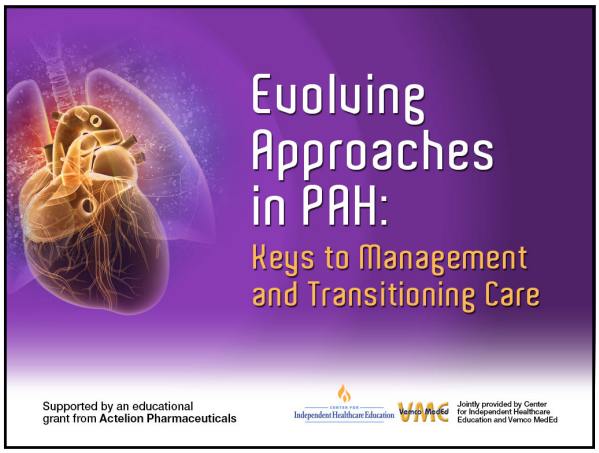


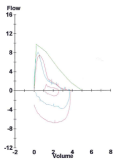
The COPD-PH Consult…

52-year-old white male with COPD, HTN, presents with progressive DOE

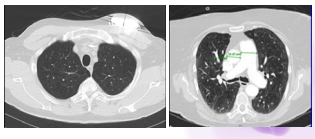
Current Meds:

- LABA/LAMA × 5 years
- ACEI × 1 year

Pulmonary Function Testing		
FVC	3.79 (75%)	3.87 (77%) +2
FEV1	2.39 (62%)	2.56 (66%) +7
FEV1/FVC ratio	63	66
TLC	7.01 (103%)	
RV	3.05 (136%)	
DLCO (adj)	7.01 (23%)	

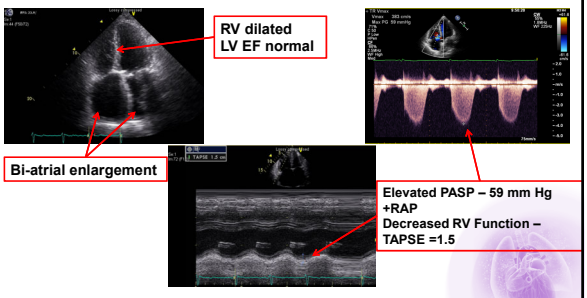


- 2 exacerbations in last year
- 2 LPM oxygen × 6 mo
- An echo is ordered…



DOE, dyspnea on exertion; HTN, hypertension; LPM, liters per minute; LABA, long-acting beta-agonist; LAMA, long-acting muscarinic antagonist; ACEI ACE inhibitor; TLC, total lung capacity; RV, residual volume; DLCO, diffusing capacity of lungs for carbon monoxide

The COPD-PH Consult…



RV, right ventricle; LV, left ventricle; EF, ejection fraction; PASP, pulmonary artery systolic pressure; RAP, right atrial pressure; TAPSE, tricuspid, annular plane systolic excursion

When to Consider Pulmonary Vascular Disease

Pulmonary Consult

- Moderate obstructive lung disease stable
- Abnormal echo
- Continue present management of COPD

IT'S NOT THE LUNGS
IT'S THE HEART

Cardiology Consult

- Normal left ventricular systolic function
- Abnormal PFTs
- Continue present management of HTN

IT'S NOT THE HEART
IT'S THE LUNGS

WHO Clinical Classification of PH Guidelines 2013 (Nice, France)

Group 1—PAH

- 1.1 Idiopathic PAH
- 1.2 Heritable
  - 1.2.1 BMPR2
  - 1.2.2 ALK-1, endoglin, SMAD 9, CAV-1, KCNK3
  - 1.2.3 Unknown
- 1.3 Drug- and toxin-induced
- 1.4 PAH associated with:
  - 1.4.1 Connective tissue diseases
  - 1.4.2 HIV infection
  - 1.4.3 Portal hypertension
  - 1.4.4 Congenital systemic to pulmonary shunts
  - 1.4.5 Schistosomiasis
- 1' Persistent pulmonary hypertension of newborn
- 1'' Pulmonary veno-occlusive disease or pulmonary capillary hemangiomatosis

Group 2—PH owing to left heart disease

- 2.1 Systolic dysfunction
- 2.2 Diastolic dysfunction
- 2.3 Valvular disease

Group 3—PH owing to lung diseases 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 disorder
- 3.6 Chronic exposure to high altitude
- 3.7 Developmental abnormalities

Group 4—Chronic thromboembolic PH

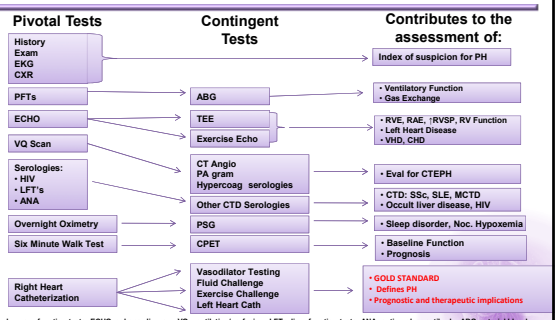
Group 5—PH with unclear multifactorial mechanisms

- 5.1 Hematologic disorders: Chronic hemolytic anemia, MPD,
- 5.2 Systemic disorders: sarcoid
- 5.3 Metabolic disorders
- 5.4 Others

The 6th World Symposium on Pulmonary Hypertension was held in Nice, France from February 27 to March 1, 2018 and updates derived from this meeting are expected to be released in late 2018 or early 2019.

Simonneau et al. *J Am Coll Cardiol.* 2013;62(25 supp D):D34-D41.

Diagnostic Algorithm for Pulmonary Hypertension



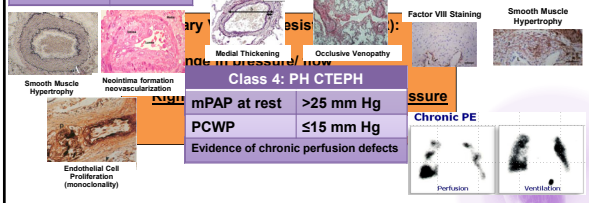
PFTs, pulmonary function tests; ECHO, echocardiogram; VQ, ventilation/perfusion; LFTs, liver function tests; ANA, anti-nuclear antibody; ABG, arterial blood gases; TEE, transesophageal echocardiography; PA gram, pulmonary angiograph; CTD, connective tissue disease; PSG, polysomnogram; CPET, cardiopulmonary exercise testing; RVE, right ventricle enlargement; RAE, right atrial enlargement; RVSP, right ventricle systolic pressure; SSc, systemic sclerosis; SLE, systemic lupus erythematosus; MCTD, mixed CTD

Clinical Classification of Pulmonary Hypertension

Class 1: PAH	
mPAP at rest	≥25 mm Hg
PCWP	≤15 mm Hg
PVR	>3 Wood

Class 2: PVH	
mPAP at rest	≥25 mm Hg
PCWP	≥15 mm Hg

Class 3: PH associated with lung disease	
mPAP at rest	>25 mm Hg
Underlying chronic lung disease	



Class 4: PH CTEPH	
mPAP at rest	>25 mm Hg
PCWP	≤15 mm Hg
Evidence of chronic perfusion defects	

mPAP, mean pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; PAH, pulmonary arterial hypertension; PVH, pulmonary venous hypertension

Echocardiographic Features of PAH vs PVH

Pulmonary Arterial Hypertension

2-D echo:
- Normal LA, LV size; small LV (<3.5 cm)
- No LVH
- Normal to high ejection fraction
- Septal bowing (systole > diastole)
- Pericardial effusion

Doppler:
- Variable PASP
- No MR
- Grade 1 diastolic dysfunction (E<A)

Pulmonary Venous Hypertension

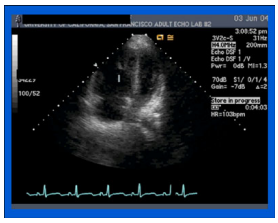
2-D echo
- Dilated LA
- Normal of dilated LV ± LVH
- Variable LV ejection fraction
- RV/LV ratio <1
- LV remains round in short axis

Doppler
- Variable PASP
- > 2+ MR
- E>A diastolic dysfunction (Grade 2-3)

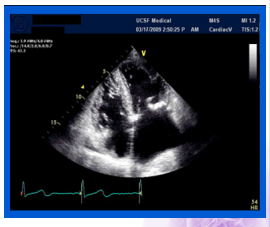
LA, left atrium; LV, left ventricle; LVH, left ventricle hypertension; RV, right ventricle; PASP, pulmonary artery systolic pressure; MR, mitral regurgitation

Echocardiographic Features of PAH vs PVH

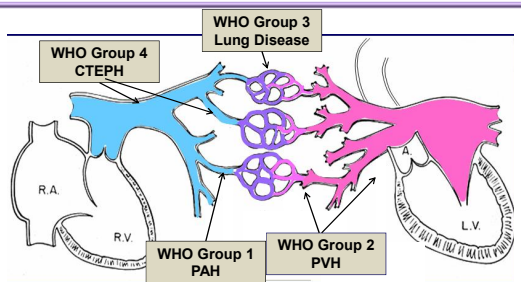
Pulmonary Arterial Hypertension



Pulmonary Venous Hypertension



Where is the Lesion?



How Common is Pulmonary Hypertension?

WHO Group I PAH

- Prevalence 10–20 cases/million population*
- US population 311 million
  - US cases of PAH: 4,665 (orphan disease <200K in US)
- Worldwide population: 6 billion
  - Worldwide cases of PAH: 90,000

WHO Group I PAH is a rare, orphan disease
But PH is not…

*Humbert M et al. *AJRCCM.* 2006; 173(9):1023-30.
Hoeper M et al *ERR*, 2014 23: 450-457.

How Common is Pulmonary Hypertension?

WHO Category	Estimated US prevalence (n)
Group I (PAH)	4,665
Group II (PVH)	millions
Group III (PH due to ↓O_2)	>200,000
Group IV (chronic PE)	90,000

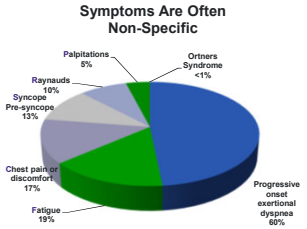
* http://www.pubmed.org; ** http://www.google.com; † http://www.clinicaltrials.gov

How Common is Pulmonary Hypertension?

WHO Category	Estimated US prevalence (n)	Pubmed citations* (n)	Google hits** (n)	Clinical trials† (n)*	
				Completed (N=330)	Ongoing (n=194)
Group I (PAH)	4,665	36,629 (6,134)	1.18 million (586,000)	140 (42%)	58 (30%)
Group II (PVH)	millions	4,724	64,900	8 (2%)	28 (14%)
Group III (PH due to ↓O_2)	>200,000	5,186	355,000	74 (22%)	34 (17%)
Group IV (chronic PE)	90,000	3,129	38,100	33 (10%)	5 (3%)

* http://www.pubmed.org; ** http://www.google.com; † http://www.clinicaltrials.gov

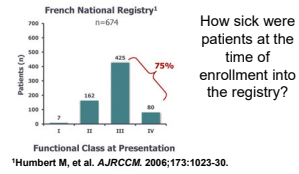
Presenting Symptoms of PAH



REVEAL Registry	
Dates	3/2006 – 9/2007
Number Pts	2525
	All Patients
% Female	**79.5**
Age, yr (range)	**50.1 ± 14.4**
NYHA III-IV (%) At diagnosis	73.6
NYHA III-IV (%) At enrollment (25mo)	55.6
Time from Symptom to RHC (mo)	**34.1 ± 1.2**

RHC, right heart catheterization
Badesch D, et al. *CHEST*. 2010;137;376-87.

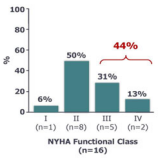
The Importance of Early Diagnosis



¹Humbert M, et al. *AJRCCM*. 2006;173:1023-30.

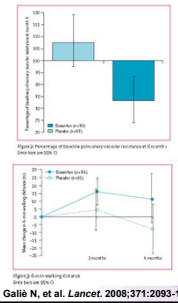
How sick were patients at the time of enrollment into the registry?

Performed a study of screening new scleroderma patients for PAH



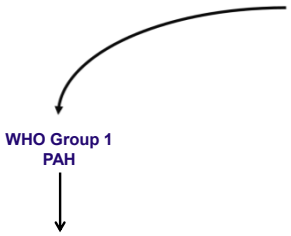
Hachula E, et al. *Arthritis Rheum*. 2005;52:3792-800.

EARLY TRIAL

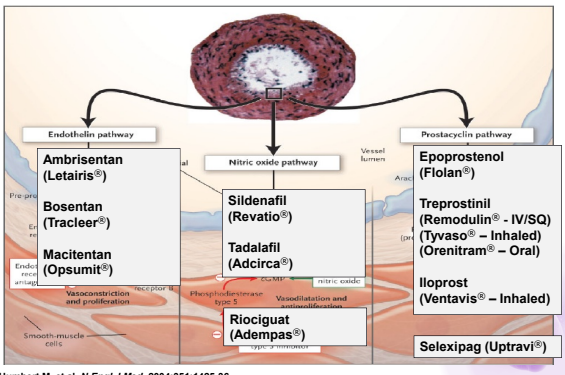


Galiè N, et al. *Lancet*. 2008;371:2093-100.

Treatment of PH



Treatment of Group 1 PAH



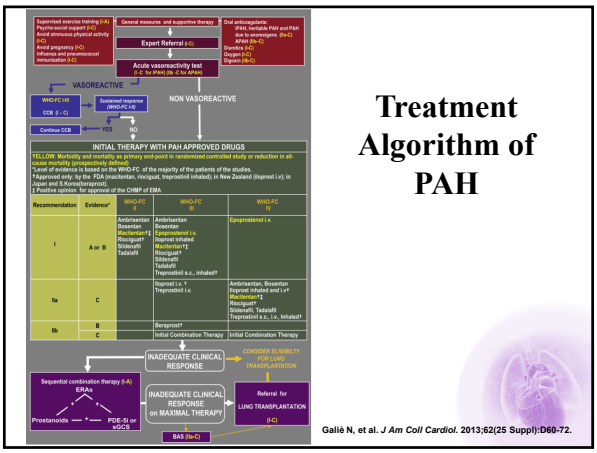
Humbert M, et al. *N Engl J Med*. 2004;351:1425-36.

Treatment Goals in Group 1 PAH

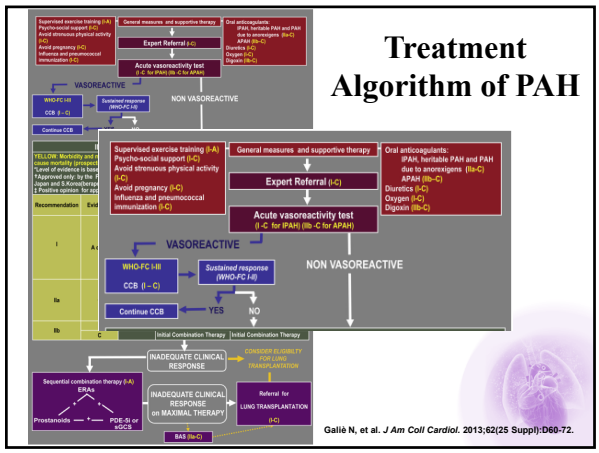
Table 1 Goals recommended by the latest European Society of Cardiology/European Respiratory Society guidelines for pulmonary hypertension

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 and II	WHO FC	IV
Longer (>500 m)#	6MWT	Shorter (<300 m)
Peak V_{O_2} >15 mL·min^{-1}·kg^{-1}	Cardiopulmonary exercise testing	Peak V_{O_2} <12 mL·min^{-1}·kg^{-1}
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^{-1}·m^{-2}	Haemodynamics	RAP >15 mmHg or CI ≤2.0 L·min^{-1}·m^{-2}

RAP, right atrial pressure; CI, cardiac index; TAPSE, tricuspid annular plane systolic excursion
Sitbon O, Galiè N. *Eur Respir Rev*. 2010;19:272-8.

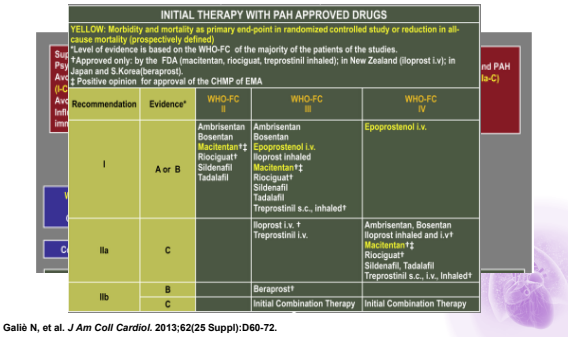


Galiè N, et al. *J Am Coll Cardiol.* 2013;62(25 Suppl):D60-72.



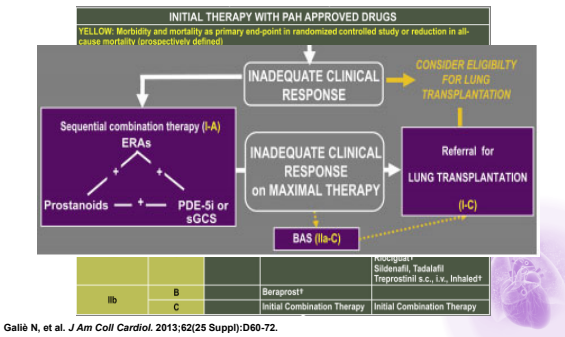
Galiè N, et al. *J Am Coll Cardiol.* 2013;62(25 Suppl):D60-72.

Treatment Algorithm of PAH



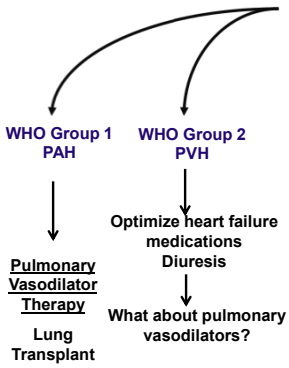
Galiè N, et al. *J Am Coll Cardiol.* 2013;62(25 Suppl):D60-72.

Treatment Algorithm of PAH



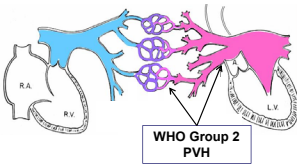
Galiè N, et al. *J Am Coll Cardiol.* 2013;62(25 Suppl):D60-72.

Treatment of PH



Pulmonary Vasodilators in Group 2: PVH

Theoretical risk of pulmonary edema



Prostacyclin		ERA	
Trial	Outcome	Trial	Outcome
FIRST	Incr. Mortality	VERITAS	Lack of efficacy
		ENABLE	Incr heart failure adm.
		ENCOR	Trend increase mortality
		EARTH	Lack of efficacy

Pulmonary Vasodilators in Group 2: PVH

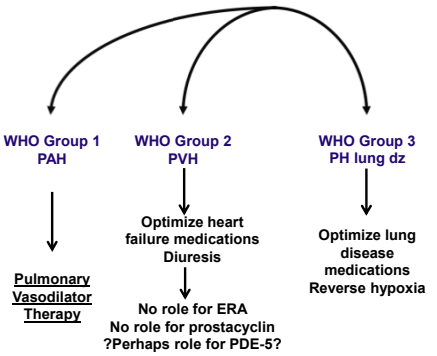
PDE-5 inhibitors:

- Most promising
- Small trials with encouraging results

PDE-5 Inhibitor	
TRIAL	**OUTCOME**
Lewis 2007	Improved exercise capacity and QOL in systolic HF with PH
Guazzi 2007	Improved exercise capacity, improved PAP, decreased hospitalization

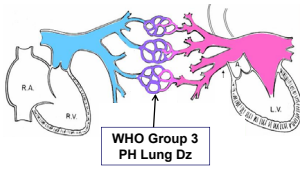
Lewis GD, et al. *Circulation*. 2007;116:1555-62.
Guazzi M, et al. *J Am Coll Cardiol*. 2007;50:2136-44.

Treatment of PH



Pulmonary Vasodilators in Group 3: PH lung disease

Theoretical risk of increasing VQ mis-matching and worsening hypoxemia



PH-ILD

No clear benefit from PAH specific therapy
Trend towards increased oxygen requirements*

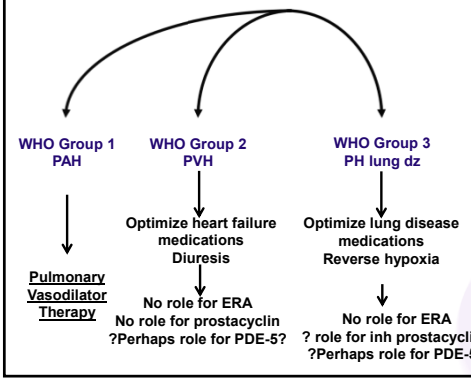
VQ, ventilation/perfusion; ILD, interstitial lung disease
*Le Pavec J, et al. *Arthritis Rheum*. 2011;63:2456-64.

Pulmonary Vasodilators in Group 3: PH

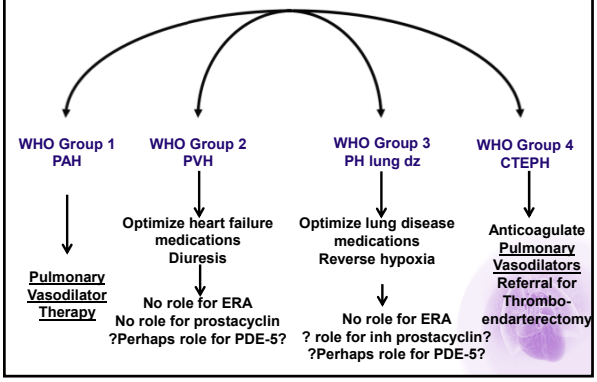
- PH-COPD
  - Multiple small studies, poorly-defined patients
  - Prostacyclins
    - IV showed worsening oxygenation[a]
    - Inhaled showed improved oxygenation[b]
  - ERA
    - Showed trends towards worsening oxygenation, decline in 6MWT, and worse QOL[c]
  - PDE-5
    - Well tolerated, attenuated exercise, induced rise in mPAP[d]

[a]Archer SL, et al. *CHEST*. 1996;109:750-5.
[b]Dernaika TA, et al. *Respiration*. 2010;79:377-82.
[c]Stolz D, et al. *Eur Respir J*. 2008;32:619-28.
[d]Holverda S, et al. *Pulm Pharmacol Ther*. 2008;21:558-64.

Treatment of PH

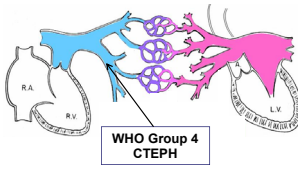


Treatment of PH



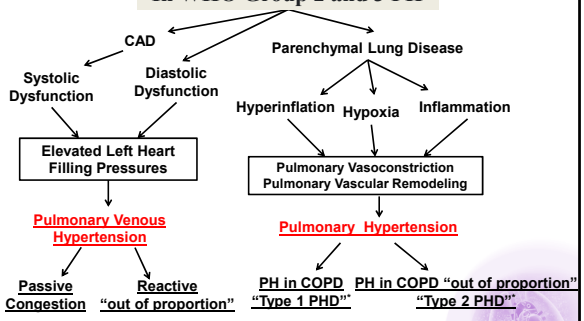
Pulmonary Vasodilators in Group 4: CTEPH

- Anticoagulation is the backbone
- Clear role for pulmonary vasodilators in non-operative candidates



Thromboendarterectomy is treatment of choice as it offers a durable cure.

Pulmonary Vascular Disease In WHO Group 2 and 3 PH



* Forfia PR, et al. *Pulm Circ.* 2013:3:5-19.

Pulmonary Vasodilators in "Select" COPD-PH?

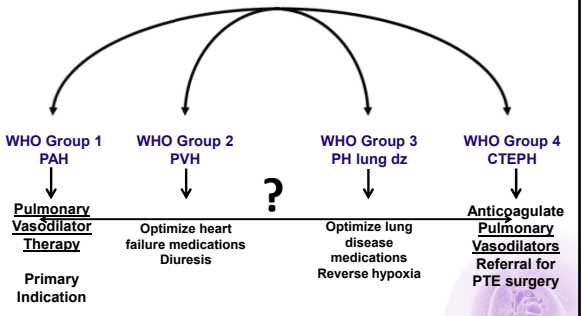
CHEST Original Research

What is the difference between "severe COPD-PH" and "PAH with comorbid COPD"?

- COPD one of the most commonly reported comorbid conditions
- On average GOLD 2 severity
- 498/2959 – 17% reporting COPD

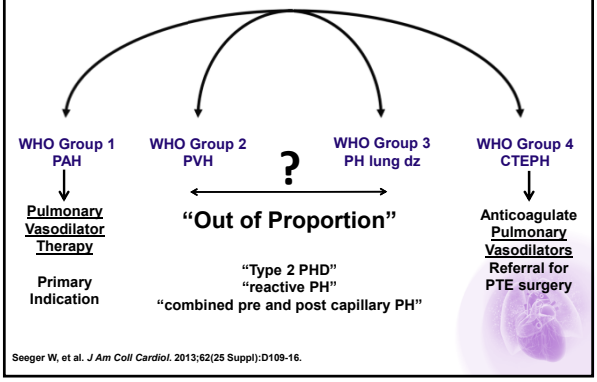
Poms AD, et al. *CHEST.* 2013;144:169-76.

How Do We Know What To Treat?



Seeger W, et al. *J Am Coll Cardiol.* 2013;62(25 Suppl):D109-16.

How Do We Know What To Treat?



Seeger W, et al. *J Am Coll Cardiol.* 2013;62(25 Suppl):D109-16.

How Do We Know What To Treat?

"Out of Proportion"

Lung Disease without PH (COPD/ILD/CPFE)	Lung Disease with PH (COPD/ILD/CPFE)	Lung Disease with severe PH (COPD/ILD/CPFE)
mPAP <25 mm Hg	mPAP >25 mm Hg	mPAP ≥35 mm Hg or mPAP >25 mm Hg and low CI (<2.0 L/min/m²)

Seeger W, et al. *J Am Coll Cardiol.* 2013;62(25 Suppl):D109-16.

Lung Disease with Severe PH

- Represents a minority of chronic lung disease patients suspected to have severe vascular abnormalities
- Circulatory impairment is primary driver of reduced exercise capacity rather than the ventilatory impairment related to the lung disease

Ventilatory and Cardiocirculatory Exercise Profiles in COPD

The Role of Pulmonary Hypertension

Bart G. Boerrigter, MD; Harm J. Bogaard, MD, PhD; Pia Trip, MD; Herman Groepenhoff, MSc; Heleen Rietema, MD; Sebastiaan Holverda, PhD; Anco Boonstra, MD, PhD; Pieter E. Postmus, MD, PhD, FCCP; Nico Westerhof, PhD; and Anton Vonk-Noordegraaf, MD, PhD, FCCP

Impact of pulmonary hemodynamics on 6-min walk test in idiopathic pulmonary fibrosis

Omar A. Minai [a,b,*], Jose F. Santacruz [a], Joan M. Alster [c], Marie M. Budev [a,b], K. McCarthy [a]

Seeger W, et al. *J Am Coll Cardiol.* 2013;62(25 Suppl):D109-16.
Boerrigter BG, et al. *CHEST.* 2012;142:1166-74.
Minai OA, et al. *Respir Med.* 2012;106:1613-21.

Conclusions

Pulmonary hypertension is a complex comorbid condition with many faces and therefore many potential treatment pathways.

- Hemodynamic distinctions (need for right heart catheterization)
- Pathologic distinctions (driving the question “where is the lesion”)
- Treatment distinctions (not all PH benefits from PH drugs)

Data to guide decision-making outside of WHO Group 1 PAH and CTEPH are limited. We need to better understand….

- how it develops?
- how the different faces effect patients?
- does intervention actually effect outcomes?