Ipertensione polmonare : Inquadramento clinico e le possibili opzioni terapeutiche

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European Heart Journal (2009) **30**, 2493–2537
doi:10.1093/eurheartj/ehp297

ESC/ERS GUIDELINES

Guidelines for the diagnosis and treatment of pulmonary hypertension

The Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT)

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Table 5 Important definitions

- Pulmonary hypertension (PH) is a *haemodynamic and pathophysiological condition* defined as an increase in mean pulmonary arterial pressure (PAP) ≥25 mmHg at rest as assessed by right heart catheterization (*Table 3*). PH can be found in multiple clinical conditions (*Table 4*).
- The definition of PH on exercise as a mean PAP >30 mmHg as assessed by right heart catheterization is not supported by published data.
- Pulmonary arterial hypertension (PAH, group 1) is *a clinical condition* characterized by the presence of pre-capillary PH (*Table 3*) in the absence of other causes of pre-capillary PH such as PH due to lung diseases, chronic thromboembolic PH, or other rare diseases (*Table 4*). PAH includes different forms that share a similar clinical picture and virtually identical pathological changes of the lung microcirculation (*Table 4*).

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Table 3 Haemodynamic definitions of pulmonary hypertension[a]

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

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Table 4 Updated clinical classification of pulmonary hypertension (Dana Point, 2008[1])

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 hypoxaemia
- 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

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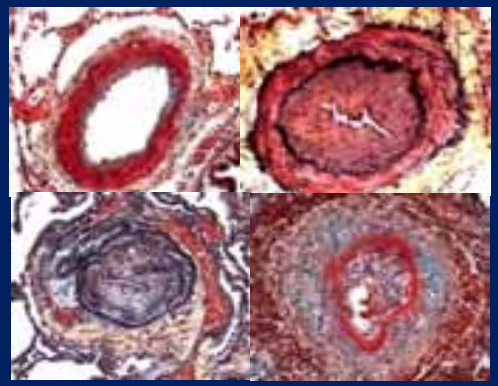
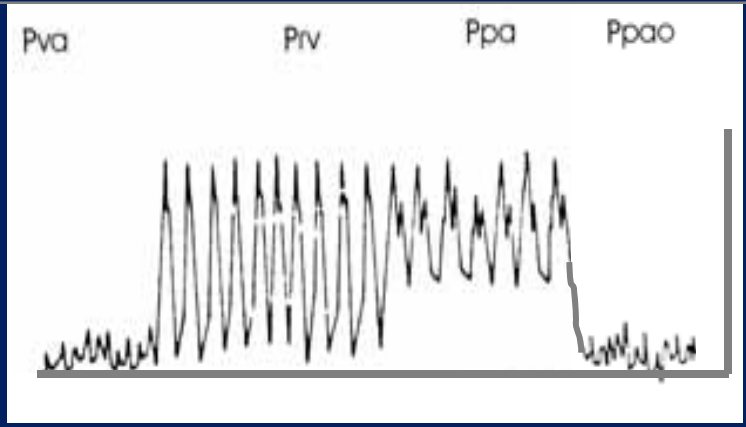
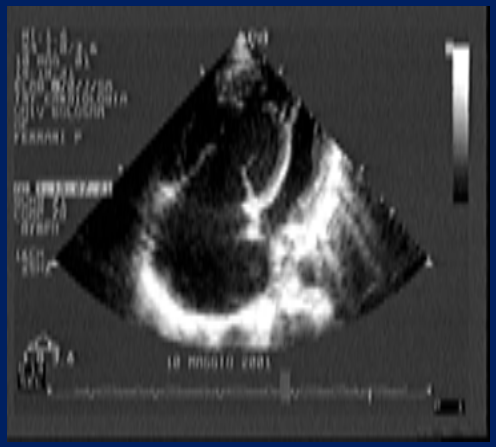
Pulmonary Arterial Hypertension (Group 1)



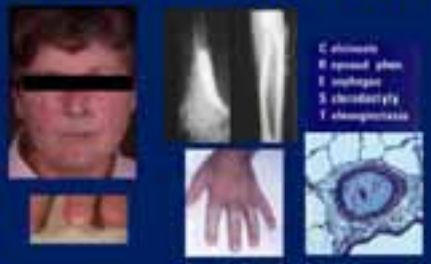




Heritable PAH

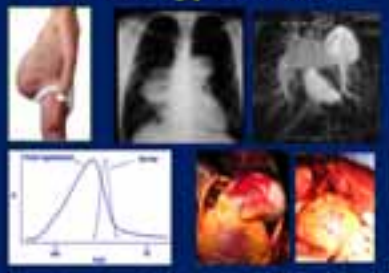
Eisenmenger's Syndrome

Limited Cutaneous SSc



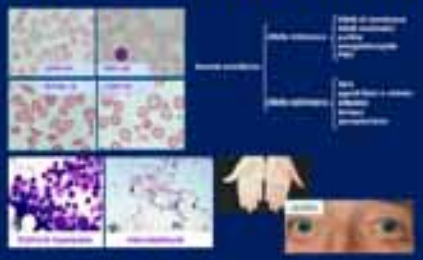
HIV infection

Portal Hypertension



Schistosomiasis

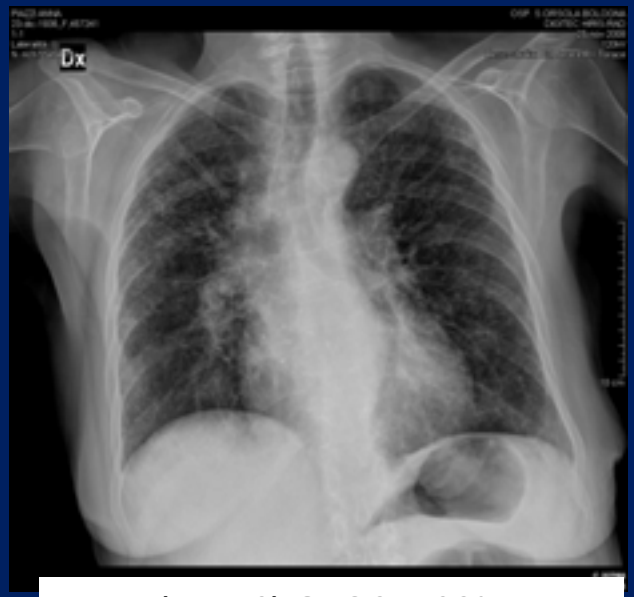
Chronic Haemolytic Anaemia



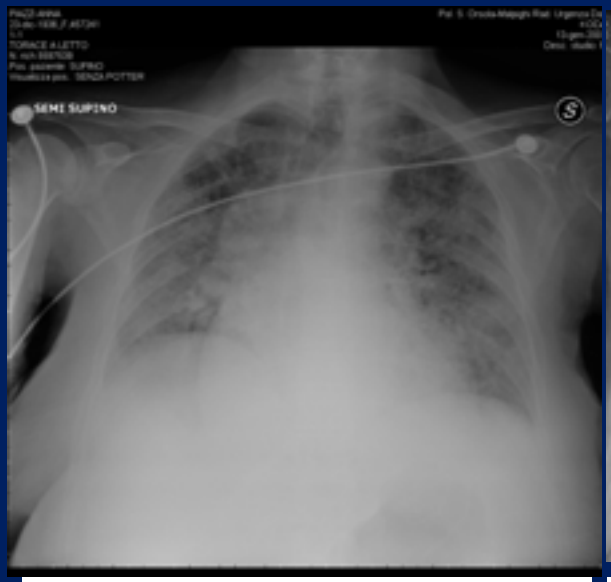
Drug and Toxins

- Aminorex
- Fenfluramine
- Dexfenfluramine
- Toxic rapeseed oil

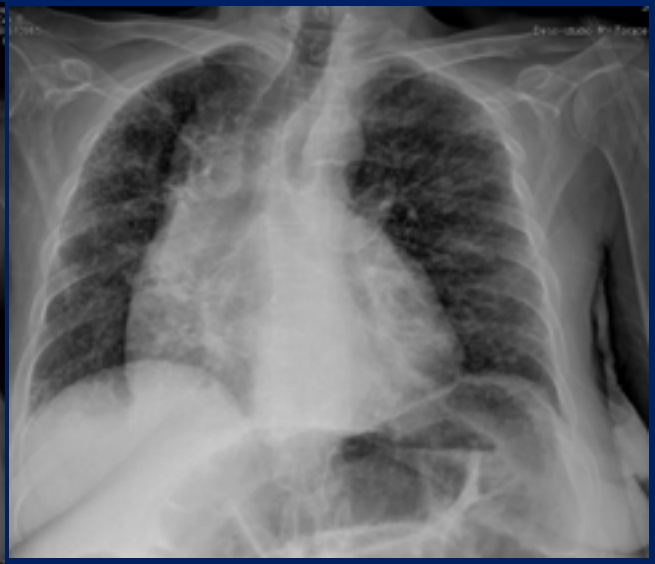
Pulmonary Veno-Occlusive Disease (Group 1')



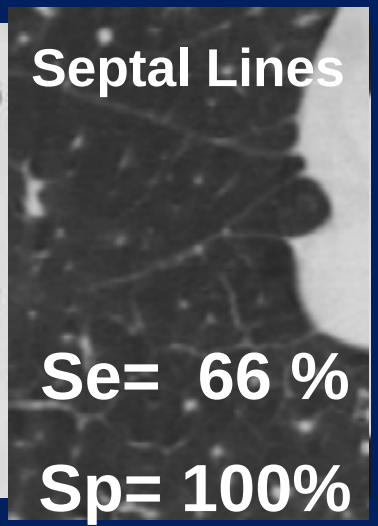
(DAY 0) SaO2 = 93%

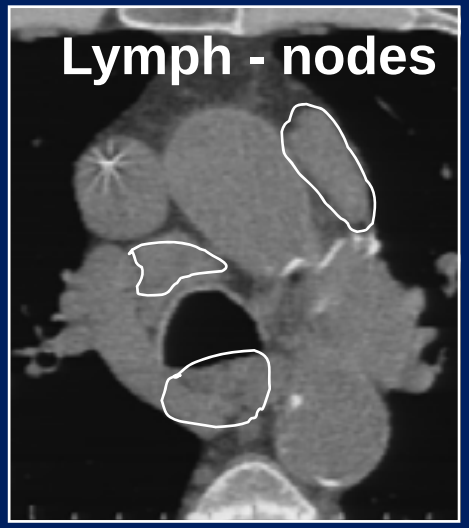


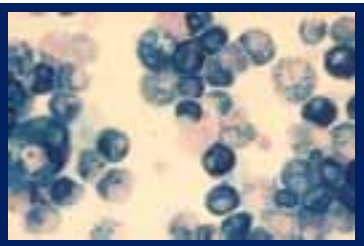
Sildenafil (Day 15) SaO_2 = 73%

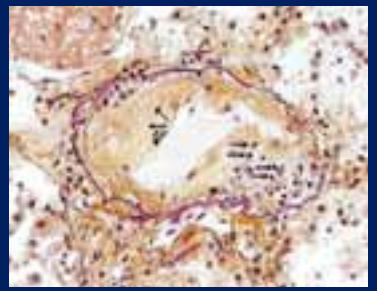


Diuretic (Day 21) SaO_2 = 92%

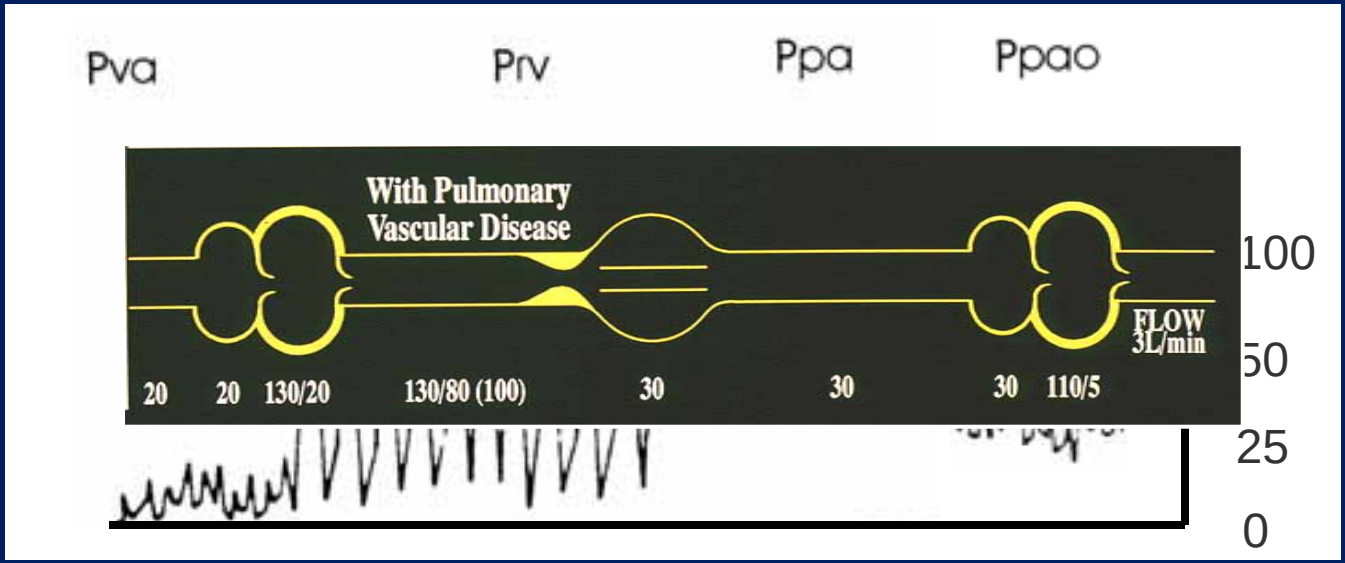


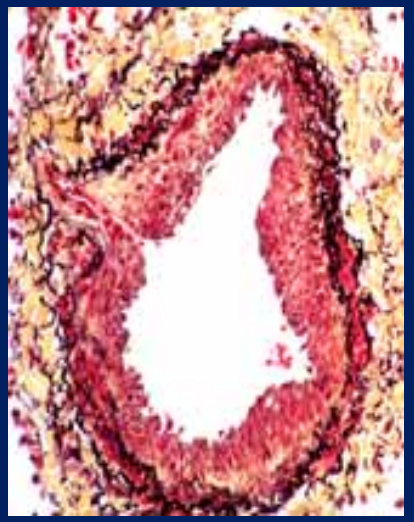


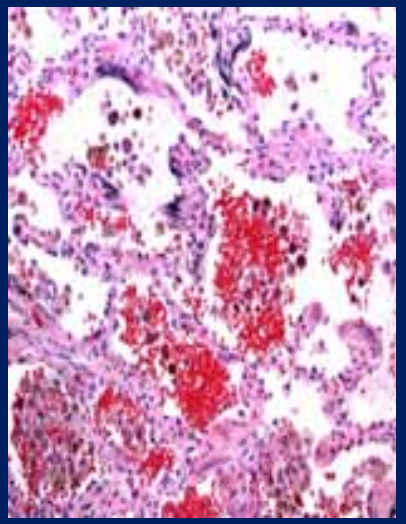


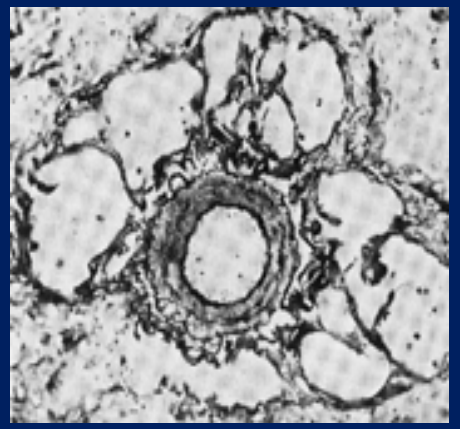


Pulmonary Hypertension with Left Heart Disease (Group 2)

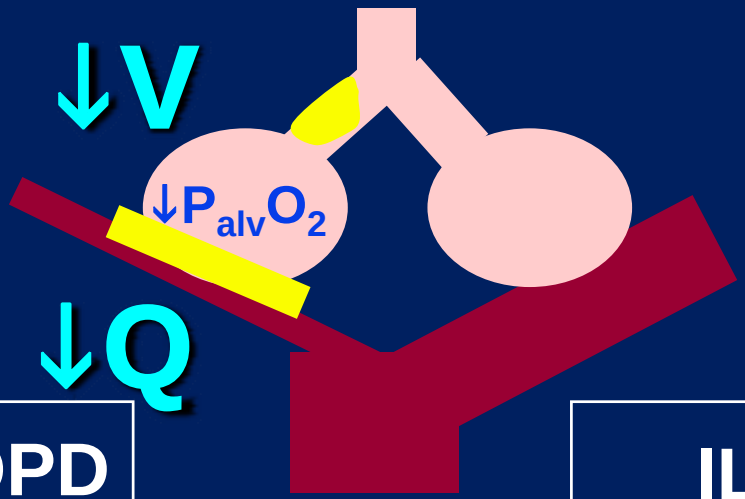


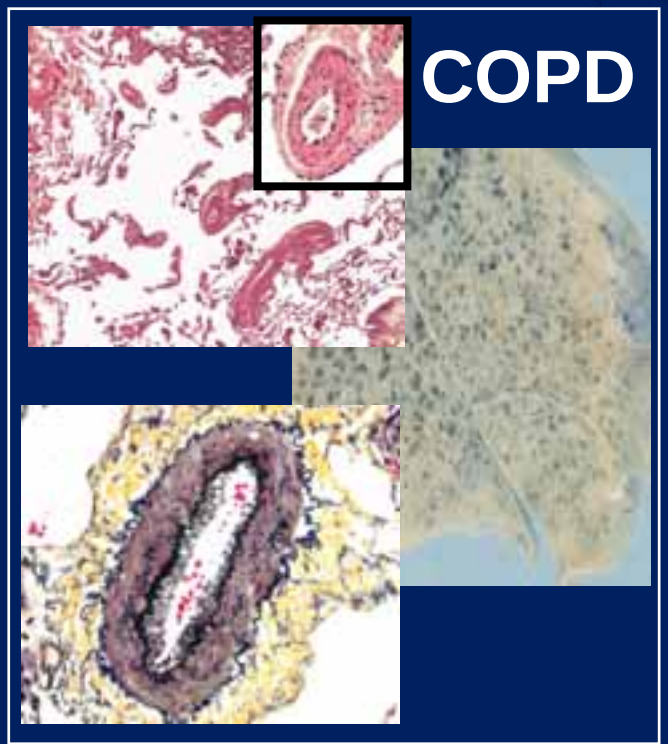


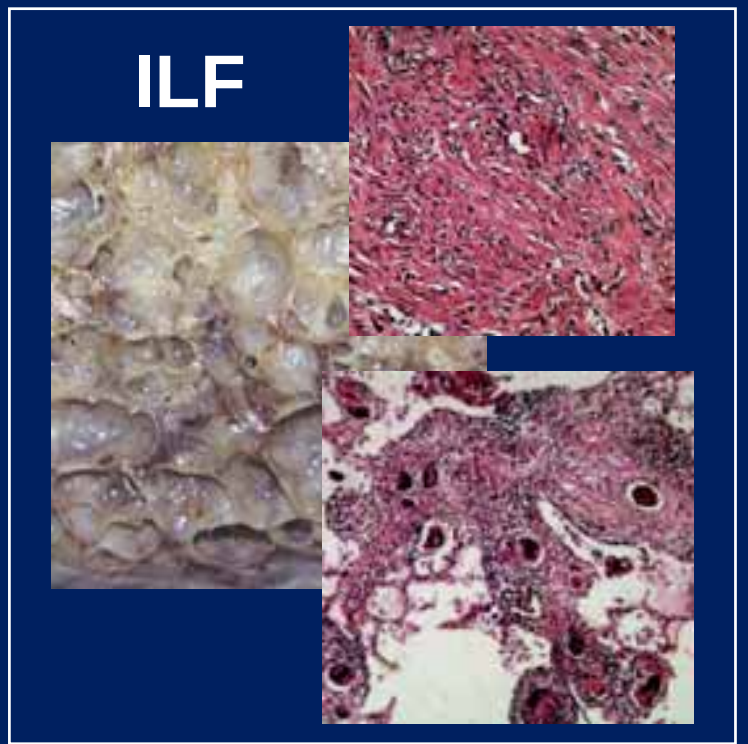




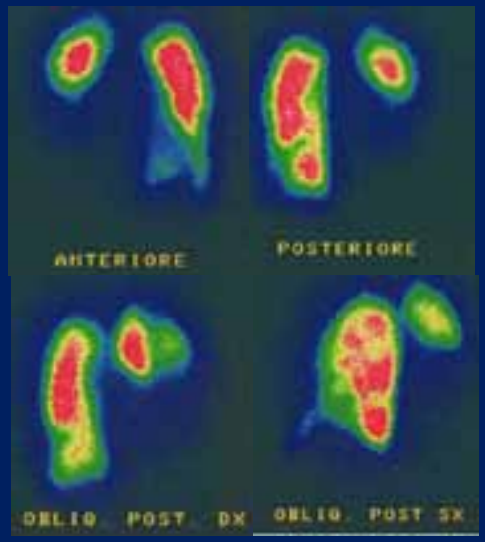
Pulmonary Hypertension with with Lung Diseases/Hypoxemia (Group 3)

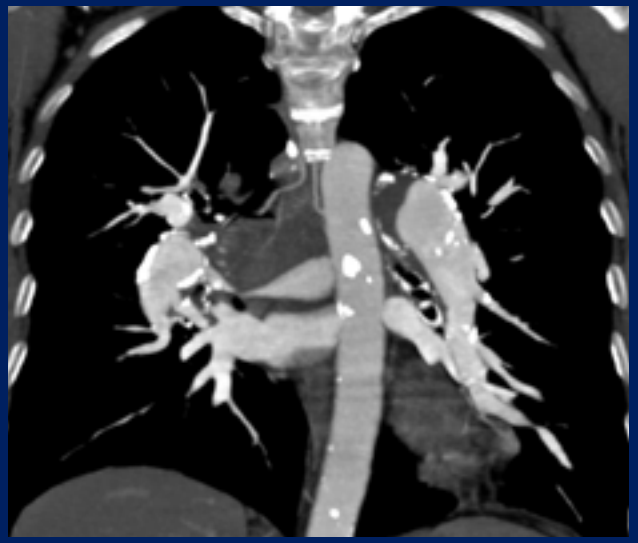


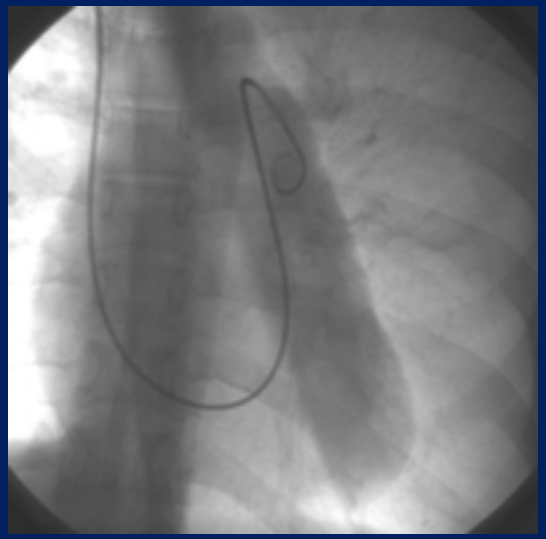




Chronic Thromboembolic Pulmonary Hypertension (Group 4)







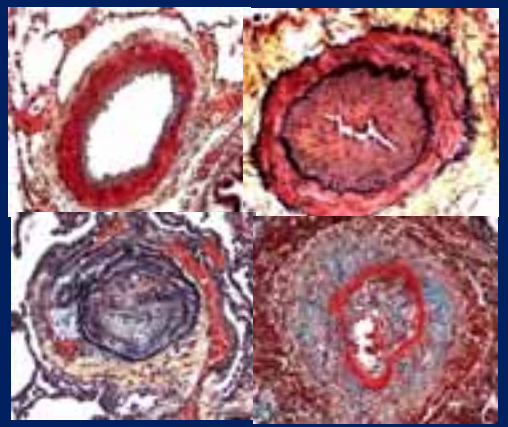


Table 4 Updated clinical classification of pulmonary hypertension (Dana Point, 2008[1])

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

PH Epidemiology in an Echo lab

(480 patients with SPAP > 40mmHG)

1. Pulmonary arterial hypertension

3.5%

2. PH ass with left heart disease

78%

3. PH ass with lung diseases

10%

4. PH due to chronic TE disease

1.5%

5. Miscellaneous

Mixed

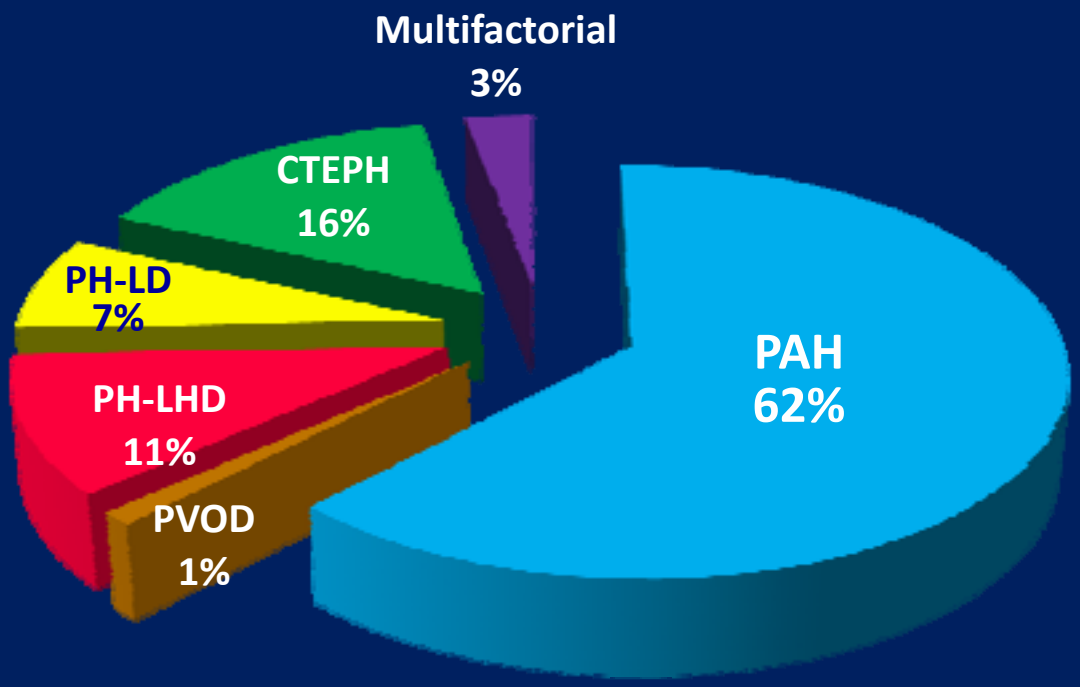
7%

Gabbay et al ATS 2007

Pulmonary Vascular Diseases Center
Institute of Cardiology
Bologna University Hospital

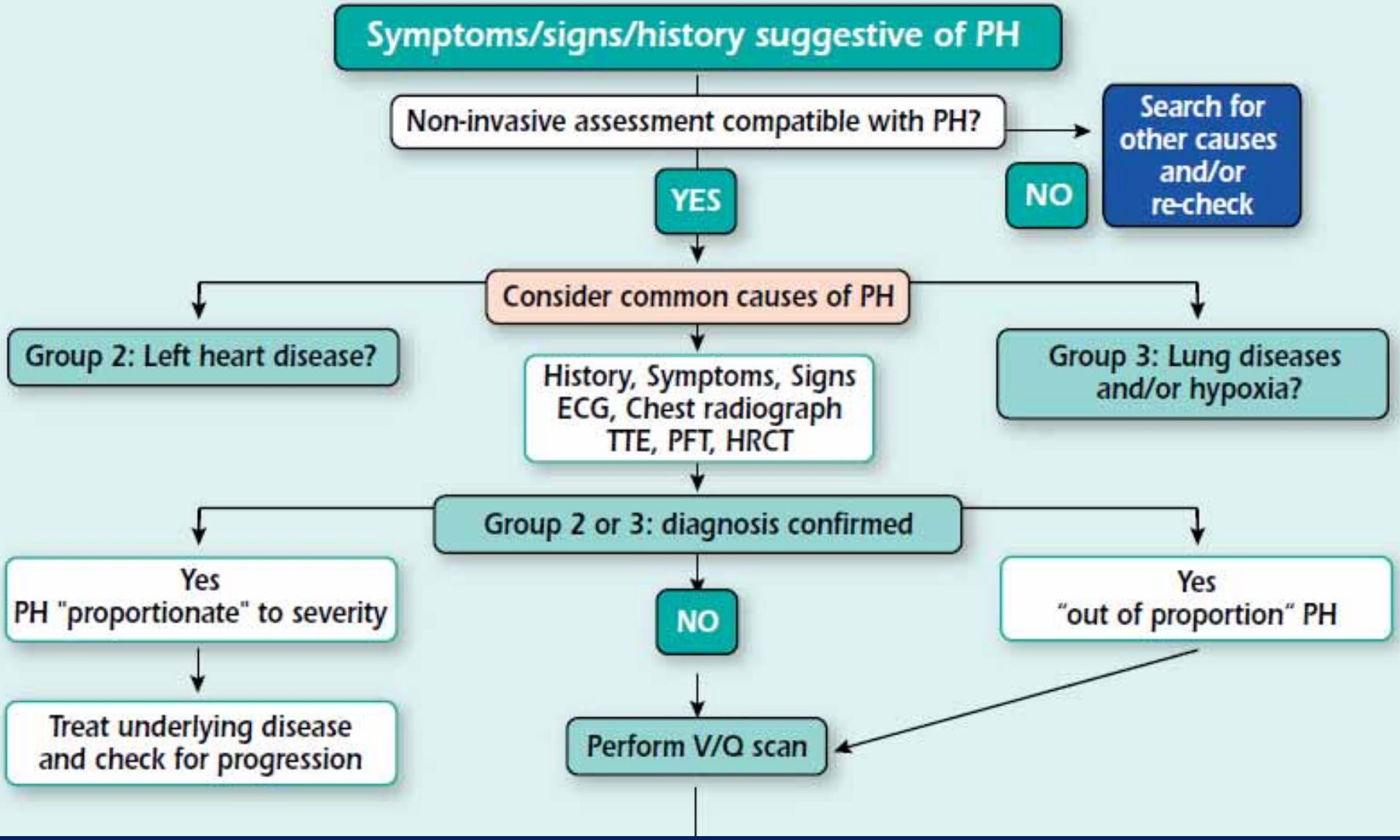
As of 11 November 2009

Etiology of PH (n=1344)



Etiology	Patients (nr)
Group 1 - PAH	837
Group 1' – PVOD	15
Group 2 – PH+LHD	148
Group 3 – PH+LD	99
Group 4 – CTEPH	207
Group 5 - Multifactorial	38
Total	**1344**

Figure 1 Diagnostic algorithm



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Pulmonary Arterial Hypertension (group 1)
Symptoms, Risk Factors, Associated Conditions

Symptoms

Dyspnoea
Fatigue
Syncope
…

Risk Factors

Definite
Aminorex
Fenfluramine
Dexfenfluramine
Toxic rapeseed oil
Benfluorex

Likely
Amphetamines
L-tryptophan
Methamphetamines

Associated Conditions

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

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Table 9: Arbitrary Echo Criteria for Estimation of PH based on TRV and assumed RAP of 5 mm Hg

PH Present?	Peak TRV (m/s)	PAsP (mmHg)	Additional Echo Signs of PH	R/E
Unlikely	≤2.8	≤35	No	I-B
Possible	≤2.8	≤35	Yes	IIa-C
	2.9 – 3.4	36 – 50	No/Yes	IIa-C
Likely	>3.4	>50	No/Yes	I-B

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Table 12: Probability of PAH Diagnosis

PH by Echo	Symptoms	Risk Factors/AC	PAH Probability	Work-up	R/E
Unlikely	No	Yes/No	Low	No	I-C
	Yes	Yes		Echo F-up	I-C
	Yes	No		Other causes	I-C
Possible	No	No	Intermediate	Echo F-up	I-C
	Yes	Yes		RH Cath	IIb-C
	Yes	No		Echo F-up*	IIb-C
Likely	Yes	Yes/No	High	RH Cath	I-C
	No	Yes/No		RH Cath	IIa-C

* Consider also other causes and if symptoms at least moderate also RH cath

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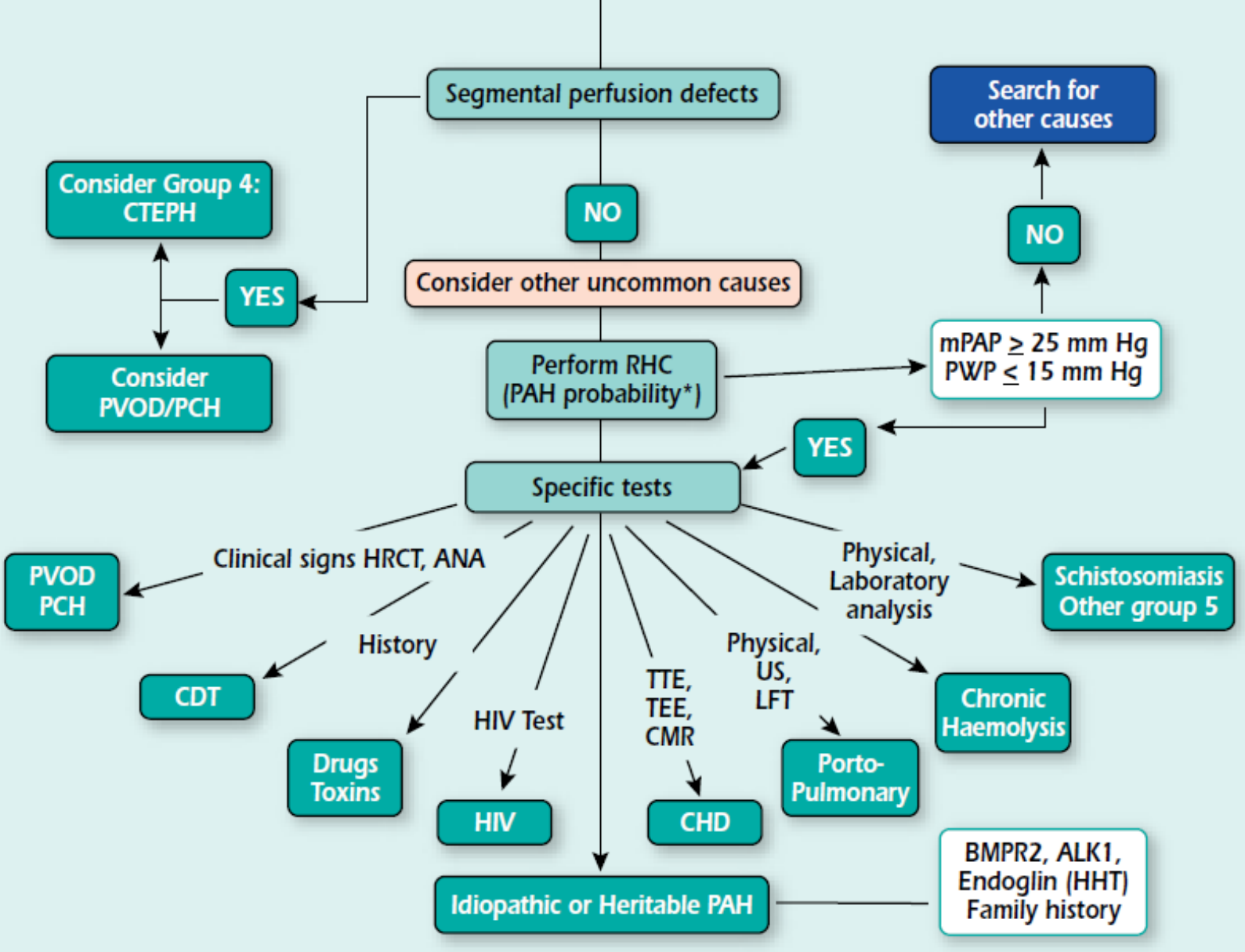

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Table 15 Parameters with established importance for assessing disease severity, stability and prognosis in PAH

Better Prognosis	Determinants of Prognosis	Worse Prognosis
No	Clinical evidence of RV failure	Yes
Slow	Rate of progression of symptoms	Rapid
No	Syncope	Yes
I, II	WHO-FC	IV
Longer (> 500m)*	6MWT	Shorter (< 300 m)
Peak O_2 Consumption > 15 ml/min/kg	Cardio-pulmonary exercise testing	Peak O_2 consumption < 12 ml/min/kg
Normal or near-normal	BNP/NT-proBNP plasma levels	Very elevated and rising
No pericardial effusion TAPSE† > 2.0 cm	Echocardiographic findings†	Pericardial effusion TAPSE† < 1.5 cm
RAP < 8 mmHg and CI ≥ 2.5 L/min/m²	Haemodynamics	RAP >15 mmHg or CI ≤ 2.0 L/min/m²

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Prognosis & Clinical Status

Determinants of Prognosis	Better Prognosis	Worse Prognosis
Clinical evidence of RV failure	No	Yes
Rate of progression of symptoms	Slow	Rapid
Syncope	No	Yes
WHO-FC	I, II	IV
6MWT	Longer (> 500m)*	Shorter (< 300 m)
Cardio-pulmonary exercise testing	Peak O_2 Consumption > 15 ml/min/kg	Peak O_2 consumption < 12 ml/min/kg
BNP/NT-proBNP plasma levels	Normal or near-normal	Very elevated and rising
Echocardiographic findings†	No pericardial effusion TAPSE† > 2.0 cm	Pericardial effusion TAPSE† < 1.5 cm
Haemodynamics	RAP < 8 mmHg and CI ≥ 2.5 L/min/m²	RAP >15 mmHg or CI < 2.0 L/min/m²

Clinical Status ▶ **Stable and Satisfactory** | **Stable and NOT Satisfactory** | **Unstable and Deteriorating**

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Table 4 Updated clinical classification of pulmonary hypertension (Dana Point, 2008[1])

1. Pulmonary Arterial Hypertension

- 1.1 Idiopathic
- 1.2 Heritable (BMPR2, ALK1)
- 1.3 Drugs and Toxins
- 1.4 Associated with
  CTD, CHD, Portal Hypertension, HIV infection, Schistosomiasis, Chronic Haemolitic anaemia
- 1.5 Persistent PH of the newborn

1'. Pulmonary veno-occlusive disease and/or PCH

2. PH due to Left Heart Disease

- 2.1 LV systolic dysfunction
- 2.2 LV diastolic dysfunction
- 2.3 Valvular heart diseases

3. PH ass with Lung Dis/Hypoxia

- 3.1 COPD
- 3.2 ILD
- 3.3 Mixed restrictive and obstructive
- 3.4 Sleep –disordered breathing
- 3.5 Alveolar hypoventilation
- 3.6 Chronic exposure to high altitude
- 3.7 Developmental abnormalities

4. CTEPH

5. PH with unclear/multifactorial Mech.

Haematological d, Sarcoidosis, LLM, Histiocytosis, metabolic d. (Glicogen. Gaucher), thyroid d., tumor obstruction F. mediastinitis, CRF & dialysis

Table 4 Updated clinical classification of pulmonary hypertension (Dana Point, 2008[1])

1. Pulmonary Arterial Hypertension

Treatment Algorithm

1'. Pulmonary veno-occlusive disease and/or PCH TA

2. PH due to Left Heart Disease

Treatment Algorithm

3. PH ass with Lung Dis/Hypoxia

Treatment Algorithm

4. CTEPH Treatment Algorithm

5. PH with unclear/multifactorial Mech.

Treatment Algorithm

European Heart Journal
doi:10.1093/eurheartj/ehp022

CLINICAL RESEARCH

A meta-analysis of randomized controlled trials in pulmonary arterial hypertension

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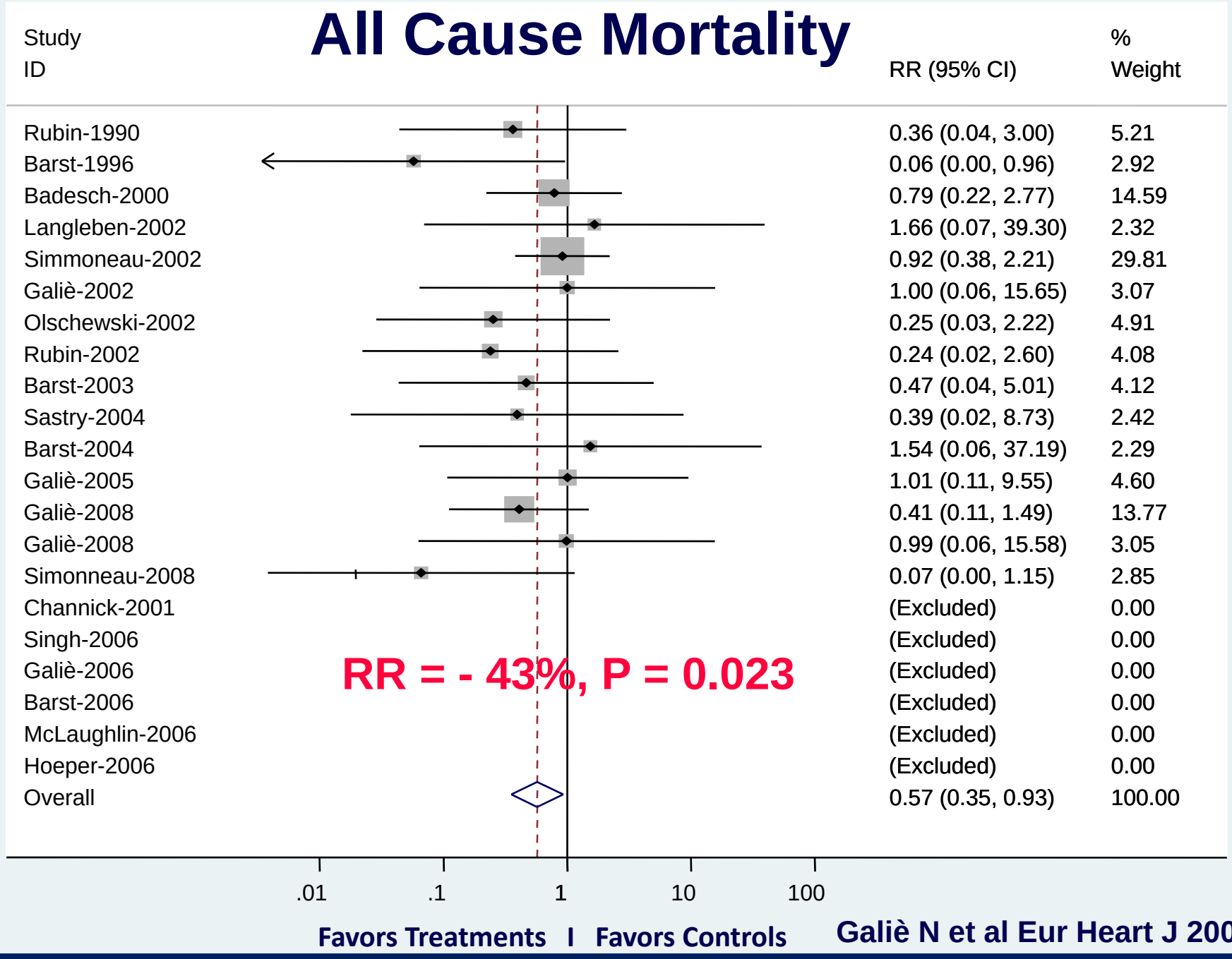
Received 9 December 2008; revised 18 December 2008; accepted 9 January 2009

- **Medline search from January 1990 to October 2008**
- **23 RCTs, 3199 patients**

All Cause Mortality



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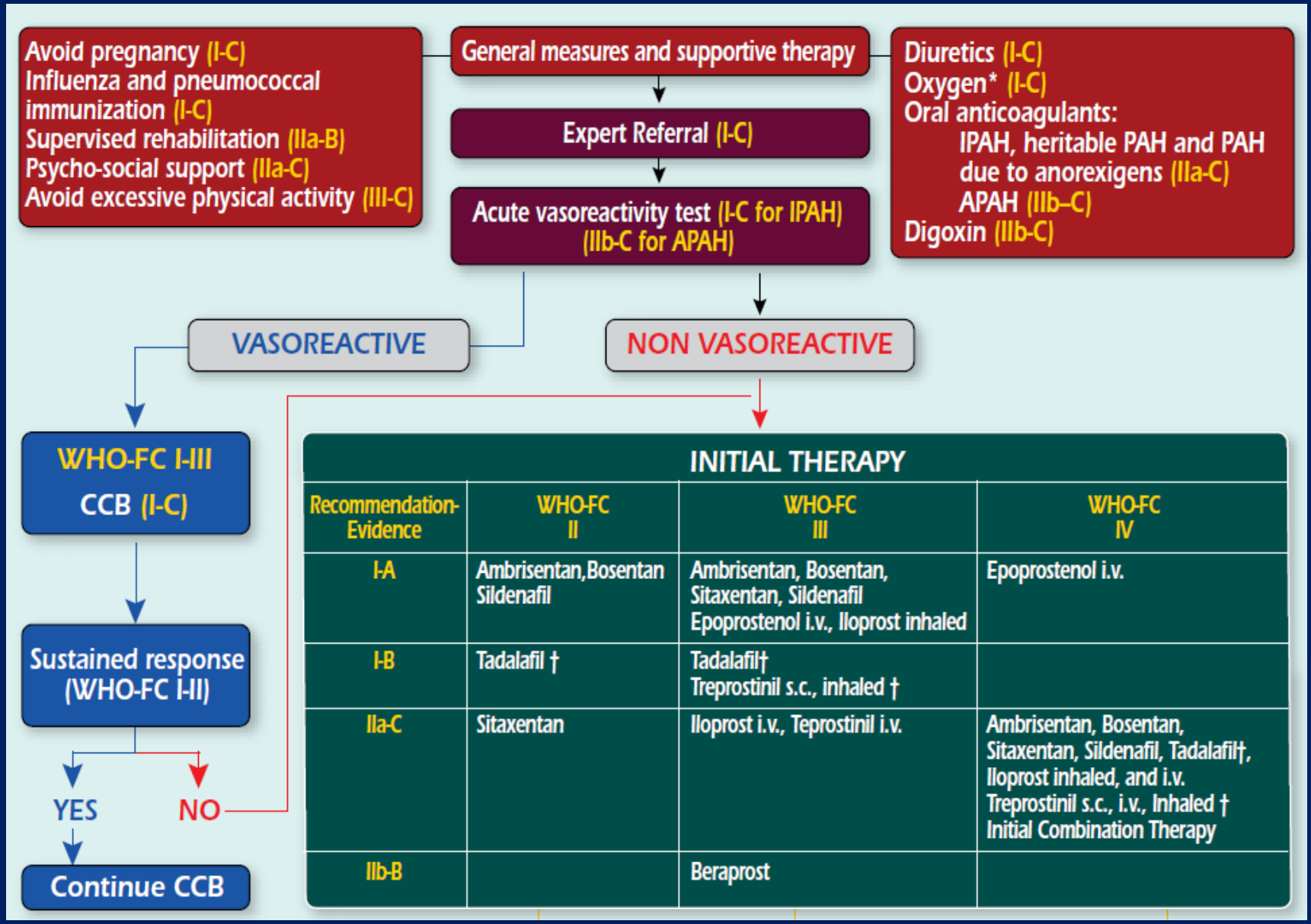

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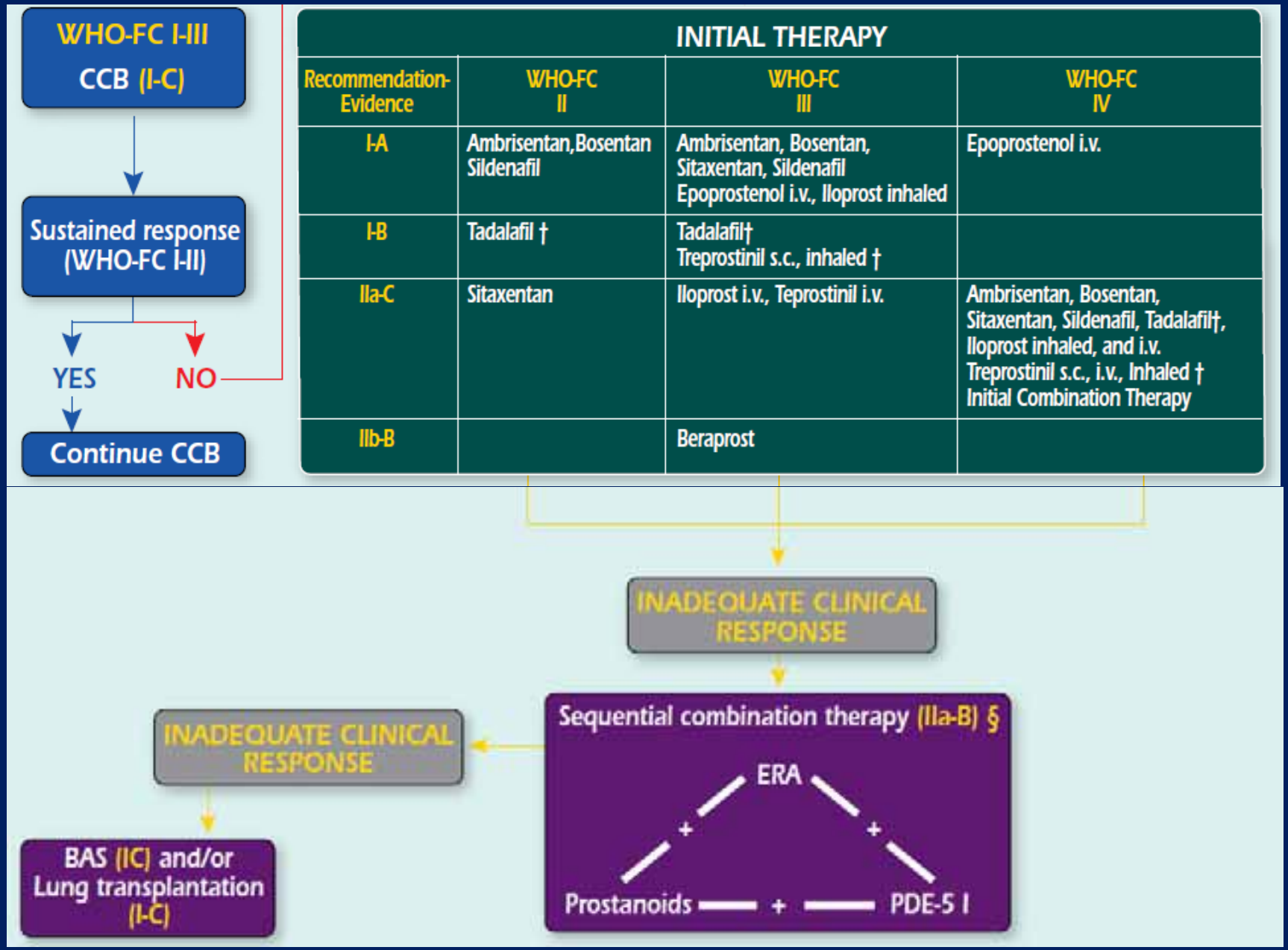

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Prognosis, Clinical Status and Clinical Response

Determinants of Prognosis	Better Prognosis	Worse Prognosis
Clinical evidence of RV failure	No	Yes
Rate of progression of symptoms	Slow	Rapid
Syncope	No	Yes
WHO-FC	I, II	IV
6MWT	Longer (> 500m)*	Shorter (< 300 m)
Cardio-pulmonary exercise testing	Peak O_2 Consumption > 15 ml/min/kg	Peak O_2 consumption < 12 ml/min/kg
BNP/NT-proBNP plasma levels	Normal or near-normal	Very elevated and rising
Echocardiographic findings†	No pericardial effusion TAPSE† > 2.0 cm	Pericardial effusion TAPSE† < 1.5 cm
Haemodynamics	RAP < 8 mmHg and CI ≥ 2.5 L/min/m²	RAP >15 mmHg or CI < 2.0 L/min/m²

Clinical Status ▶ Stable and Satisfactory | Stable and NOT Satisfactory | Unstable and Deteriorating

Clinical Response ▶ Adequate | Inadequate

Galiè.N et al Eur Heart J and Eur Respir J, 2009

European Heart Journal
doi:10.1093/eurheartj/ehp297

ESC/ERS GUIDELINES

Guidelines for the diagnosis and treatment of pulmonary hypertension

The Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT)

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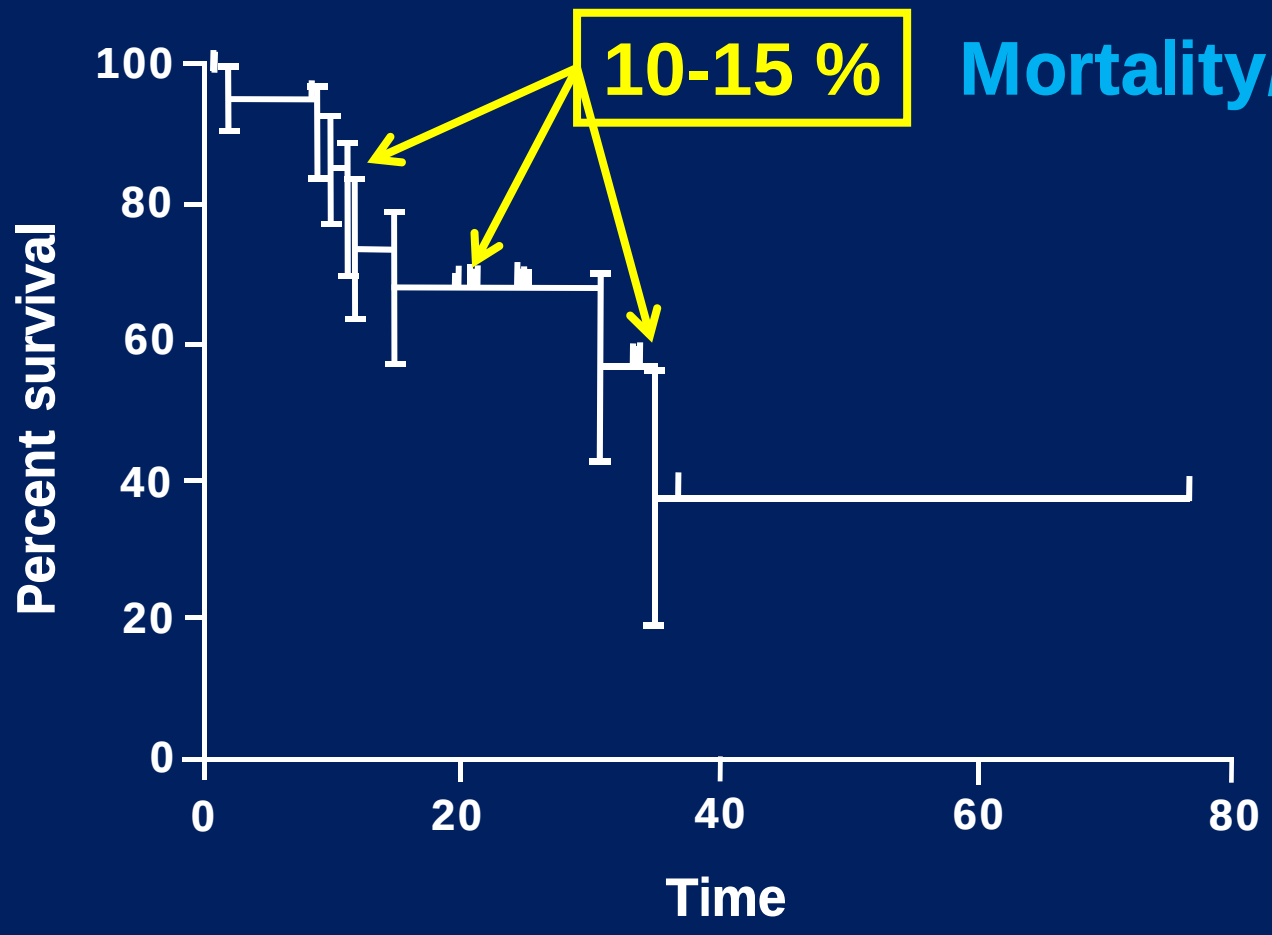
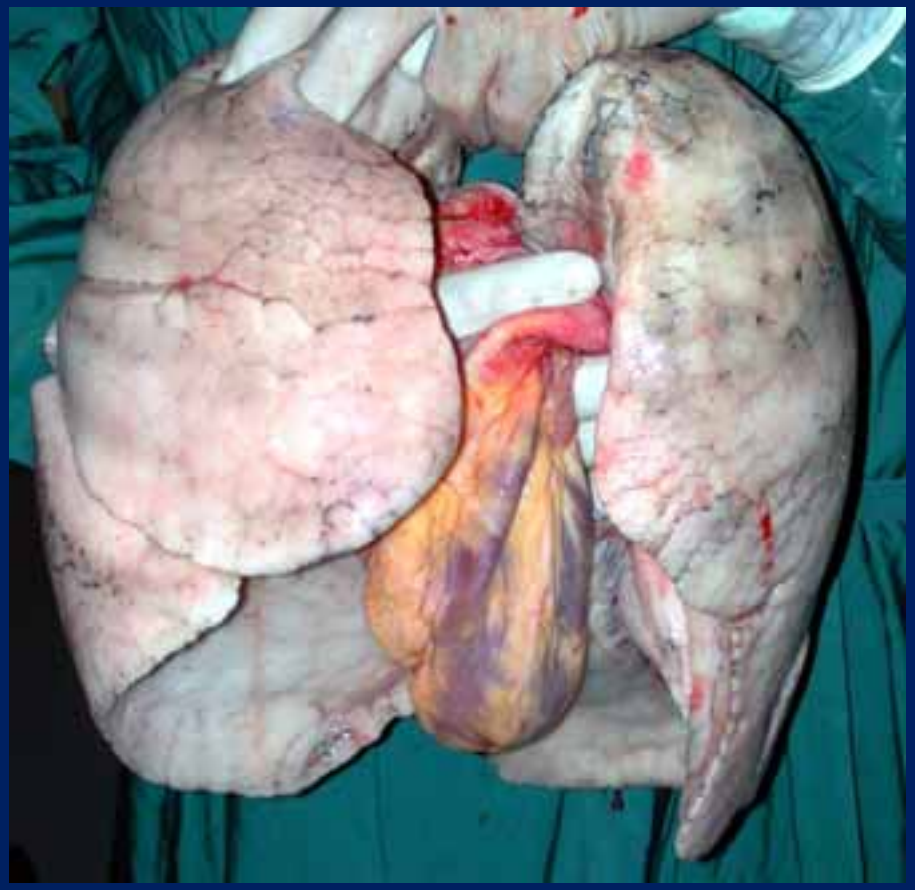
Limitations & gaps of evidence

Bosentan & Sildenafil + Epoprostenol (*n* = 22)



Negro L, *et al*. Presented at ATS 2009.

Heart/Lung Transplantation



Heart/Lung and Double Lung Tx

	Age/Gender	W L	DIAGNOSIS	Tx Type
BG	24 yo male	4	PVOD	HLTx
OC	30 yo female	9	Eisenmenger S.	HLTx
FV	26 yo male	11	IPAH	DLTx
KS	28 yo female	8	PVOD	DLTx
BL	44 yo male	2	SSc-PAH	DLTx
MV	32 yo male	12	IPAH	DLTx
GG	28 yo female	17	CTEPH	DLTx

PH due to Left Heart Disease (group 2)

Table 31 Recommendations for PH due to left heart disease

Statement	Class[a]	Level[b]
The optimal treatment of the underlying left heart disease is recommended in patients with PH due to left heart disease.	I	C
Patients with "out of proportion" PH due to left heart disease should be enrolled in RCTs targeting PH specific drugs.	IIa	C
Increased left-sided filling pressures may be estimated by Doppler echocardiography.	IIb	C
Invasive measurements of PWP or LV end-diastolic pressure may be required to confirm the diagnosis of PH due to left heart disease.	IIb	C
RHC may be considered in patients with echocardiographic signs suggesting severe PH in patients with left heart disease.	IIb	C
The use of PAH specific drug therapy is not recommended in patients with PH due to left heart disease.	III	C

Galiè.N et al Eur Heart J and Eur Respir J, 2009

PH due to Lung Diseases (group 3)

Table 32 Recommendations for PH due to lung diseases

Statement	Class[a]	Level[b]
Echocardiography is recommended as screening tool for the assessment of PH due to lung diseases.	I	C
RHC is recommended for a definite diagnosis of PH due to lung diseases.	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
Patients with "out of proportion" PH due to lung diseases should be enrolled in RCTs targeting PAH specific drugs.	IIa	C
The use of PAH specific drug therapy is not recommended in patients with PH due to lung diseases.	III	C

Chronic Thromboembolic PH (group 4)

Table 33 Recommendations for chronic thromboembolic pulmonary hypertension

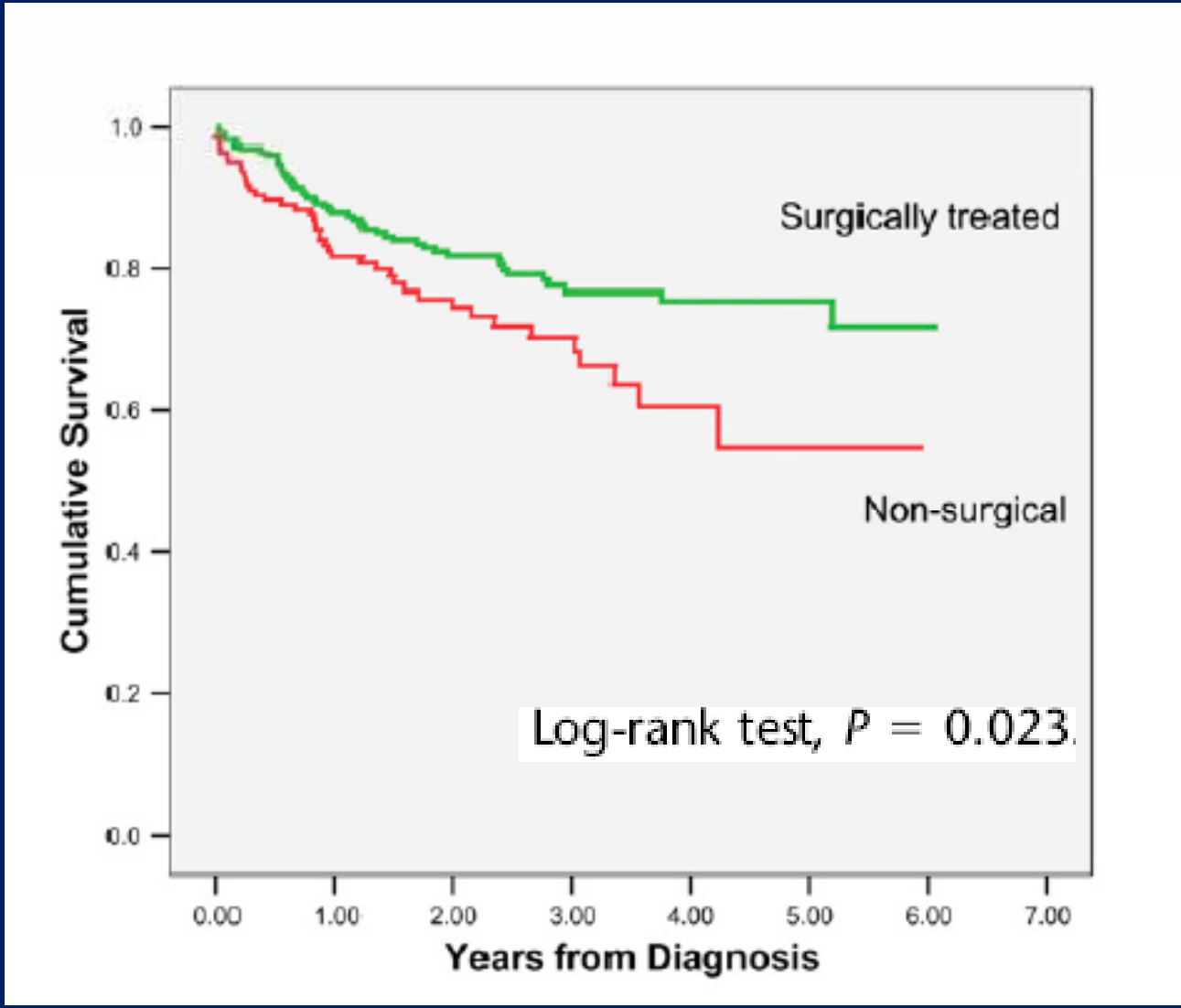
Statement	Class[a]	Level[b]
The diagnosis of CTEPH is based on the presence of precapillary PH (mean PAP ≥ 25 mmHg, PWP ≤ 15 mmHg, PVR > 2 WU) in patients with multiple chronic/organized occlusive thrombi/emboli in the elastic pulmonary arteries (main, lobar, segmental, sub-segmental).	I	C
In patients with CTEPH lifelong anticoagulation is indicated.	I	C
Surgical pulmonary endarterectomy is the recommended treatment for patients with CTEPH.	I	C
Once perfusion scanning and/or CT angiography show signs compatible with CTEPH, the patient should be referred to a centre with expertise in surgical pulmonary endarterectomy.	IIa	C
The selection of patients for surgery should be based on the extent and location of the organized thrombi, on the degree of PH and on the presence of comorbidities.	IIa	C
PAH specific drug therapy may be indicated in selected CTEPH patients such as patients not candidates for surgery or patients with residual PH after PEA.	IIb	C

Galiè.N et al Eur Heart J and Eur Respir J, 2009

Improved Outcomes in Medically and Surgically Treated Chronic Thromboembolic Pulmonary Hypertension

Robin Condliffe[1,2], David G. Kiely[2], J. Simon R. Gibbs[3]

Am J Respir Crit Care Med Vol 177. pp 1122–1127, 2008



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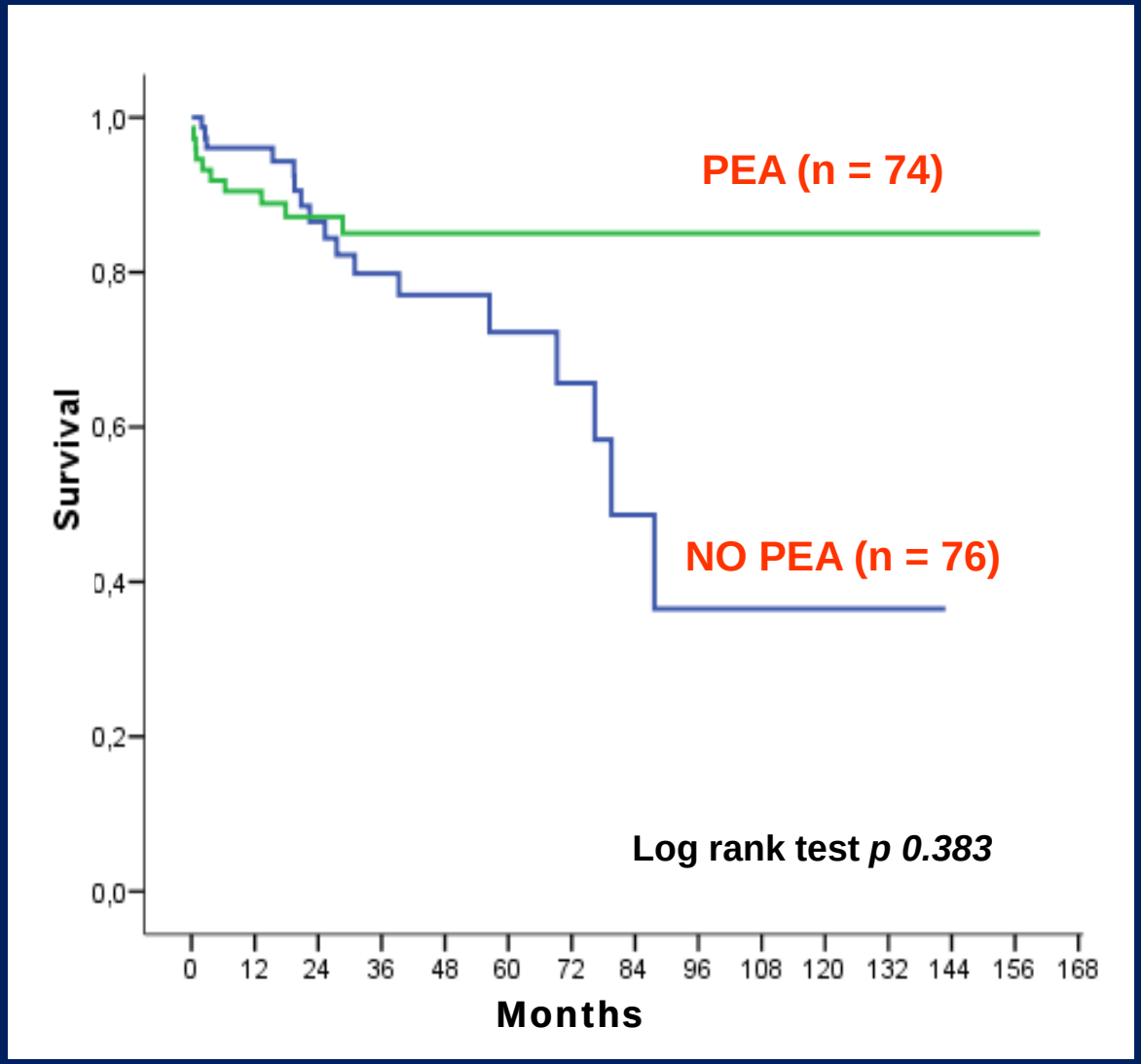

Comments-1

- Appropriate diagnosis of different PH clinical groups is mandatory
- Treatment strategies are extremely different among PH clinical groups
- PAH (clinical group 1) is a severe condition with a specific drug treatment strategy and requires invasive diagnostic confirmation and appropriate follow-up
- Goal-oriented and combination therapy may optimize the use of PAH specific medications
- Despite the progresses PAH remains a severe and chronic disease and interventional procedures such as transplantation are often required in young patients
- PEA in CTEPH operable patients is mandatory

Comments-2

- Drugs approved for PAH are not indicated in patients with left heart disease or lung diseases (benefit to risk ratio not established)