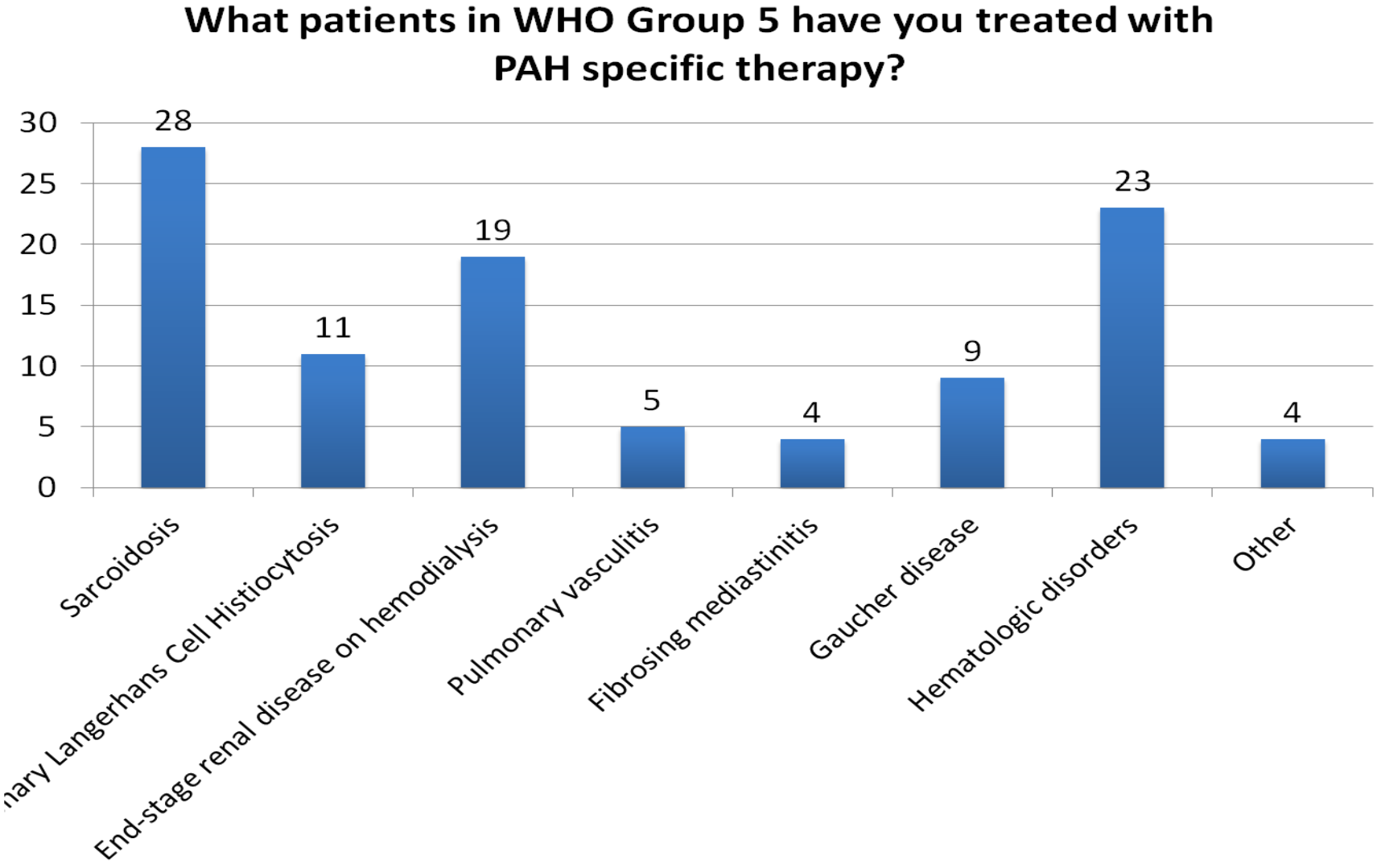
2 Pulmonary hypertension due to left heart disease
- 2.1 Systolic dysfunction
- 2.2 Diastolic dysfunction
- 2.3 Valvular disease

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 abnormalities

4 Chronic thromboembolic pulmonary hypertension

5 PH with unclear and/or multifactorial mechanisms
- 5.1 Haematological disorders: myeloproliferative disorders, splenectomy.
- 5.2 Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis, lymphangioleiomyomatosis, neurofibromatosis, vasculitis
- 5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
- 5.4 Others: tumoural obstruction, fibrosing mediastinitis, chronic renal failure on dialysis

Survey of PAH specific therapy in Group 5 (Ivan .Robbins)



5TH

WORLD SYMPOSIUM ON PULMONARY HYPERTENSION

NICE ACROPOLIS, Nice February 27-28 / March 1, 2013