Update of Diagnosis and Treatment of Pulmonary Arterial Hypertension

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폐혈관 School 2016

Overview

- Definition
- Classification and Epidemiology
- WHO classification group I : PAH
- Diagnosis and Assessment
- Treatment

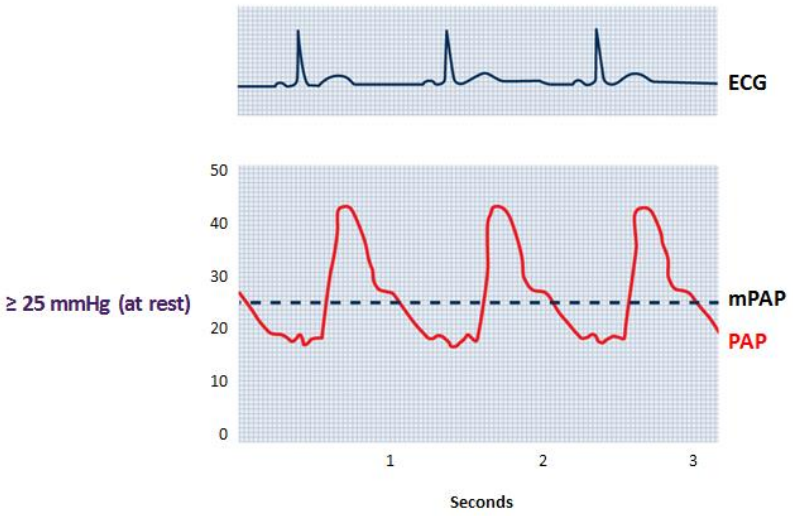
Definition of Pulmonary Hypertension

Pulmonary Hypertension

Mean PAP ≥ 25 mmHg at rest by right heart catheterization (RHC)

Pulmonary Arterial Hypertension (PAH)

Mean PAP ≥ 25 mmHg at rest by RHC + PCWP/LVEDP ≤ 15 mmHg + Pulmonary vascular Resistance > 3 Wood units (240 dynes·sec·cm^{-5})

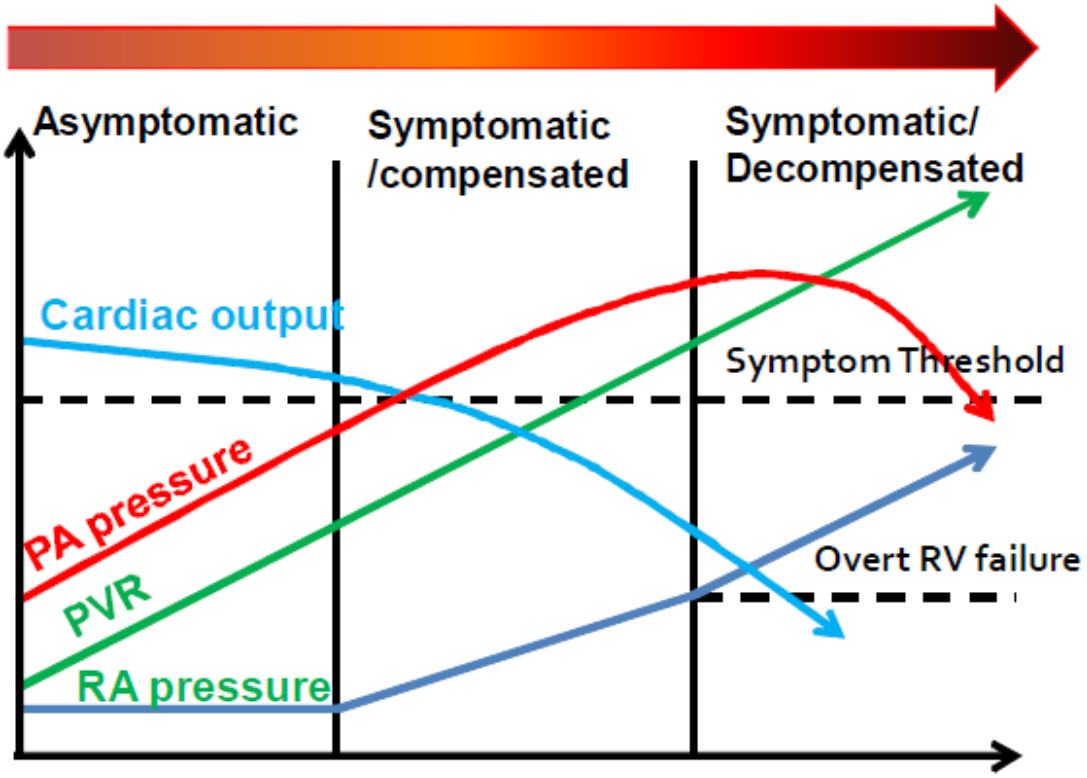


PVR = (meanPAP – PCWP)/Cardiac Output

meanPAP = PVR x Cardiac Output + PCWP

J Am Coll Cardiol. 2013;62:D42-50
Eur Heart J 2016;37:67-119

Hemodynamic change of PAH

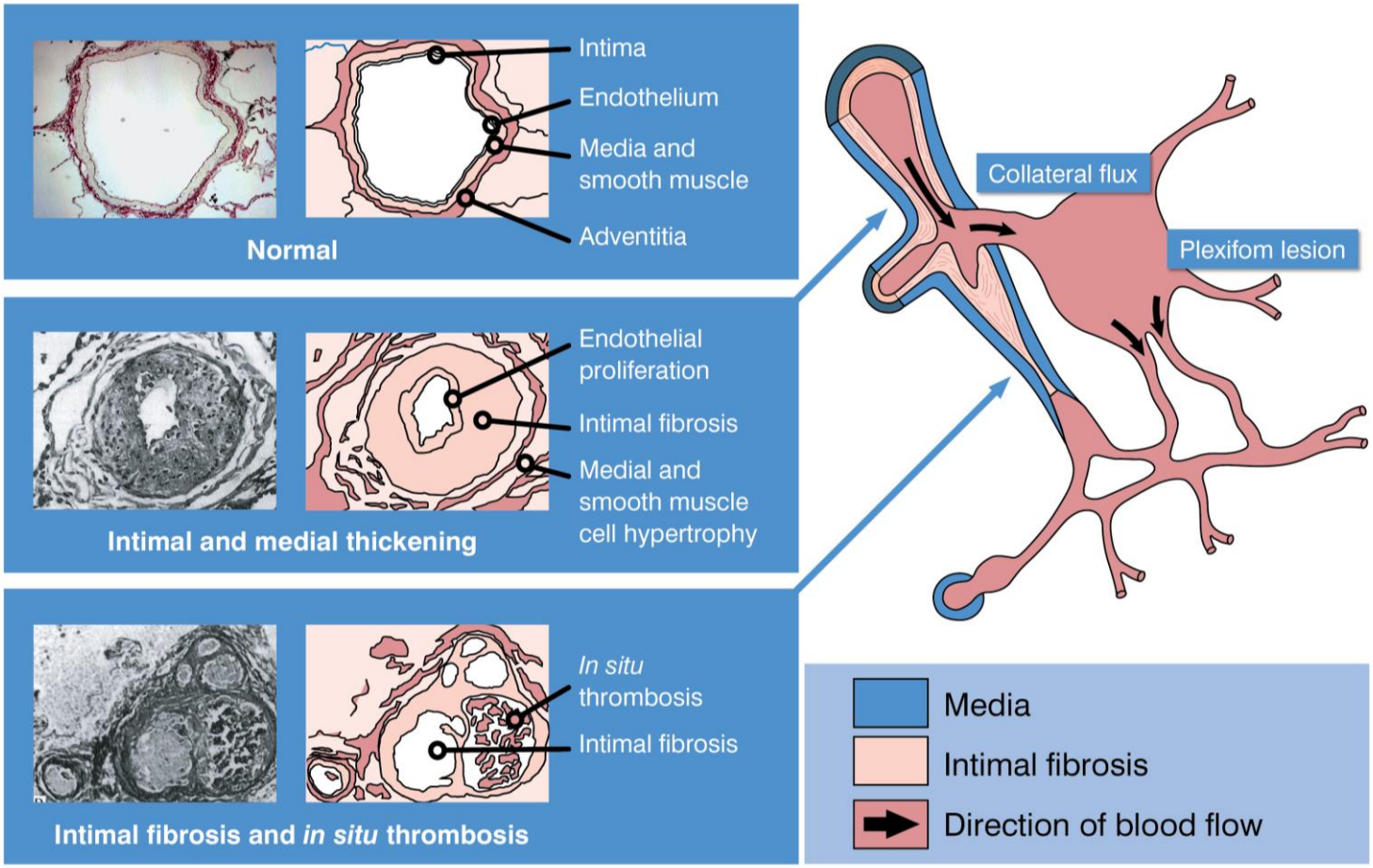


▶ 폐동맥압 : 심박출량이 유지되는 동안에는 폐 혈관저항이 증가함에 따라 함께 증가
→ decompensated heart failure 단계에 다다르면, 폐동맥압력도 함께 저하
→ 진행된 폐동맥고혈압 환자에서 치료효과의 판정기준이 되지 못하며, 예후와의 연관성 희박

▷ **심박출량, 폐혈관저항, 우심실의 기능저하** : 환자의 상태를 평가하는데 매우 중요한 요소

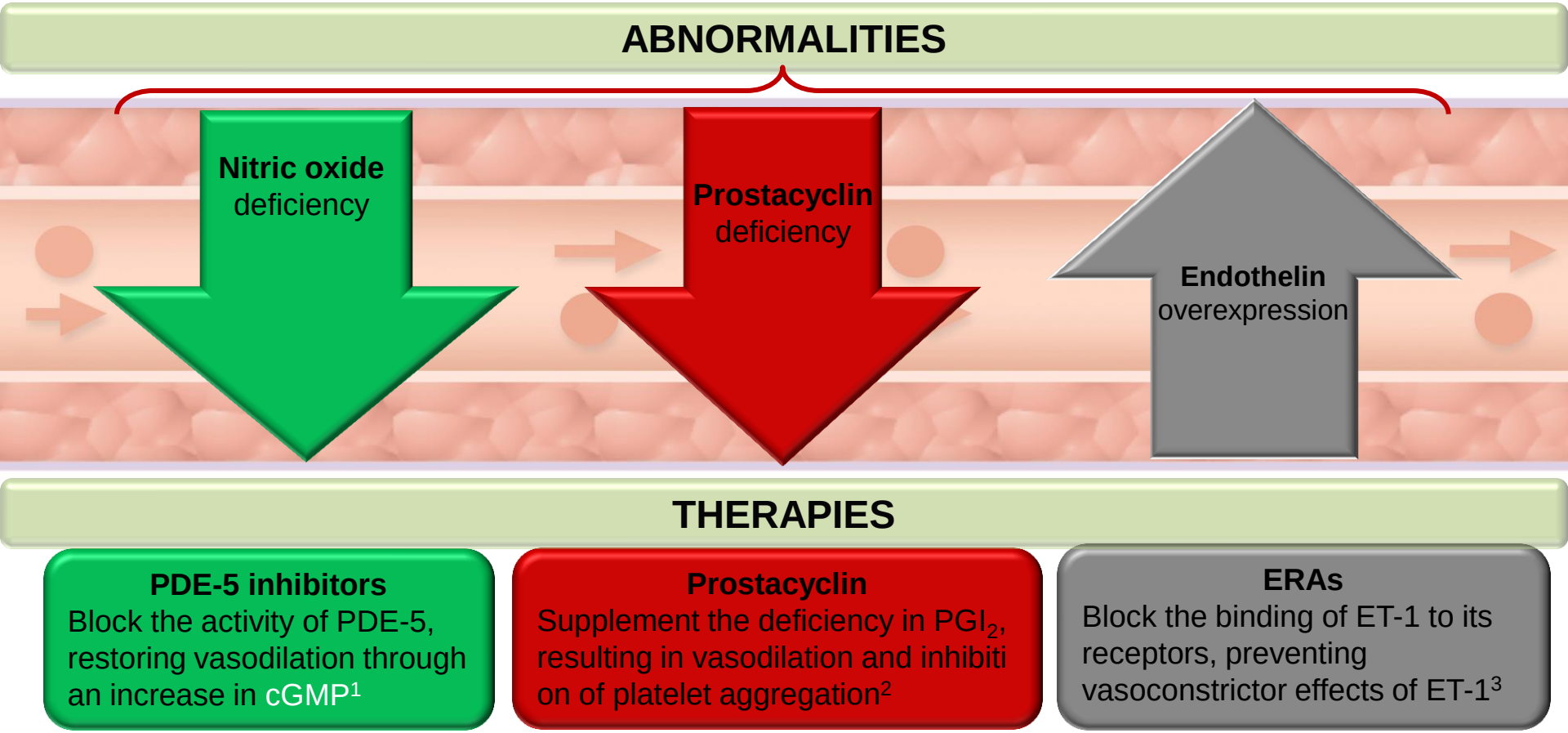
The Korean Journal of Medicine: Vol. 78, No. 1, 2010

Changes in the pulmonary arteries in PAH
- histopathological features



Eur Heart J 2009;30:2493–537

Vasoactive Mediators Involved in PAH



cGMP, cyclic guanosine monophosphate; ERA, endothelin receptor antagonist; ET-1, endothelin; PDE-5, phosphodiesterase type 5; PGI_2, prostacyclin.

1. *Humbert et al. J Am Coll Cardiol. 2004;43(suppl S):13S-24S.* ***2.*** *Humbert et al. N Engl J Med. 2004;351:1425-1436.*
3. *Galiè et al. Eur Heart J. 2004;25:2243-2278.*

European Heart Journal (2016) **37**, 67–119
doi:10.1093/eurheartj/ehv317

ESC/ERS GUIDELINES

2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension

The Joint 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: Association for European Paediatric and Congenital ciety for Heart and Lung

Classes of recommendations	Definition	Suggested wording to use
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.	Is recommended/is indicated
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.	
Class IIa	*Weight of evidence/opinion is in favour of usefulness/efficacy.*	Should be considered
Class IIb	*Usefulness/efficacy is less well established by evidence/opinion.*	May be considered
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.	Is not recommended

Level of evidence A	Data derived from multiple randomized clinical trials or meta-analyses.
Level of evidence B	Data derived from a single randomized clinical trial or large non-randomized studies.
Level of evidence C	Consensus of opinion of the experts and/ or small studies, retrospective studies, registries.

European Heart Journal. 2016;37:67-119.

Diagnostic Classification (NICE 2013)

1. Pulmonary arterial hypertension (PAH)

- **1.1. Idiopathic PAH (IPAH)**
- **1.2. Heritable (HPAP)**
  - 1.2.1. BMPR2
  - 1.2.2. ALK1, ENG, SMAD9, CAV1, KCNK3
  - 1.2.3. Unknown
- **1.3. Drug- and toxin-induced**
- **1.4. Associated with (APAH)**
  - 1.4.1. Connective tissue diseases (CTD)
  - 1.4.2. HIV infection
  - 1.4.3. Portal hypertension
  - 1.4.4. Congenital heart diseases
  - 1.4.5. Schistosomiasis
- 1’ Pulmonary veno-occlusive disease and/or Pulmonary capillary hemangiomatosis
- 1’’ Persistent PH of the newborn

2. PH 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

3. PH due to lung diseases and/or hypoxemia

- 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

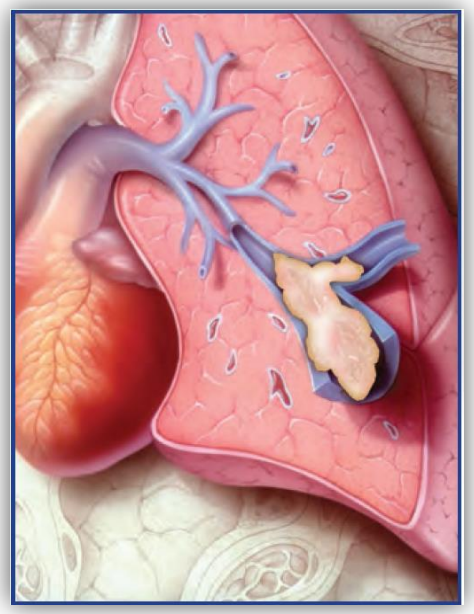
4. Chronic thromboembolic PH

5. PH with unclear multifactorial mechanisms

- 5.1. Hematologic disorders: chronic hemolytic anemia, 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: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, segmental PH

Simonneau G, et al. J Am Coll Cardiol. 2013;62(25 Suppl):D34-41.

Chronic Thromboembolic Pulmonary Hypertension (CTEPH)



- **Defining CTEPH**

  → After 3 months of therapeutic anticoagulation

  • mPAP ≥ 25 mmHg

  • Persistent perfusion defect(s) with chronic/organized occlusive thrombi/emboli

- The obstruction of pulmonary arteries with fibrotic material and vascular remodelling that leads to increased pulmonary arterial pressure and right ventricular failure.

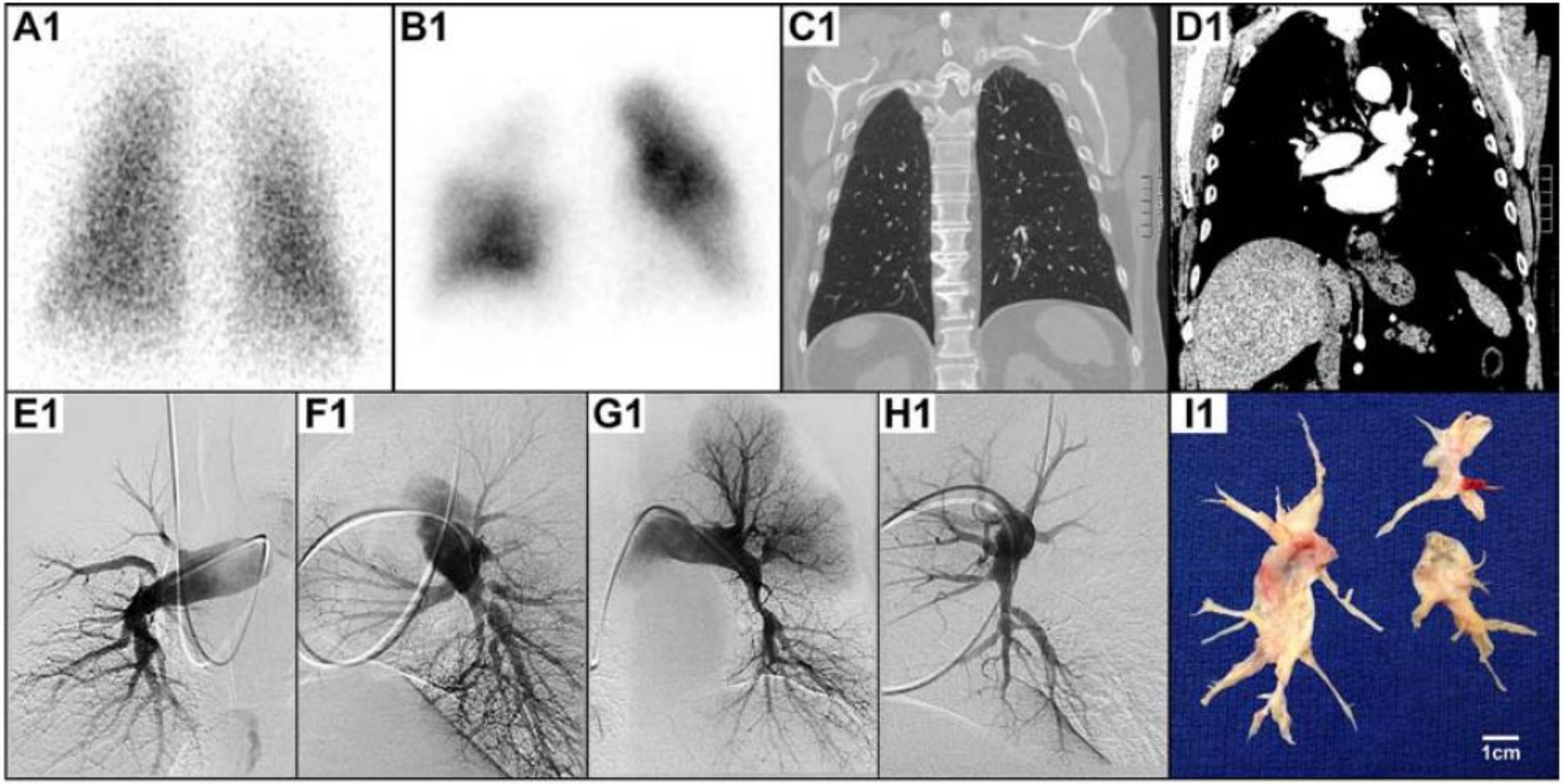
- CTEPH is thought to develop following a pulmonary embolism (PE) that fails to resolve in between 0.57% and 9.1% of patients.

Eur Respir Rev 2012; 21: 123, 27–31

Ventilation/perfusion lung scan should be performed to screen CTEPH.

Pulmonary Angiogram is required for the workup of CTEPH.

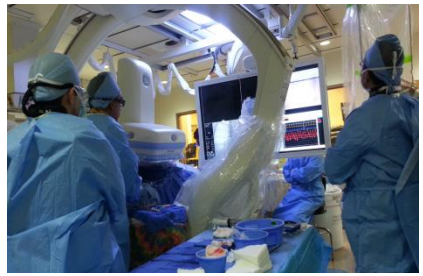
Pulmonary endarterectomy (PEA) is the treatment of choice.

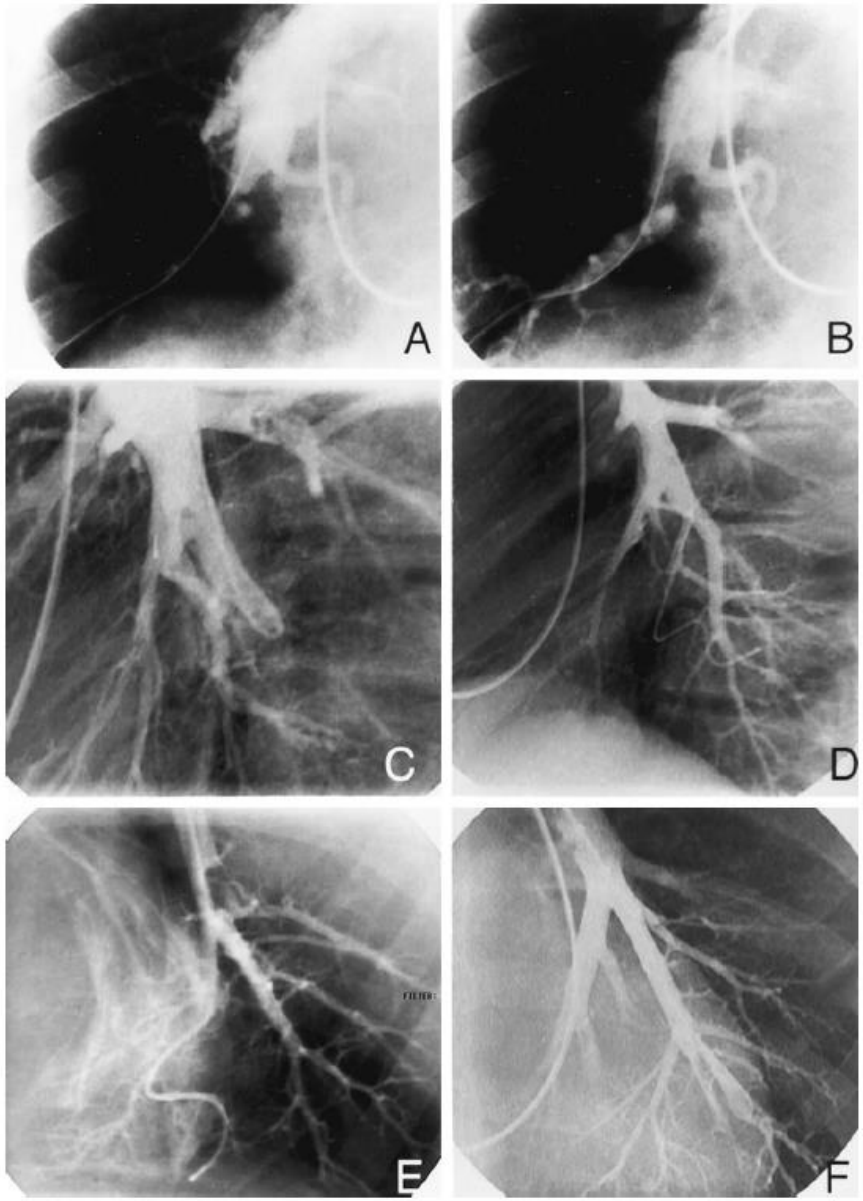


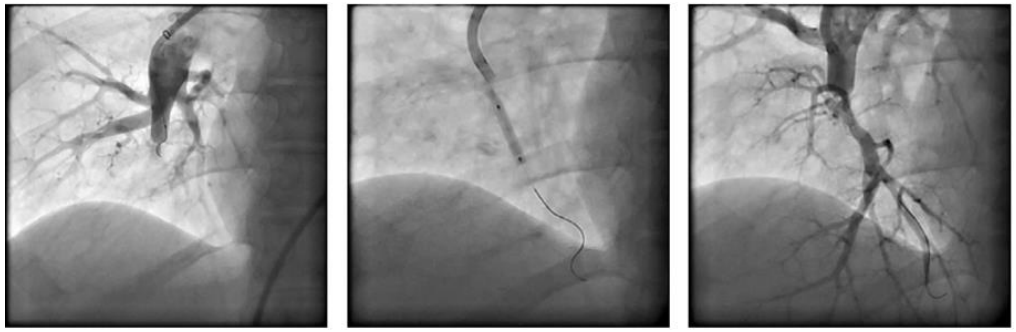
Stenosis, Cutoff **Narrowing**

Circulation. 2014;130:508-518

Balloon Pulmonary Angioplasty (BPA) in CTEPH





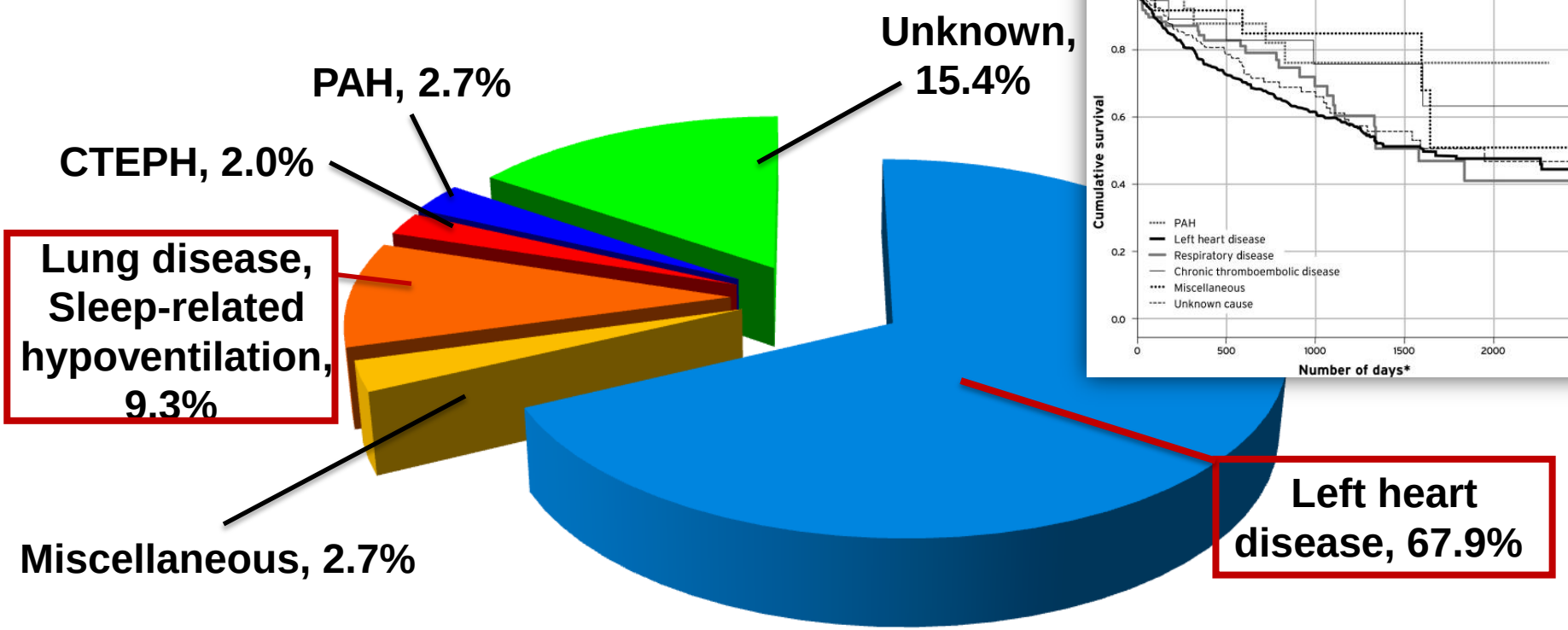


- Angiographic appearance of occluded (A, C), and stenotic (E) lower lobe pulmonary artery segmental branches.
- They are horizontally paired with angiograms performed immediately after successful BPA (B, D, and F).

Circulation. 2001;103:10-13

Epidemiology of Pulmonary Hypertension

- Single echo lab / Australian community of 165,450
- Etiology of PH noted on echocardiogram
- ~10% of patients had estimated sPAP>40 mm Hg
  - Only 2.7% with PAH after full evaluation



N=936 of 10,314 patients with echo PASP >40 mm Hg.
Strange G et al. *Heart*. 2012;98:1805-1811.

PH in Chronic Lung Diseases

Underlying Lung Disease	mPAP <25 mm Hg at Rest	mPAP ≥25 and <35 mm Hg at Rest	mPAP ≥35 mm Hg at Rest*
COPD with FEV1 ≥60% of predicted IPF with FVC ≥70% of predicted CT: absence of or only very modest airway or parenchymal abnormalities	No PH No PAH treatment recommended	PH classification uncertain No data currently support treatment with PAH-approved drugs	PH classification uncertain: discrimination between PAH (group 1) with concomitant lung disease or PH caused by lung disease (group 3) Refer to a center with expertise in both PH and chronic lung disease
COPD with FEV1 <60% of predicted IPF with FVC <70% of predicted Combined pulmonary fibrosis and emphysema on CT	No PH No PAH treatment recommended	PH-COPD, PH-IPF, PH-CPFE No data currently support treatment with PAH-approved drugs	Severe PH-COPD, severe PH-IPF, severe PH-CPFE Refer to a center with expertise in both PH

COPD/IPF/CPFE without PH

COPD/IPF/CPFE with PH

COPD/IPF/CPFE with severe PH

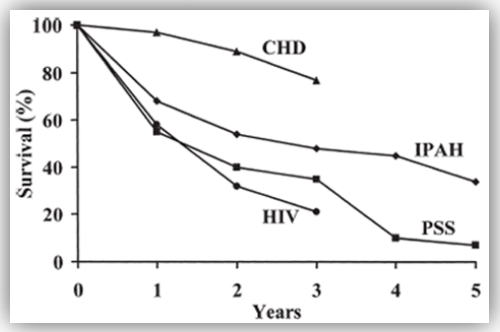
Key Points
Group III PH is Generally Associated with Mild to Moderate Elevations in mPAP
The presence of group III PH is correlated with worse functional status and outcomes
Treatment should be aimed at optimization of the underlying pulmonary condition along with oxygen therapy, pulmonary rehabilitation, diuretics and vaccinations
There is limited data to support the use of pulmonary vasodilator therapy for group III PH

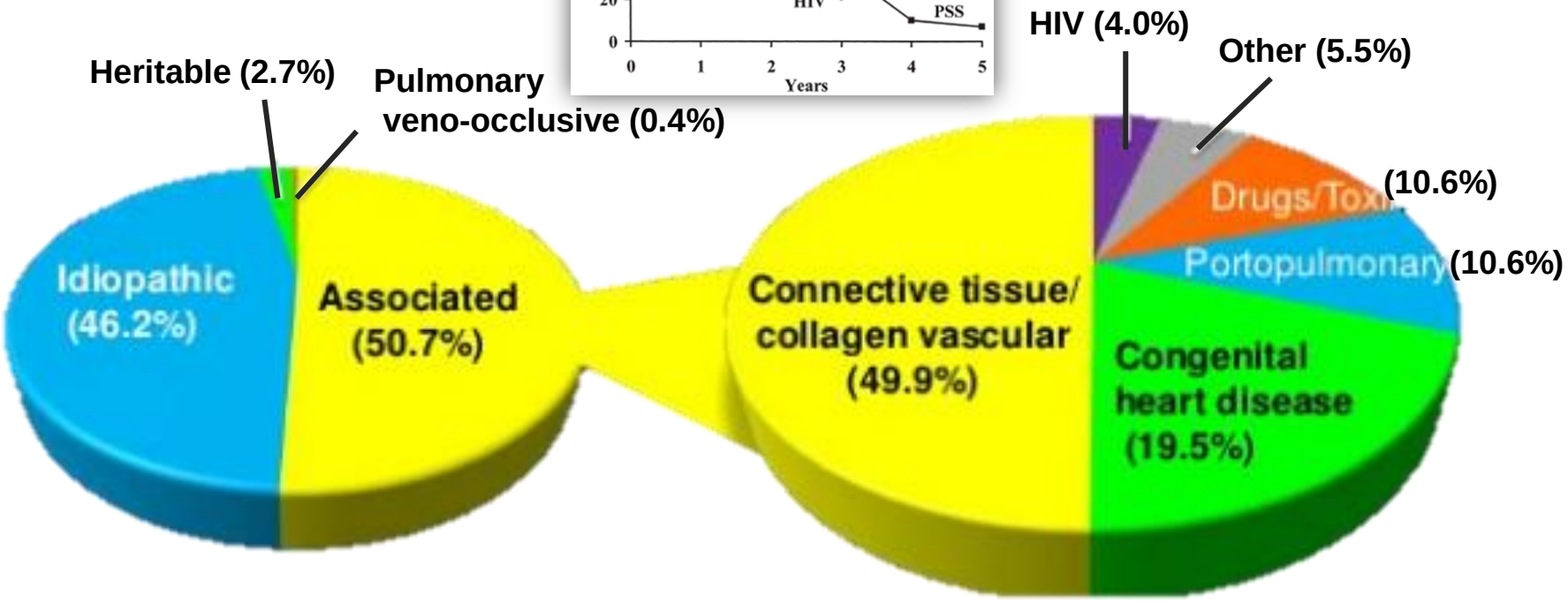
J. Clin. Med. 2016, 5, 75; doi:10.3390/jcm5090075
JAmColl Cardiol 2013;62:D109–16

Epidemiology of PAH from REVEAL Registry

Prevalence : 15 cases/1 million, Incidence : 2.4/1 million

N = 2525
Mean age = 53 years old
Female = 79.5% population



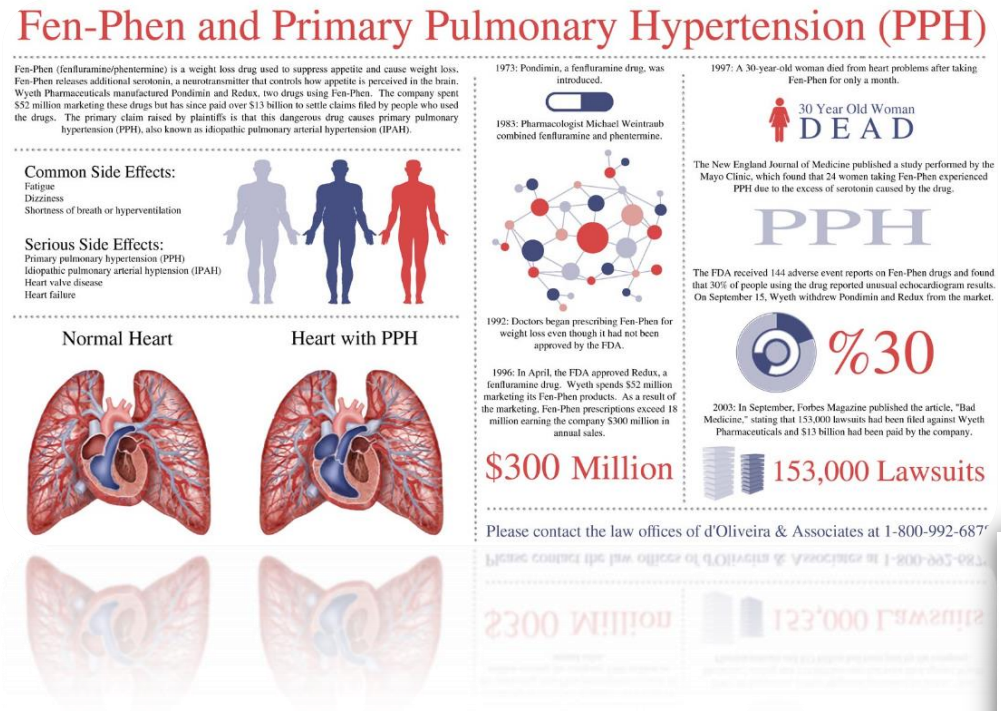


CHEST 2010; 137(2):376–387
Semin Respir Crit Care Medicine 2005

WHO group I (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 disease (Table 6)
1.4.5 Schistosomiasis
1'. Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis
1'.1 Idiopathic
1'.2 Heritable
1'.2.1 EIF2AK4 mutation
1'.2.2 Other mutations
1'.3 Drugs, toxins and radiation induced
1'.4 Associated with:
1'.4.1 Connective tissue disease
1'.4.2 HIV infection

Drug/Toxins known to induced PAH



Definite	Likely	Possible
• Aminorex • Fenfluramine • Dexfenfluramine • Toxic rapeseed oil • Benfluorex • Selective serotonin reuptake inhibitors[a]	• Amphetamines • Dasatinib • L-tryptophan • Methamphetamines	• Cocaine • Phenylpropanolamine • St John's Wort • Amphetamine-like drugs • Interferon α and β • Some chemotherapeutic agents such as alkylating agents (mytomycine C, cyclophosphamide)[b]

Eur Heart J 2016;37:67-119

Clinical classification of PAH associated with congenital heart disease

1. Eisenmenger's syndrome

Includes all large intra- and extra-cardiac defects which begin as systemic-to-pulmonary shunts and progress with time to severe elevation of PVR and to reversal (pulmonary-to-systemic) or bidirectional shunting; cyanosis, secondary erythrocytosis, and multiple organ involvement are usually present.

2. PAH associated with prevalent systemic-to-pulmonary shunts

- Correctable[a]
- Non-correctable

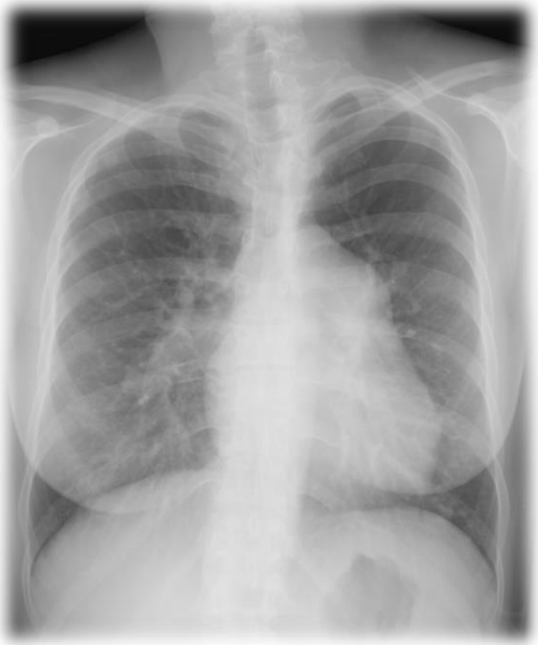
Includes moderate to large defects; PVR is mildly to moderately increased, systemic-to-pulmonary shunting is still prevalent, whereas cyanosis at rest is not a feature.

3. PAH with small/coincidental defects[b]

Marked elevation in PVR in the presence of small cardiac defects (usually ventricular septal defects <1 cm and atrial septal defects <2 cm of effective diameter assessed by echo), which themselves do not account for the development of elevated PVR; the clinical picture is very similar to idiopathic PAH. Closing the defects is contra-indicated.

4. PAH after defect correction

Congenital heart disease is repaired, but PAH either persists immediately after correction or recurs/develops months or years after correction in the absence of significant postoperative haemodynamic lesions.



Impressions/Diagnoses:
1) PAH/CHD - Eisenmenger's
2) NYHAC III
3) Secondary polycythemia

Eur Heart J 2016;37:67-119

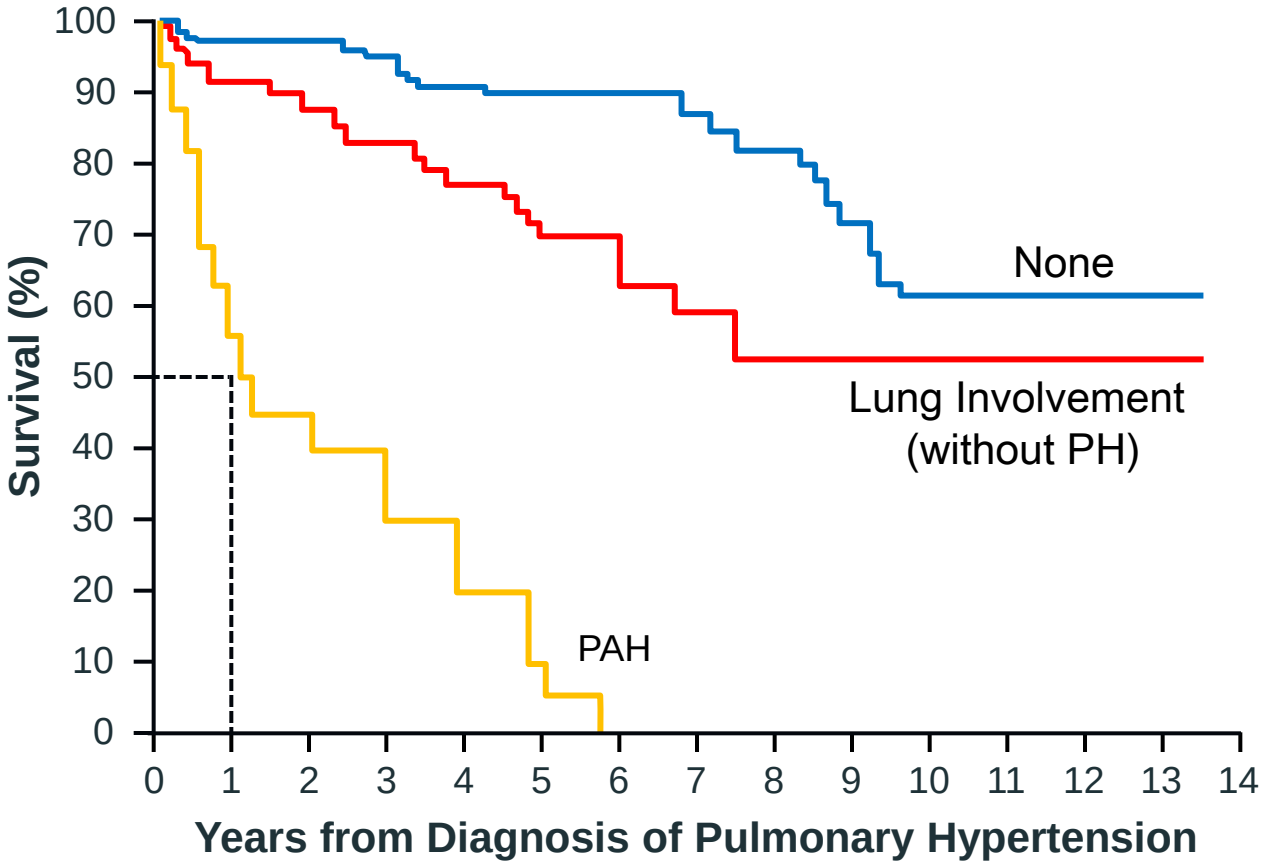
Epidemiology of PAH from Korean PAH Registry

Parameters	All patients	IPAH	All patients with APAH	*P* value	APAH subgroup		
					CHD	CTD	Other
Patients, No. (%)	625 (100)	145 (23.2)	480 (76.8)		159 (25.4)	311 (49.8)	10 (1.6)
Age, mean ± SD (yr)	47.6 ± 15.7	45.1 ± 15.7	48.4 ± 15.7	0.027	41.1 ± 13.4	52.2 ± 15.6	47.7 ± 10.0
19-64, No. (%)	513 (82.1)	121 (83.5)	392 (81.7)	NS	149 (93.7)	233 (74.9)	10 (100)
65-74, No. (%)	74 (11.8)	18 (12.4)	56 (11.7)		8 (5.0)	48 (15.4)	-
> 75, No. (%)	38 (6.1)	6 (4.1)	32 (6.7)		2 (1.3)	30 (9.7)	-
Female, No. (%)	503 (80.5)	106 (73.1)	397 (82.7)	0.011	116 (73.0)	274 (88.1)	7 (70.0)
Functional class, No. (%)				< 0.001			
I	136 (21.8)	5 (3.5)	131 (27.3)		9 (5.7)	121 (38.9)	1 (10.0)
II	218 (34.9)	48 (33.1)	170 (35.4)		71 (44.7)	96 (30.9)	3 (30.0)
III	240 (38.4)	82 (56.6)	158 (32.9)		76 (47.8)	77 (24.8)	5 (50.0)
IV	31 (5.0)	10 (6.9)	21 (4.4)		3 (1.9)	17 (5.5)	1 (10.0)
Systolic BP (mean ± SD)	114 ± 16.8	116 ± 17.6	113 ± 16.1	NS	113 ± 14.8	111 ± 18.3	118 ± 21.3
BNP (pg/mL)	516 ± 1,093	465 ± 1,001	562 ± 1,176	NS	645 ± 1,423	362 ± 444	871 ± 662
NT proBNP (pg/mL)	2,798 ± 6,375	2,192 ± 3,244	2,876 ± 6,673	NS	1,900 ± 5,047	3,234 ± 7,152	687 ± 978
6MWD (mean ± SD, m)	376 ± 124	398 ± 116	364 ± 127	NS	382 ± 119	347 ± 133	277 ± 162
D_{LCO} (%)	64.1 ± 24.3	74.1 ± 20.7	59.3 ± 24.5*	< 0.001	95.1 ± 34.5	56.3 ± 20.9	52.2 ± 22.5

The incidence of systemic lupus erythematosus (SLE) (35.3%) was comparable to that of systemic sclerosis (SSc) (28.3%) in CTD-PAH.

J Korean Med Sci 2015; 30: 1429-1438

Survival Curves of Scleroderma Patients Based on Organ Involvement



Koh et al. Brit J Rheumatol. 1996;35:989-993.

Pulmonary Veno-Occlusive Disease

- Preferentially affects the **post-capillary venous pulmonary vessels** and may include significant pulmonary capillary dilatation/proliferation.
- The pathologic hallmark of PVOD is the **extensive and diffuse occlusion of pulmonary veins by fibrous tissue.**

Pulmonary Hypertension

Pulmonary edema (with specific PAH therapy)

Low PaO_2, low DLCO/VA

Chest X-Ray, HRCT of the chest (ground-glass or centrilobular opacities, septal lines, lymph nodes enlargement)

Broncho-alveolar lavage: occult alveolar hemorrage

↓

PVOD — Lung biopsy usually not possible *(high-risk procedure)*

↓

PAH basic therapy

O2, Warfarin, diuretics

↓

NYHA Functional Class III, IV

↓

Consider

PAH specific therapy under close medical monitoring

Lung transplantation if eligible

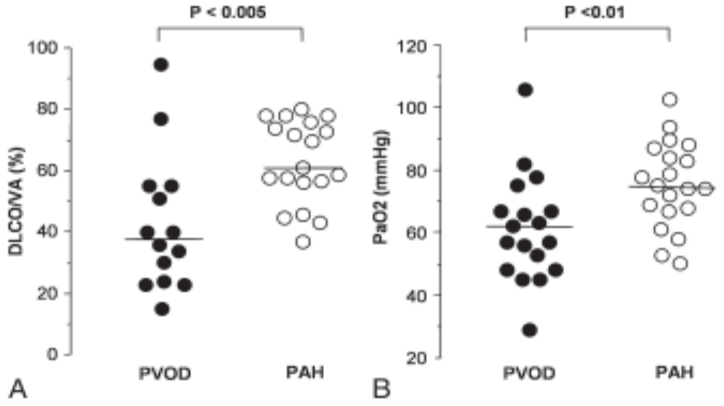


FIGURE 3. Pulmonary function tests. DLCO/VA and PaO2 in patients with PVOD (black circles) and PAH (white circles). **A.** DLCO/VA (%) was significantly lower in patients with PVOD compared with patients with idiopathic or familial PAH. **B.** PaO2 (mm Hg) was significantly lower in patients with PVOD compared with patients with idiopathic or familial PAH.

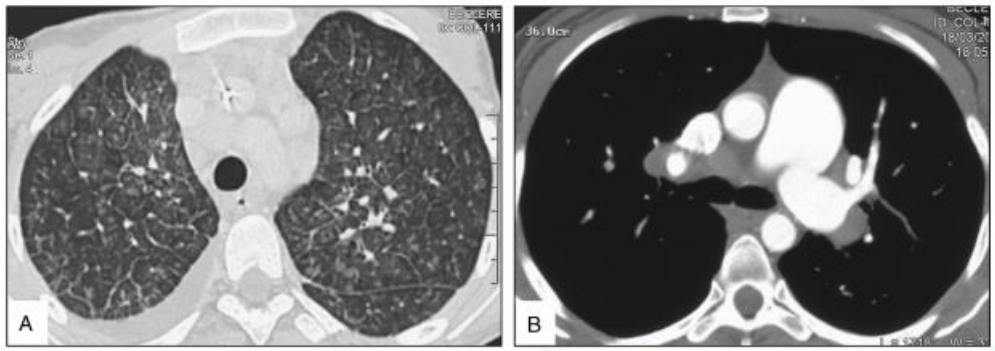


FIGURE 4. High-resolution CT of the chest in PVOD. **A.** High-resolution CT of the chest showing marked ground-glass opacities with centrilobular pattern, poorly defined nodular opacities, septal lines, and minimal right pleural effusion. **B.** High-resolution CT of the chest showing mediastinal lymph node enlargement.

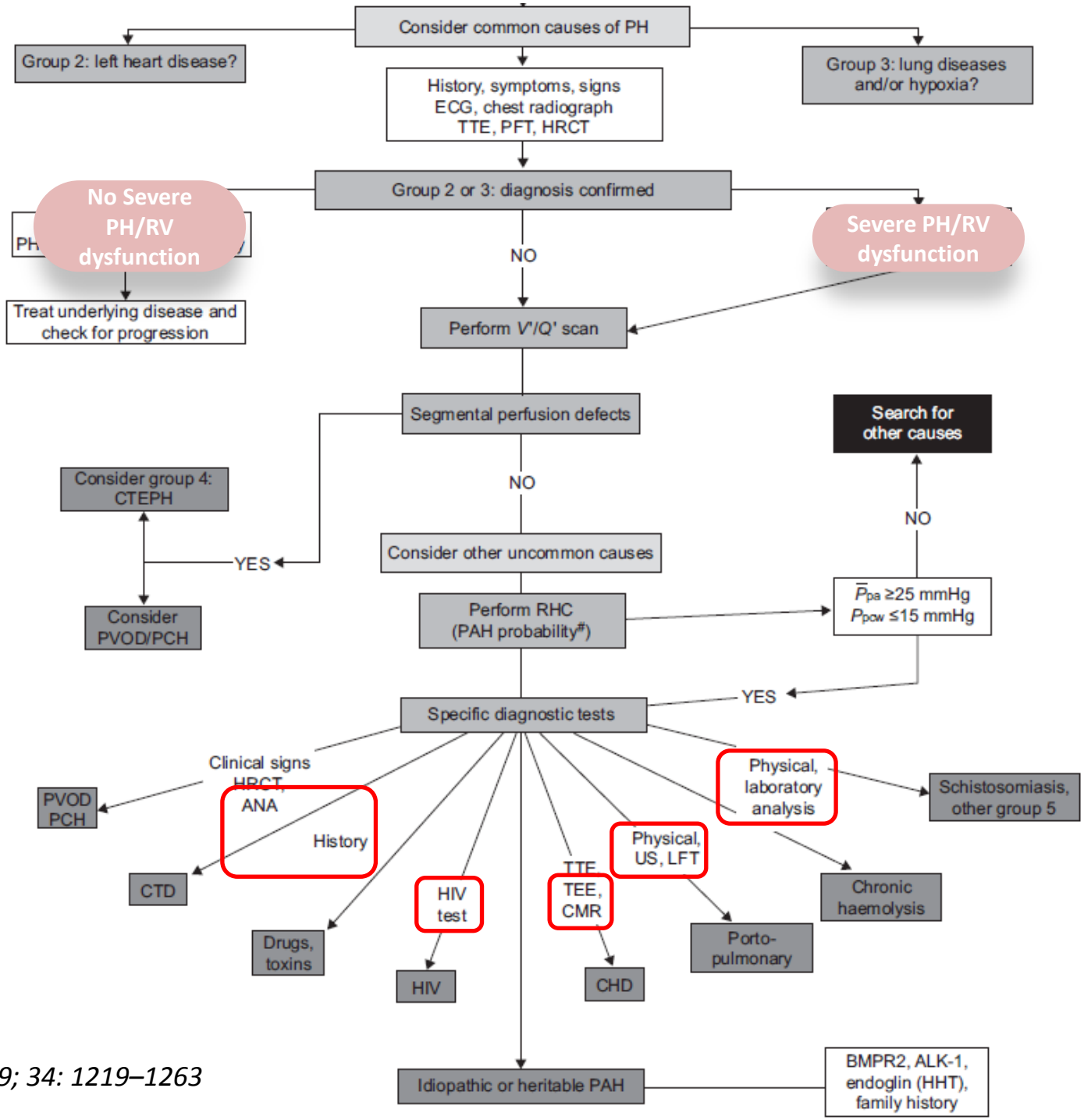
Medicine 2008;87:220–233

Diagnosis and Assessment of Pulmonary Arterial Hypertension

Four stage approach to diagnosis of PAH

- Stage 1 ; Clinical suspicion & Screening of PH with Echo
  - Symptoms, known risk factors
- Stage 2 ; Exclude other causes of PH
  - **Exclusion of Group 2 (left heart disease) and Group 3 (lung disease) PH** : ECG, echocardiography, chest radiograph, PFTs, HRCT, PSG with overnight oxymetry
  - **Exclusion of Group 4 (CTEPH) PH** : ventilation/perfusion lung scan
- Stage 3 ; Confirm PAH right heart catheterisation (RHC)
- Stage 4 ; Characterize PAH
  - Cardiac MRI, haematology, biochemistry, serology, and ultrasonography
  - Functional class and exercise capacity

Galiè N, et al. *Eur Heart J* 2009;30:2493–537



Eur Respir J 2009; 34: 1219–1263

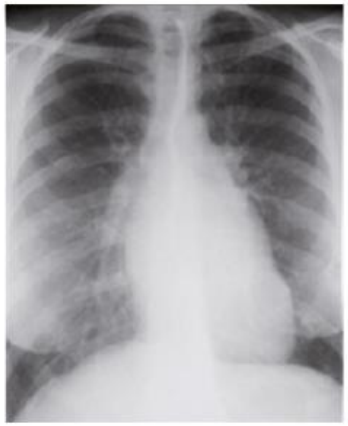
Stage 1: Diagnosis of PH

Clinical suspicion of pulmonary hypertension

- progressive dyspnea on exertion (>90%)
- fatigue, angina, syncope (mostly exercise-induced)
- signs of right heart failure (abdominal distension and ankle edema)
- Screening of patients with associated conditions
  - -- Connective Tissue Disease (systemic sclerosis)
  - -- Congenital Heart Disease
  - -- HIV, Sickle Cell Disease, portal hypertension

Detection of pulmonary hypertension

- Chest radiograph
- ECG (p-pulmonale, Rt axis deviation, RBBB)
- Doppler echocardiography
- Early clues for PH : BNP, low paCO2



PAH with evidence of cardiomegaly and enlarged pulmonary arteries

Recommendations for PAH screening

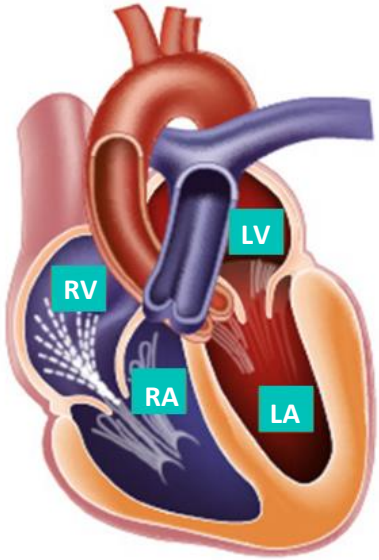
Recommendations	Class [a]	Level [b]
Resting echocardiography is recommended as a screening test in asymptomatic patients with systemic sclerosis.	I	B
Resting echocardiography is recommended as a screening test in *BMPR2* mutation carriers or first-degree relatives of patients with HPAH and in patients with PoPH referred for liver transplantation.	I	C
A combined approach (including biomarkers, PFTs and echocardiography) should be considered to predict PH in systemic sclerosis.	IIa	B
Systemic sclerosis patients with a mean PAP ranging from 21 to 24 mmHg should be closely monitored, because of a higher risk of PAH.	IIa	B
Initial screening using the stepwise DETECT algorithm may be considered in adult systemic sclerosis patients with >3 years' disease duration and a DLCO <60% predicted.	IIb	B
Annual screening with echocardiography, PFTs and biomarkers may be considered in patients with systemic sclerosis.	IIb	B
In individuals who test positive for PAH-causing mutations and first-degree relatives of HPAH cases may be considered to have an annual screening echocardiogram.	IIb	C
Exercise echocardiography is not recommended to predict PH in high risk population.	III	C

Web addenda

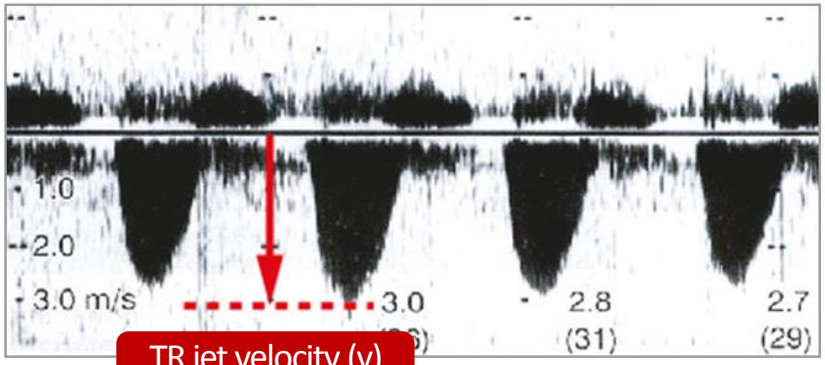
European Heart Journal doi:10.1093/eurheartj/ehv317

Stage 1: Diagnosis of PH

Tricuspid regurgitation by Doppler echo



Tricuspid regurgitation (TR)



Syst PAP = right ventricular systolic pressure
(in the absence of pulmonary outflow obstruction)

RVSP = $4v^2$ + estimated right atrial pressure

mPAP = 0.6 X sPAP + 2

Overestimation & underestimation of sPAP by Doppler echocardiography occurred

Echocardiographic Probability of PH in Symptomatic Patients With a Suspicion of PH

Peak Tricuspid Regurgitation Velocity (m/s)	Presence of Other Echocardiographic PH Signs*	Echocardiographic Probability of PH
≤2.8 or not measurable	No	Low
≤2.8 or not measurable	Yes	Intermediate
2.9 to 3.4	No	
2.9 to 3.4	Yes	High
>3.4	Not required	

*Other PH signs include the dimensions of the RV, the PA, and the IVC (see next slide)

Galiè N, et al. *Eur Heart J*. 2016;37:67-119.

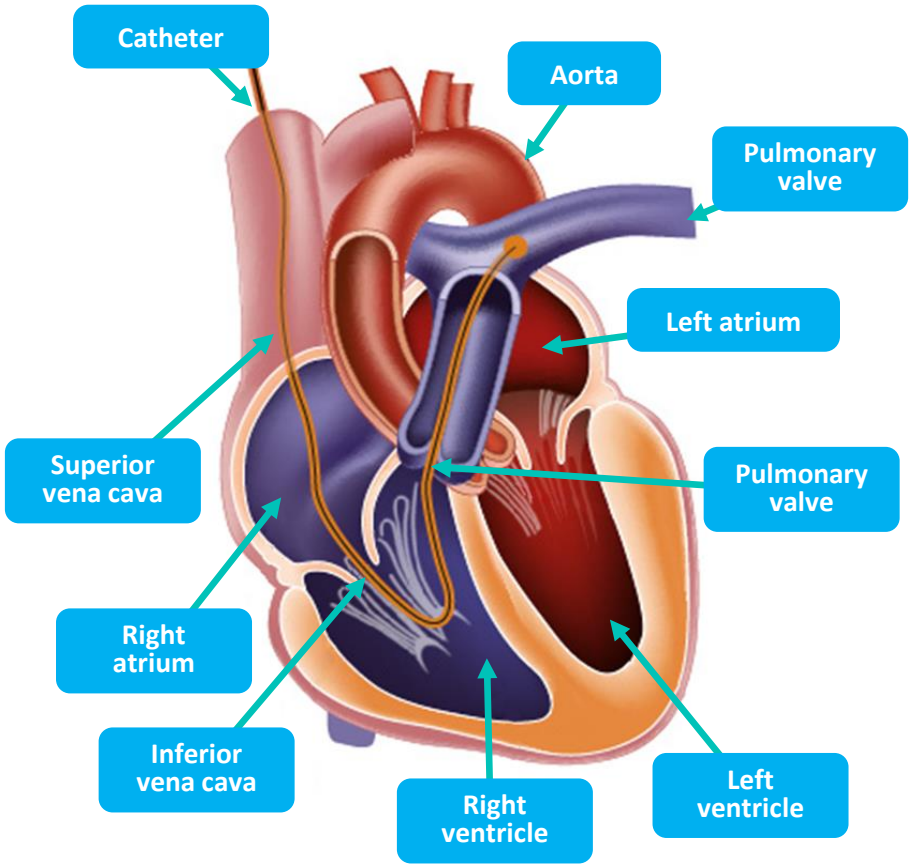
Other Echocardiographic PH signs

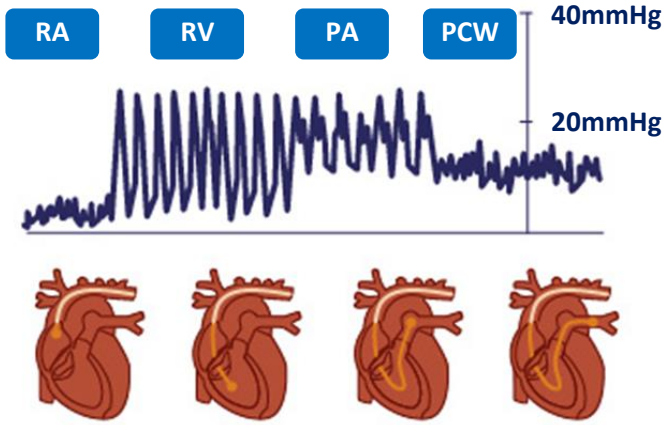
A: The ventricles[a]	B: Pulmonary artery[a]	C: Inferior vena cava and right atrium[a]
Right ventricle/ left ventricle basal diameter ratio >1.0	Right ventricular outflow Doppler acceleration time <105 msec and/or midsystolic notching	Inferior cava diameter >21 mm with decreased inspiratory collapse (<50 % with a sniff or <20 % with quiet inspiration)
Flattening of the interventricular septum (left ventricular eccentricity index >1.1 in systole and/or diastole)	Early diastolic pulmonary regurgitation velocity >2.2 m/sec	Right atrial area (end-systole) >18 cm^2
	PA diameter >25 mm.	

* Echocardiographic signs from at least two different categories (A/B/C) from the list should be present to alter the level of echocardiographic probability of PH.

Eur Heart J 2016;37:67-119

Stage 3: Confirm PAH
Right heart catheterization





Characteristic intracardiac pressure waveforms during passage through the heart

Galiè et al. *Eur Heart J* 2015

Hemodynamic definitions of PH as Assessed by RHC

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.

Eur Heart J 2016;37:67-119

Vasoreactivity testing

- **Agents for vasodilator testing**
  - Inhaled NO (10 → 20 ppm)
  - IV epoprostenol (2 → 12 ng/kg/min)
  - cf. IV adenosine, inhaled iloprost
- **Responder Criteria**
  - Fall in mPAP ≥ 10 mmHg
  - Absolute mPAP ≤ 40 mmHg

Drug	Route	Half-life	Dose range[d]	Increments[e]	Duration[f]	Class[a]	Level[b]
Nitric oxide	Inh	15–30 sec	10–20 ppm	-	5 min[g]	I	C
Epoprostenol	i.v.	3 min	2–12 ng/kg/min	2 ng/kg/min	10 min	I	C
Adenosine	i.v.	5–10 sec	50–350 µg/kg/min	50 µg/kg/min	2 min	IIa	C
Iloprost	Inh	30 min	5–20 µg	-	15 min	IIb	C

Galie N, et al. Eur Respir J. 2015;46:903-975.
European Heart Journal doi:10.1093/eurheartj/ehv317

Web addenda

Recommendations for vasoreactivity testing

Recommendations	Class[a]	Level[b]
Vasoreactivity testing is indicated only in expect centres	I	C
Vasoreactivity testing is recommended in patients with **IPAH, HPAH and PAH associated with drugs** use to detect patients who can be treated with high doses of a CCB	I	C
A positive response to vasoreactivity testing is defined as a reduction of mean PAP ≥ 10 m mHg to reach an absolute value of mean PAP ≤ 40mmHg with an increased or unchanged cardiac output	I	C
Nitric oxide is recommended for performing vasoreactivity testing	I	C
Intravenous epoprostenol is recommended for performing vasoreactivity testing as an altern ative	I	C
Adenosine should be considered for performing vasoreactivity testing as an alternative	IIa	C
Inhaled iloprost may be considered for performing vasoreactivity testing as an alternative	IIb	C
The use of oral or intravenous CCBs in acute vasoreactivity testing is not recommended	III	C
Vasoreactivity testing to detect patients who can be safety treated with high doses of a CCB is not recommended in patients with PAH other than IPAH, HPAH and PAH associated with drugs use and is not recommended in PH groups 2,3,4 and 5	III	C

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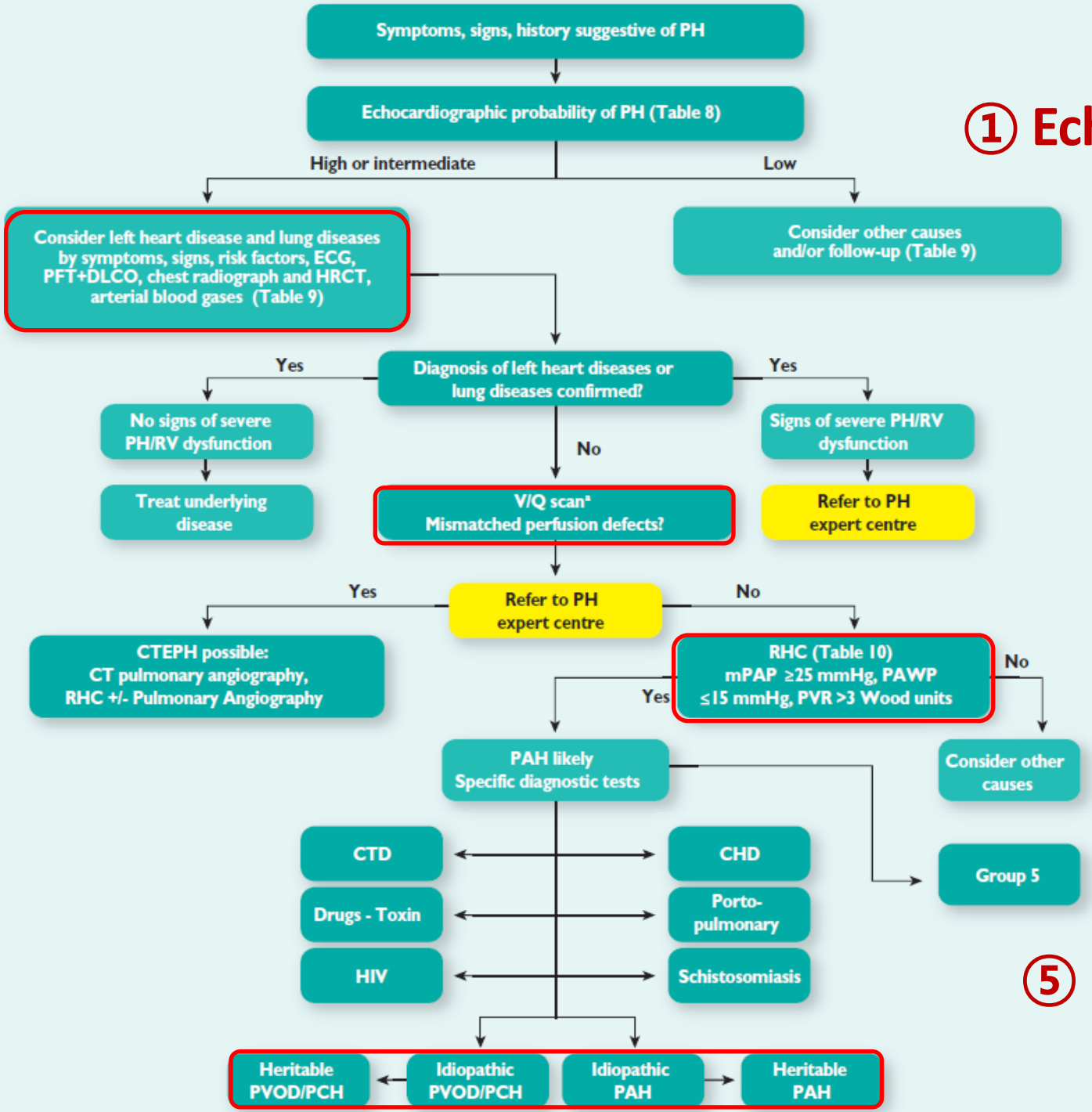


① Echocardiography

② Heart or Lung disease?

③ CTEPH?

④ RHC +-Angiogram

⑤ Classification

Eur Heart J 2016;37:67-119

Evaluation of severity : WHO Functional class

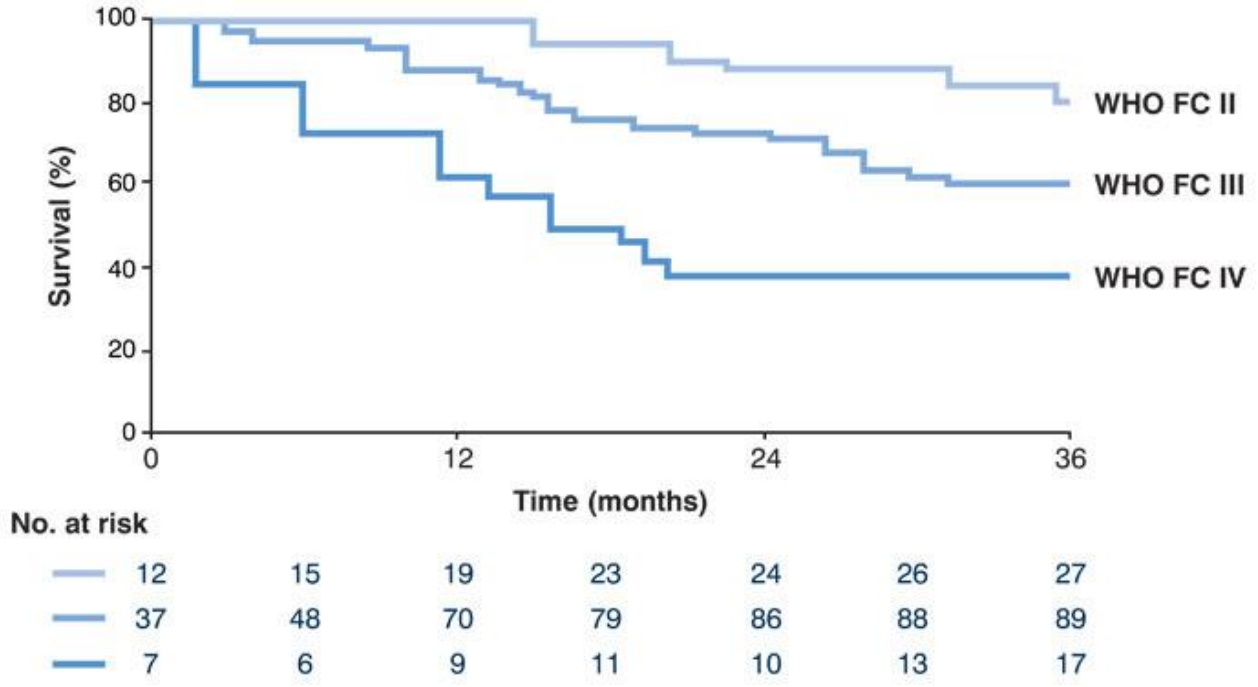
Functional Class	Symptomatic profile
I	Patients with pulmonary hypertension but without resulting limitation of physical activity. Ordinary physical activity does not cause dyspnoea or fatigue, chest pain, or near syncope
II	Patients with pulmonary hypertension resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnoea or fatigue, chest pain, or near syncope
III	Patients with pulmonary hypertension resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnoea or fatigue, chest pain, or near syncope.
IV	Patients with pulmonary hypertension with inability to carry out any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnoea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity

Adapted from Galiè N, et al. *Eur Heart J* 2009;30:2493–537

Functional class and survival

- Even with advanced medical therapy, patients in WHO FC IV continue to have extremely poor survival rates.

Survival according to functional class[2]



Humbert M et al. Circulation 2010

Risk assessment for PAH
= Treatment Goal

Updated

Determinants of prognosis[a] (estimated 1-year mortality)	Low risk <5%	Intermediate risk 5–10%	High risk >10%
Clinical signs of right heart failure	Absent	Absent	Present
Progression of symptoms	No (slow)	Slow	Rapid
Syncope	No	Occasional syncope[b]	Repeated syncope[c]
WHO functional class	I, II	III	IV
6MWD	>440 m (500m)	165–440 m	<165 m (300m)
Cardiopulmonary exercise testing (added)	Peak VO_2 >15 ml/min/kg (>65% pred.) VE/VCO_2 slope <36	Peak VO_2 11–15 ml/min/kg (35–65% pred.) VE/VCO_2 slope 36–44.9	Peak VO_2 <11 ml/min/kg (<35% pred.) VE/VCO_2 slope ≥45
NT-proBNP plasma levels (value)	BNP <50 ng/l NT-proBNP <300 ng/l	BNP 50–300 ng/l NT-proBNP 300–1400 ng/l	BNP >300 ng/l NT-proBNP >1400 ng/l
Imaging (echocardiography, CMR imaging) (No TAPSE RA area added)	RA area <18 cm^2 No pericardial effusion	RA area 18–26 cm^2 No or minimal, pericardial effusion	RA area >26 cm^2 Pericardial effusion
Haemodynamics (added)	RAP <8 mmHg CI ≥2.5 l/min/m^2 SvO_2 >65%	RAP 8–14 mmHg CI 2.0–2.4 l/min/m^2 SvO_2 60–65%	RAP >14 mmHg CI <2.0 l/min/m^2 SvO_2 <60%

Eur Heart J 2016;37:67-119; 2. Eur Heart J 2009;30:2493-537.

Treatment of Pulmonary Arterial Hypertension

Diagnostic Classification (NICE 2013)

1. Pulmonary arterial hypertension (PAH)

- **1.1. Idiopathic PAH (IPAH)**
- **1.2. Heritable**
- 1.2.1. BMPR2
- 1.2.2. ALK1, ENG, SMAD9, CAV1, KCNK3
- 1.2.3. Unknown
- **1.3. Drug- and toxin-induced**
- **1.4. Associated with (APAH)**
- 1.4.1. Connective tissue diseases (CTD)
- 1.4.2. HIV infection
- 1.4.3. Portal hypertension
- 1.4.4. Congenital heart diseases
- 1.4.5. Schistosomiasis
- 1' Pulmonary veno-occlusive disease and/or Pulmonary capillary hemangiomatosis
- 1'' Persistent PH of the newborn

2. PH due to left heart disease

- 2.1. Left ventricular systolic dysfunction
- 2.2. ction
- 2.3.
- 2.4. nflow/ outflow tract obstruction and congenital cardiomyopathies

NO APPROVED PH-TARGETED THERAPY

3. PH due to lung diseases and/or hypoxemia

- 3.1. Chronic obstructive pulmonary disease
- 3.2.
- 3.3. mixed tern
- 3.4. Sleep-disordered breathing
- 3.5. Alveolar hypoventilation disorders
- 3.6. Chronic exposure to high altitude
- 3.7. Developmental lung diseases

NO APPROVED PH-TARGETED THERAPY

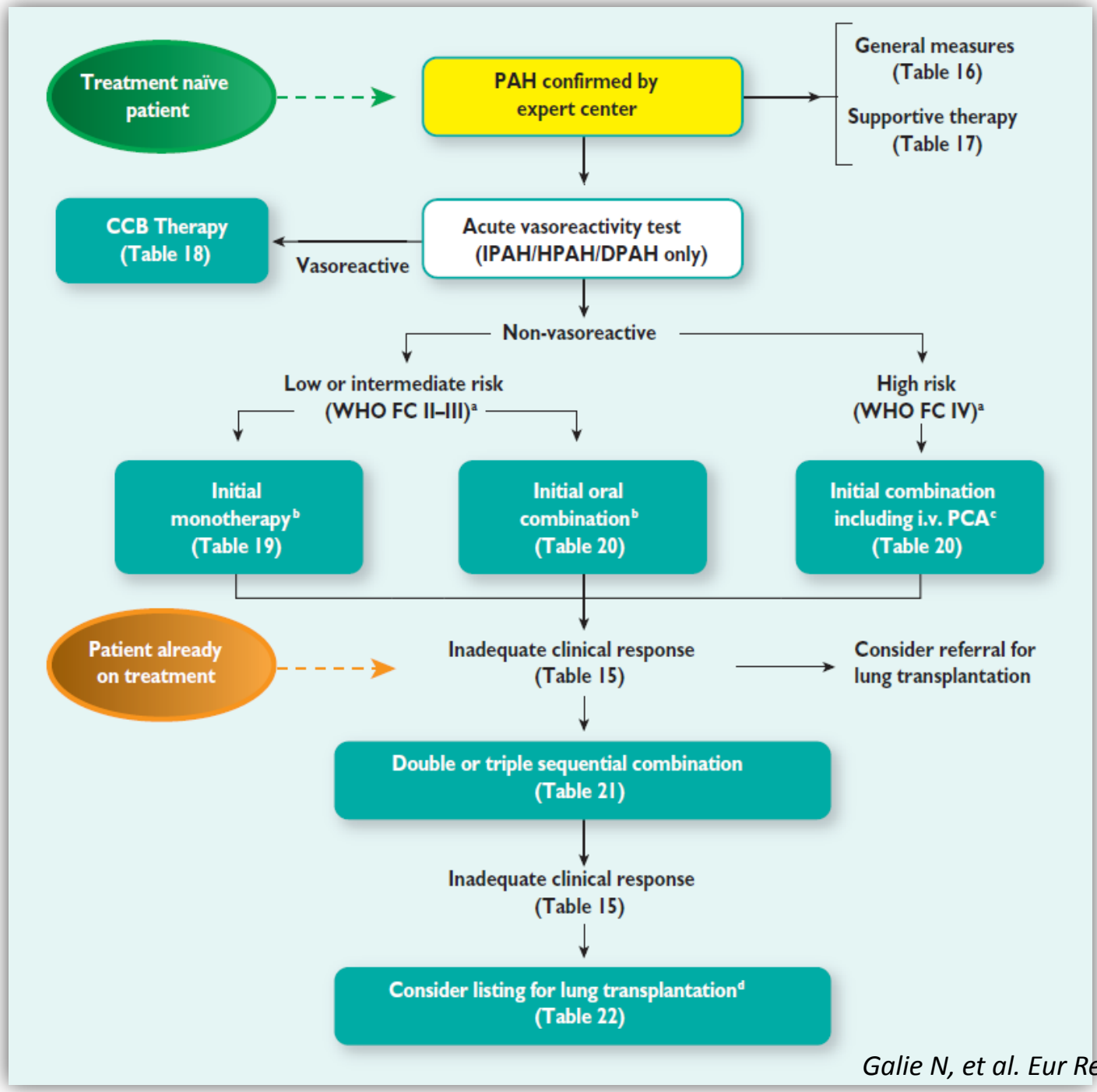
4. Chronic thromboembolic PH

5. PH with unclear multifactorial mechanisms

- 5.1. Hematologic disorders: chronic hemolytic anemia, myeloproliferative disorders splenectomy
- 5.2. ,
- 5.3. Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
- 5.4. Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, segmental PH

NO APPROVED PH-TARGETED THERAPY

Simonneau G, et al. J Am Coll Cardiol. 2013;62(25 Suppl):D34-41.



- ***IPAH ;*** *idiopathic PAH*
- ***HPAH ;*** *heritable PAH*
- ***DPAH ;*** *drug-induced PAH*

Galie N, et al. Eur Respir J. 2015;46:903-975.

PAH Treatment: General Measures

Recommendations	Class[a]	Level[b]
It is recommended that PAH patients **avoid pregnancy**	I	C
Immunization of PAH patients against influenza and pneumococcal infection is recommended	I	C
Psychosocial support is recommended in PAH patients	I	C
Supervised exercise training should be considered in physically deconditioned PAH patients under medical therapy	IIa	B
In-flight O_2 administration should be considered for patients in WHO-FC III and IV and those with arterial blood O_2 pressure consistently < 8 kPa (60 mmHg)	IIa	C
In elective surgery, **epidural rather than general anaesthesia should be preferred** whenever possible	IIa	C
Excessive physical activity that leads to distressing symptoms is not recommended in PAH patients	III	C

Galiè N, et al. *Eur Heart J*. 2016;37:67-119.

PAH Treatment: Supportive Therapy

Recommendations	Class[a]	Level[b]
Diuretic treatment is recommended in PAH patients with signs of RV failure and fluid retention	I	C
Continuous long-term O_2 therapy is recommended in PAH patients when arterial blood O_2 pressure consistently < 8 kPa (60 mmHg)	I	C
Oral anticoagulant treatment may be considered in patients with **IPAH, HPAH and PAH due to use of anorexigens**	IIb	C
Correction of anemia and/or iron status may be considered in PAH patients	IIb	C
The use of angiotensin-converting enzyme inhibitors, angiotensin-2 receptor antagonists, beta-blockers and ivabradine is not recommended in patients with PAH unless required by co-morbidities (i.e. high blood pressure, coronary artery disease or left heart failure)	III	C

Galiè N, et al. *Eur Heart J*. 2016;37:67-119.

PAH Treatment: Specific Drug Therapy

High Dose CCBs in Vasoreactive Patients

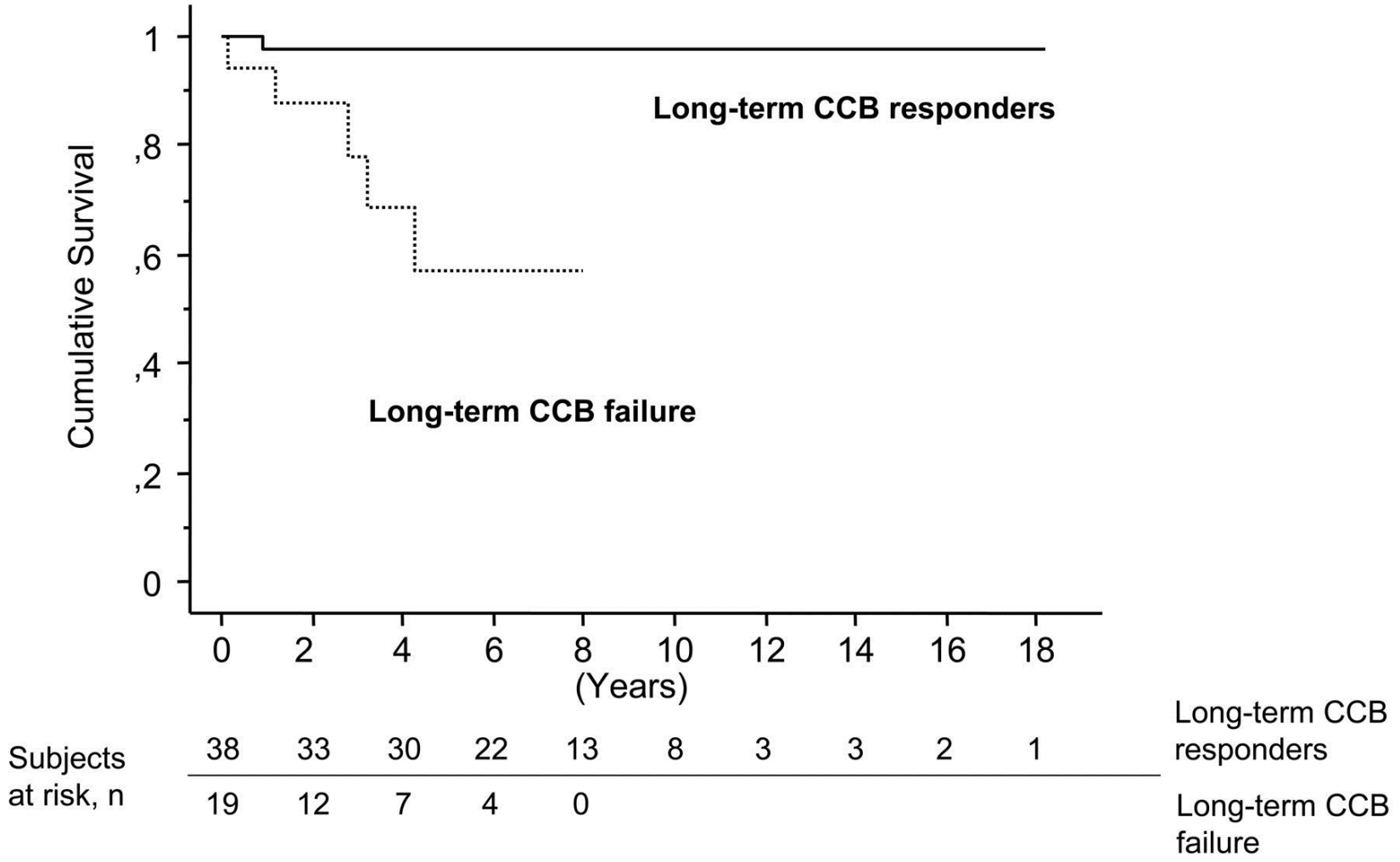
The daily doses of these drugs that have shown efficacy in IPAH are relatively high: 120–240 mg for nifedipine, 240–720 mg for diltiazem and up to 20 mg for amlodipine.

Drugs Approved for PAH

- Endothelin receptor **antagonists**
- Phosphodiesterase-5 inhibitors and guanylate cyclase stimulators
- Prostacyclin analogs and prostacyclin receptor agonists

Galiè N, et al. *Eur Heart J*. 2016;37:67-119.

Figure 2. Kaplan-Meier estimates in the 57 of 70 acute responder patients who survived after 1 year onward on CCB. The number of patients included in the long-term CCB failure subgroup was only 19 of 32, with the 13 remaining patients being dead (n=6), transplanted (n=4), or lost to follow-up (n=3, considered "dead" in the analysis) within the first year.



Olivier Sitbon et al. Circulation. 2005;111:3105-3111

Evolution of PAH Treatment

30 years ago

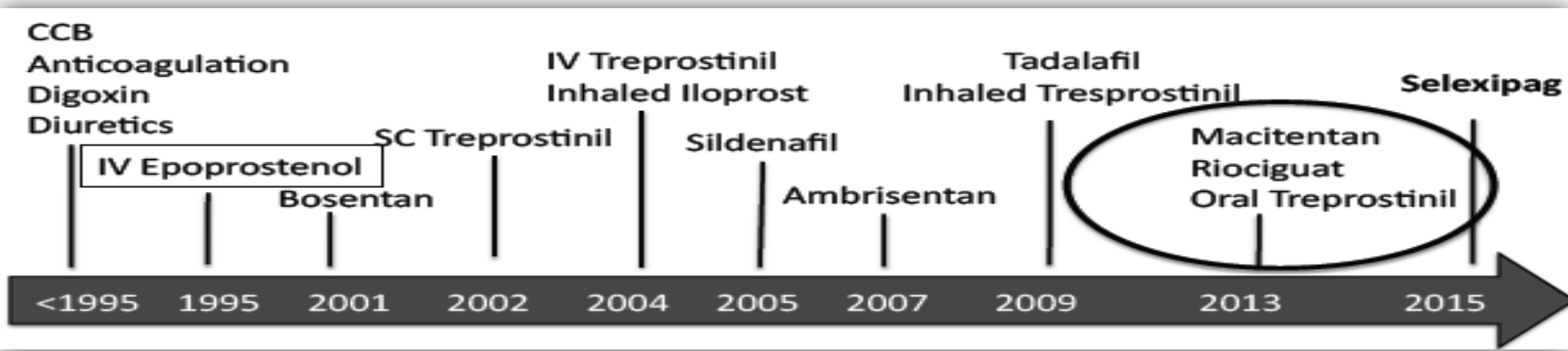
No treatments for PAH

20 years ago

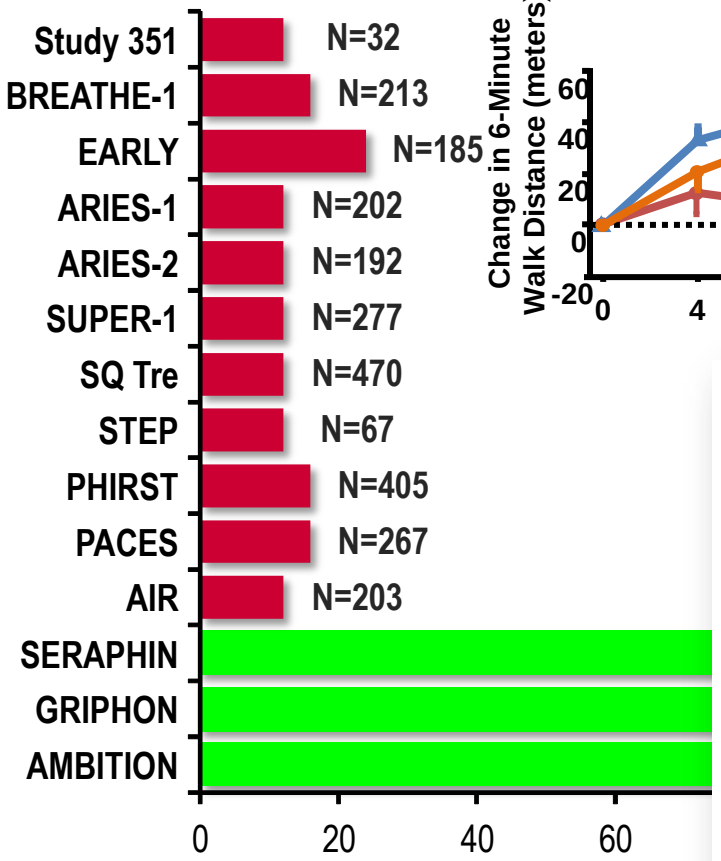
1 treatment for PAH

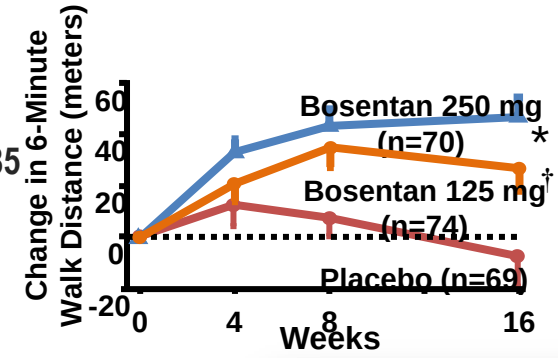
Today

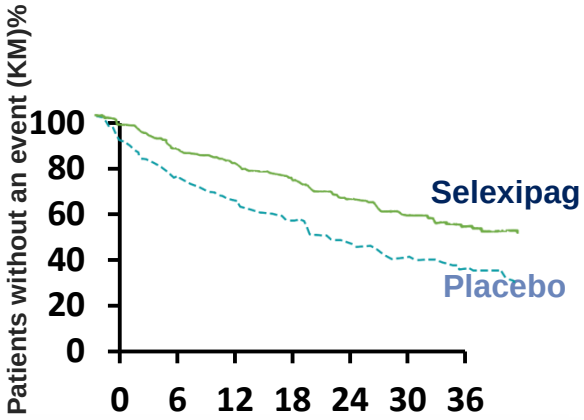
13 treatments for PAH



Evolution of double blind RCTs in PAH







Primary endpoint

Time from start of treatment to first morbidity or mortality event, defined as follows:

1. Death, or
2. Atrial septostomy, or
3. Lung transplantation, or
4. Initiation of intravenous or subcutaneous prostanoids (e.g., epoprostenol, treprostinil), or
5. Other worsening of pulmonary arterial hypertension.

Other worsening of pulmonary arterial hypertension is defined by the combination of **all** of the three following components:

- A decrease in 6MWD of at least 15% from baseline that should be confirmed by two 6-minute walk tests, performed on different days, within 2 weeks

AND

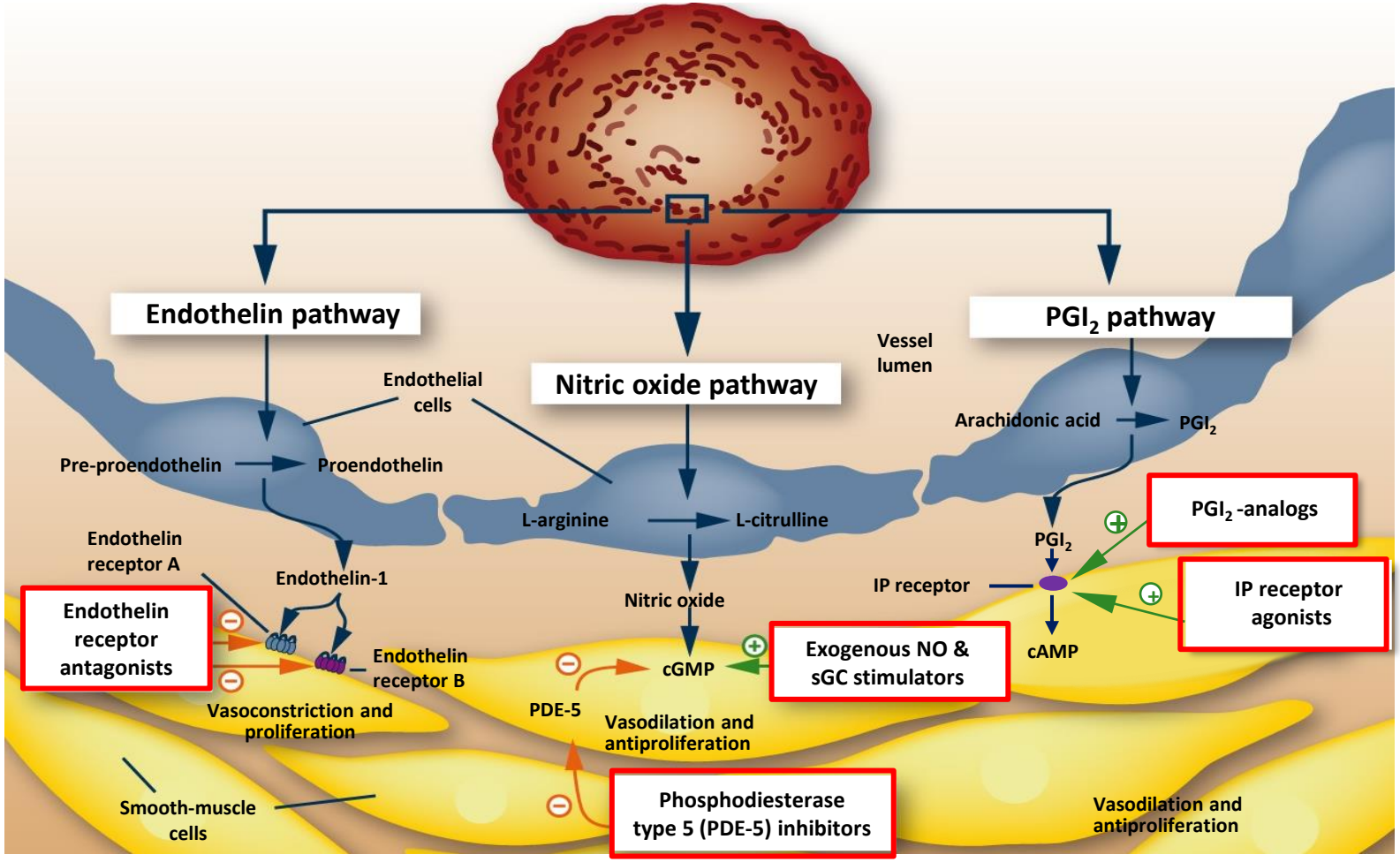
- Worsening of PAH symptoms[1]

AND

- Need for new treatment(s) for PAH[2]

Slide courtesy of Dr. Nick Kim

Target pathways of Therapeutic drugs



cAMP: cyclic adenosine monophosphate; cGMP: cyclic guanosine monophosphate; NO: nitric oxide; sGC: soluble guanylate cyclase

Adapted from Humbert et al. N Engl J Med 2004 and Humbert et al. Circulation 2014.

Recommendations for efficacy of drug monotherapy

Measure/treatment			Class[a]-Level[b]					
			WHO-FC II		WHO-FC III		WHO-FC IV	
Calcium channel blockers			I	C[d]	I	C[d]	-	-
Endothelin receptor antagonists	Ambrisentan		I	A	I	A	IIb	C
	Bosentan		I	A	I	A	IIb	C
	Macitentan[e]		I	B	I	B	IIb	C
Phosphodiesterase type 5 inhibitors	Sildenafil		I	A	I	A	IIb	C
	Tadalafil		I	B	I	B	IIb	C
	Vardenafil[g]		IIb	B	IIb	B	IIb	C
Guanylate cyclase stimulators	Riociguat		I	B	I	B	IIb	C
Prostacyclin analogues	Epoprostenol	Intravenous[e]	-	-	I	A	I	A
	Iloprost	Inhaled	-	-	I	B	IIb	C
		Intravenous[g]	-	-	IIa	C	IIb	C
	Treprostinil	Subcutaneous	-	-	I	B	IIb	C
		Inhaled[g]	-	-	I	B	IIb	C
		Intravenous[f]	-	-	IIa	C	IIb	C
		Oral[g]	-	-	IIb	B	-	-
	Beraprost[g]		-	-	IIb	B	-	-
IP receptor agonists	Selexipag (oral)[g]		I	B	I	B	-	-

Eur Heart J 2016;37:67-119

PAH Targeted Agents: Prostacyclin Analogues

	Epoprostenol	Iloprost	Treprostinil
Route	IV	Inhalation	IV, SQ, inhalation, PO
Indication	WHO Group I PAH	WHO Group I PAH	WHO Group I PAH
Contraindications	CHF or pulmonary edema during initial dose titration	None	Severe hepatic impairment for ER tablets
Side effects	Flushing, HA, jaw pain, D, N, V, rash, thrombocytopenia	Flushing, cough, hypotension, N, HA, bronchospasm	Flushing, headache, nausea, diarrhea, jaw pain, rash
Comments	AC should be initiated to decrease PE or systemic embolism risk (not guideline based)	Hemoptysis has been reported with iloprost use	Abrupt withdrawal may worsen PAH Sx, can occur with other agents in this class as well

HA = headache; D = diarrhea; N = nausea; V = vomiting; ER = extended release; PE = pulmonary embolism; Sx = symptoms. AC = anticoagulant. http://emedicine.medscape.com/article/301450-medication#3. Accessed December 21, 2014. http://www.pdr.net/browse-by-drug-name. Accessed December 21, 2014.

PAH Targeted Agents: Endothelin Antagonists

	Bosentan	Ambrisentan	Macitentan
Route	PO	PO	PO
Indication	WHO Group I PAH	WHO Group I PAH	WHO Group I PAH
Contraindications	Pregnancy Category X	Pregnancy Category X, WHO Group 3 PH, IPF	Pregnancy Category X
Side effects	Increased ALT/AST, HA, Nasal congestion, edema, decreased Hgb	Increased ALT/AST, edema, HA, nasal congestion, dyspnea, decreased Hgb	Increased ALT/AST, nasal congestion, HA, anemia, bronchitis
Comments	Serum liver enzymes at baseline & then monthly, monthly pregnancy tests	Pregnancy test at baseline & then monthly	Pregnancy test at baseline & then monthly

IPF = idopathic pulmonary fibrosis; ALT = alanine transaminase; AST = aspartate transaminase; Hgb = hemoglobin.

http://emedicine.medscape.com/article/301450-medication#3. Accessed December 21, 2014.
http://www.pdr.net/browse-by-drug-name. Accessed December 21, 2014.

PAH Targeted Agents: PDE-5 Inhibitors and sGC Stimulators

	Sildenafil	Tadalafil	Riociguat
Route	PO	PO	PO
Indication	WHO Group I PAH	WHO Group I PAH	WHO Group I PAH, WHO Group 4 PH
Contraindications	Organic nitrates in any form	Organic nitrates in any form	Pregnancy Category X
Side effects	HA, flushing, epistaxis, dyspepsia, insomnia, erythema, diarrhea	HA, myalgia, flushing, respiratory tract infection, dyspepsia, nasal congestion	HA, dyspepsia and gastritis, dizziness, N, D, V, hypotension
Comments	Vaso-occlusive crisis (PAH secondary to sickle-cell anemia)	CYP3A4 inhibitors may increase drug levels	Monthly pregnancy tests and 1 month after discontinuation

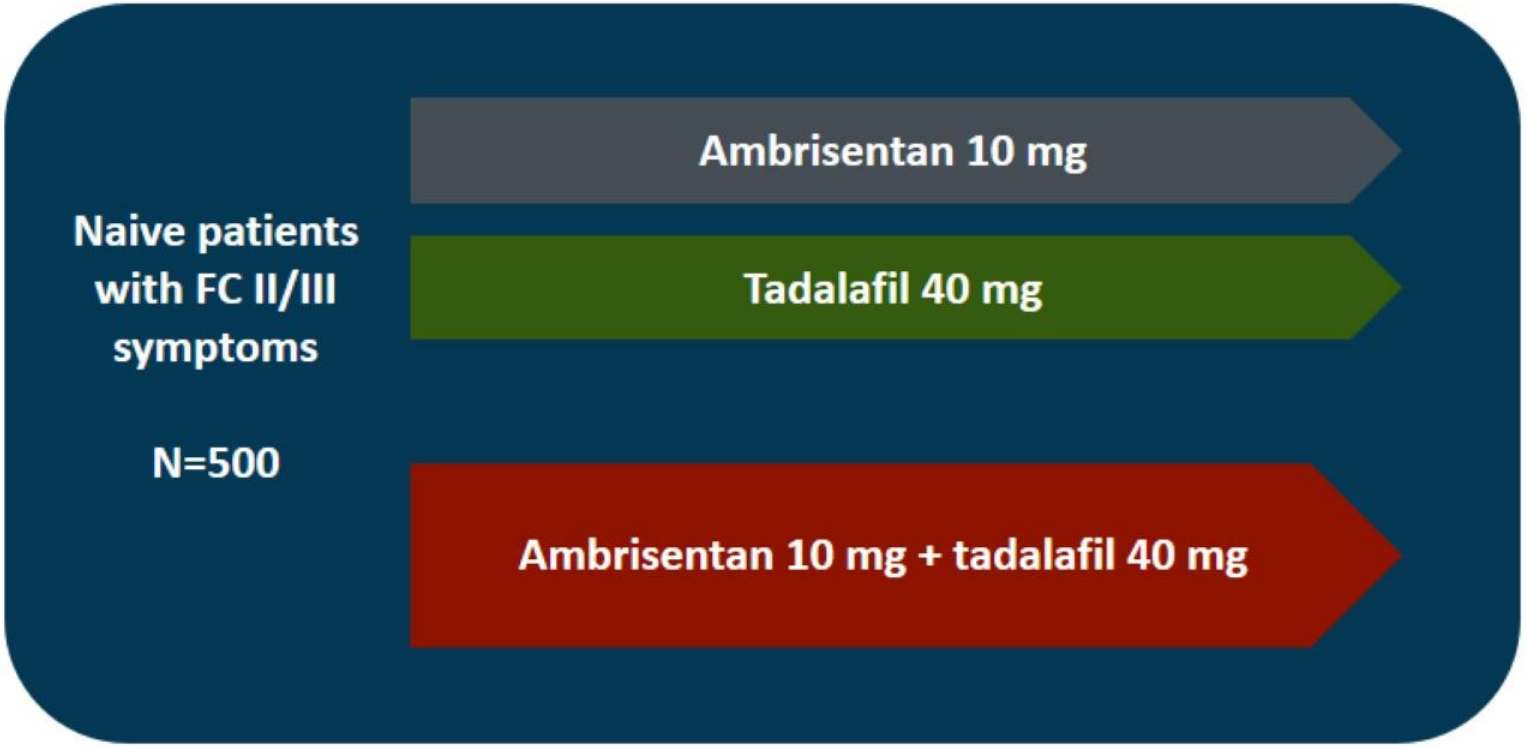
PDE-5 = phosphodiesterase type 5; sGC = soluble guanylate cyclase; NO = nitric oxide.

http://emedicine.medscape.com/article/301450-medication#3. Accessed December 21, 2014.
http://www.pdr.net/browse-by-drug-name. Accessed December 21, 2014.

Sequential drug combination therapy

Measure / treatment	Class - Level					
	WHO - FC II		WHO - FC III		WHO - FC IV	
Macitentan added to Sildenafil	I	B	I	B	IIa	C
Riociguat added to bosentan	I	B	I	B	IIa	C
Selexipag added to ERA and/or PDE-5i	I	B	I	B	IIa	C
Sildenafil added to epoprostenol	-	-	I	B	IIa	B
Treprostinil inhaled added to sildenafil or bosentan	IIa	B	IIa	B	IIa	C
Iloprost inhaled added to bosentan	IIb	B	IIb	B	IIb	C
Tadalafil added to bosentan	IIa	C	IIa	C	IIa	C
Ambrisentan added to sildenafil	IIb	C	IIb	C	IIb	C
Bosentan added to epoprostenol	-	-	IIb	C	IIb	C
Bosentan added to sildenafil	IIb	C	IIb	C	IIb	C
Sildenafil added to bosentan	IIb	C	IIb	C	IIb	C
Other double combinations	IIb	C	IIb	C	IIb	C
Other triple combinations	IIb	C	IIb	C	IIb	C
Riociguat added to sildenafil or other PDE-5i	III	B	III	B	III	B

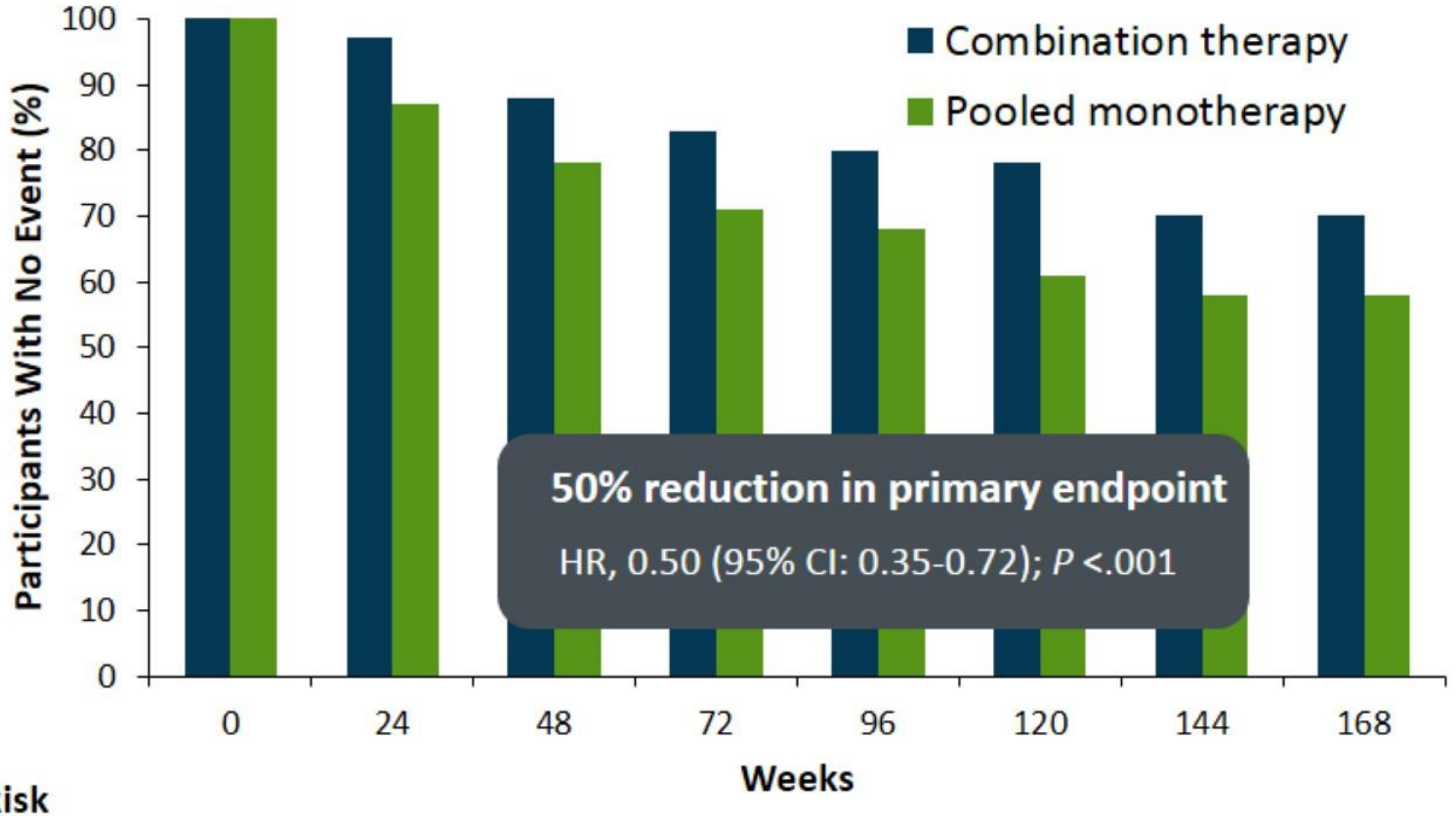
AMBITION: Initial Use of Combination Ambrisentan + Tadalafil



- Primary endpoint: time to clinical failure (death, hospitalization, disease progression, unsatisfactory clinical response)

Galiè N, et al. *N Engl J Med*. 2015;379:834-844.

AMBITION Trial: Primary Endpoint* Results



No. at Risk

Combination therapy	253	229	186	145	106	71	36	4
Pooled monotherapy	247	209	155	108	77	49	25	5

*Time to clinical failure (death, hospitalization, disease progression, unsatisfactory clinical response)

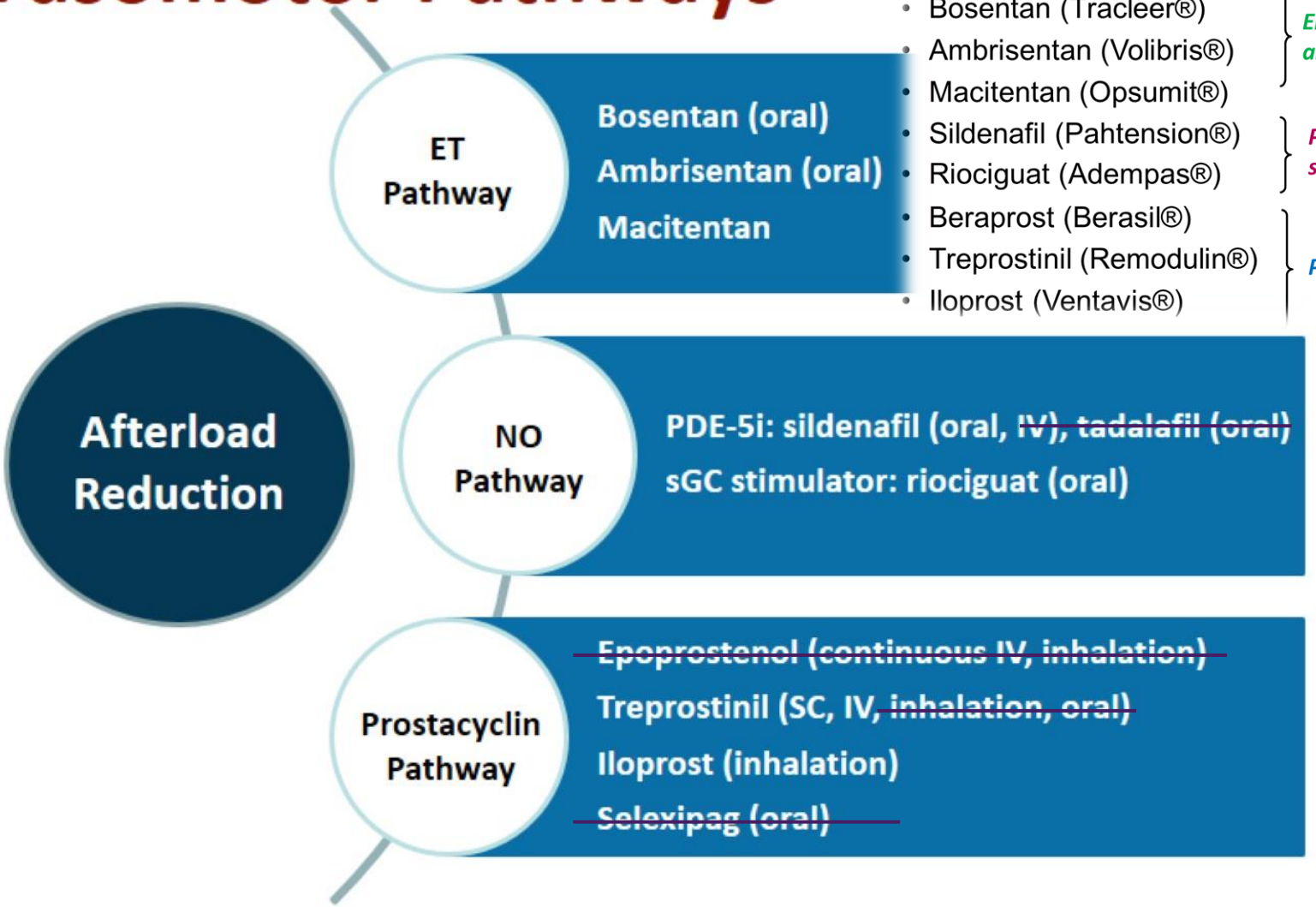
Galiè N, et al. *N Engl J Med*. 2015;373:834-844.

Initial Combination Therapy for Low/Intermediate-Risk Patients With PAH

Treatment	WHO FC II		WHO FC III	
	Rec. Class	Evidence Level	Rec. Class	Evidence Level
Ambrisentan + tadalafil	I	B	I	B
Other ERA + PDE-5i	IIa	C	IIa	C
Bosentan + sildenafil + IV epoprostenol	---	---	IIa	C
Bosentan + IV epoprostenol	---	---	IIa	C
Other ERA or PDE-5i + SC treprostinil			IIb	C
Other ERA or PDE-5i + other IV prostacyclin analog			IIb	C

Galiè N, et al. *Eur Heart J.* 2016;37:67-119.

PAH Therapies Target Diverse Vasomotor Pathways



Approved drugs in Korea

- Bosentan (Tracleer®)
- Ambrisentan (Volibris®)
- Macitentan (Opsumit®)

Endothelin receptor antagonists (ERAs)

- Sildenafil (Pahtension®)
- Riociguat (Adempas®)

PDE 5 inhibitors sGC Stimulator

- Beraprost (Berasil®)
- Treprostinil (Remodulin®)
- Iloprost (Ventavis®)

Prostaglandins

Galiè N, et al. *J Am Coll Cardiol.* 2013;62:D60-D72.
Humbert M, et al. *Thorax.* 2016;71:73-83.

Suggested assessment and timing for the follow-up of patients with PH

	At baseline	Every 3–6 months[a]	Every 6–12 months[a]	3–6 months after changes in therapy[a]	In case of clinical worsening
Medical assessment and determination of functional class	+	+	+	+	+
ECG	+	+	+	+	+
6MWT/Borg dyspnoea score	+	+	+	+	+
CPET	+		+		+[e]
Echo	+		+	+	+
Basic lab[b]	+	+	+	+	+
Extended lab[c]	+		+		+
Blood gas analysis[d]	+		+	+	+
Right heart catheterization	+		+[f]	+[e]	+[e]

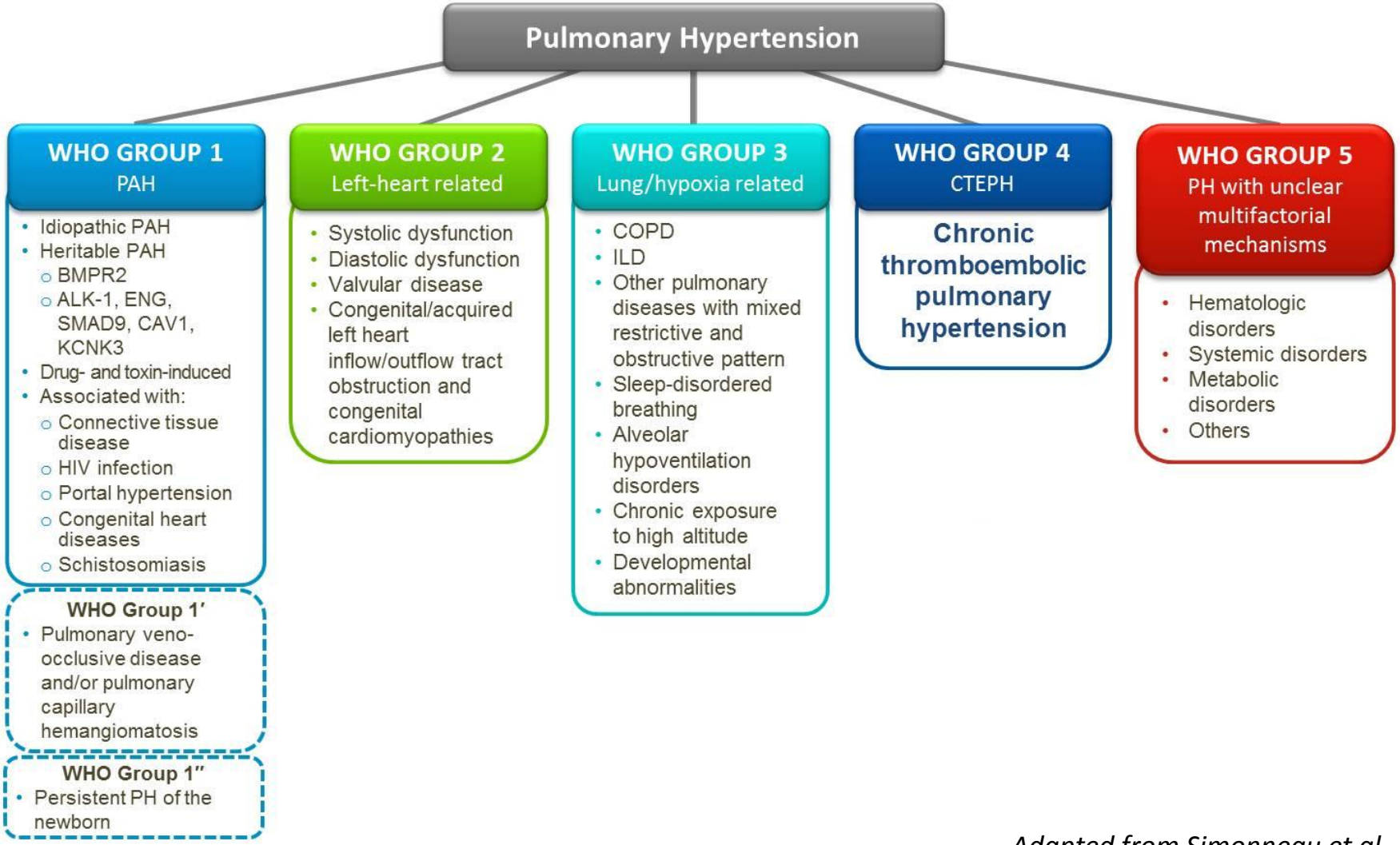
- Basic lab includes blood count, INR in patients receiving vitamin K antagonists, serum creatinine, sodium, potassium, AST/ALT (in patients receiving ERAs), bilirubin, and BNP/NT-proBNP.
- Extended lab includes TSH, uric acid, iron status (iron, ferritin, soluble transferrin receptor) and other variables according to individual patient needs.

Galie N, et al. Eur Respir J. 2015;46:903-975.

Take Home Points

- Important to accurately identify the cause of PH
  - Initial screening via echocardiography
  - Include V/Q to rule-out CTPEH
- Do not delay work-up ; RHC provides definite diagnosis
- Risk assessment before initiating therapy
- Do not delay appropriate treatment(s)
  - Oral therapies, including PDE 5 inhibitors, ERA, the GC activator (riociguat), and the selective prostacyclin IP receptor agonist (selexipag), are recommended first-line therapies for patients with mild to-moderate PAH
  - Parenteral prostacyclins for patients with more severe PAH
  - Growing data that combination PAH therapy works

Pulmonary Hypertension categorized by the WHO



Adapted from Simonneau et al
J Am Coll Cardiol 2013;62:D34–D41

Thank you !

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