Pulmonary Arterial Hypertension - Overview

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PAH Overview Outline

- Background and definition
- Clinical classification
- Epidemiology
- Pathophysiology/Natural history
- Signs and symptoms/diagnosis
- Importance of right heart catheterization
- PAH management trends and outcomes
- Treatment options

PAH Background

- Rare disease (orphan designation) of the pulmonary microvasculature affecting 15 to 50 people per million inhabitants in the Western world[1]
  - Affects all races
  - Affects all ages; however, most prevalent in 4th and 5th decades of life
  - Higher prevalence in females

1. Humbert. *Eur Respir J.* 2007;30:1-2.

PAH Background

- Global burden of PAH may be underestimated because of:[1,2]
  - Underdiagnosis (eg, nondescript symptoms)
  - Misdiagnosis (eg, asthma, left-heart disease)
  - Increasing risk factors (eg, HIV infection, schistosomiasis)

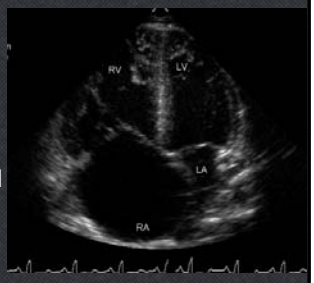
1. Humbert. *Eur Respir J.* 2007;30:1-2.
2. Humbert et al. *Chest.* 2007;132:365-367.

PAH Defined

- Mean PAP ≥ 25 mm Hg
- PCWP ≤15 mm Hg
- PVR > 3 Wood units

▸Increased pressure load on RV

▸Diagnosis of exclusion



PAH vs. PH

Table 3 Haemodynamic definitions of pulmonary hypertension[a]

Definition	Characteristics	Clincal 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]	

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The 2013 Nice Classification of PAH

5th WSPH

- Pulmonary Arterial Hypertension (1)
  - Heritable PAH (FPAH)
  - Idiopathic PAH (IPAH)
  - Drug and toxin-induced
  - Associated PAH (APAH)
    - Connective tissue disease (CTD)
    - Human immunodeficiency virus (HIV)
    - Portal hypertension
    - Schistosomiasis
    - Congenital heart disease (CHD)
  - Persistent pulmonary hypertension of the newborn (PPHN)

  1' Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis

The 2013 Nice Classification of PAH

5th WSPH

- Pulmonary Venous Hypertension (2)
  - Heart failure (normal or low EF)
  - Valvular disease
  - Congenital Heart Disease
- PH due to lung disease / hypoxemia
  - Obstructive sleep apnea
  - Interstital Lung disease
  - COPD/asthma
  - Mixed restrictive/obstructive
  - High altitude
  - Developmental disorders
- CTEPH (4)
- Multifactorial (5)
  - Metabolic - Thyroid disease
  - Hematological – splenomegaly
  - Systemic – sarcoidosis

WHO Classification: Group 1

Group 1—PAH
Idiopathic PAH
Heritable
BMPR2
ALK-1, endoglin (with or without HHT)
Unknown
Drug and toxin-induced
PAH associated with:
Connective tissue diseases
HIV infection
Portal hypertension
Congenital systemic to pulmonary shunts
Schistosomiasis
Chronic hemolytic anemia
Persistent pulmonary hypertension of newborn
Pulmonary veno-occlusive disease or pulmonary capillary hemangiomatosis

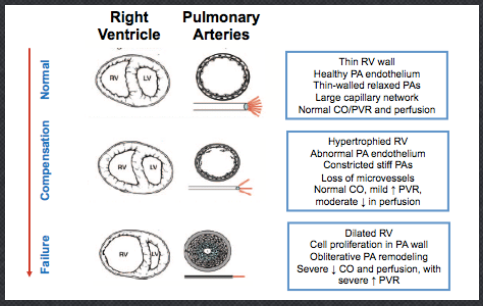
Epidemiology of PAH (WHO Group 1)

- Prevalence of PAH in associated conditions:
  - CTD[a]: 8%-12%[2,3]
  - CHD: 15%-30%[4]
  - PoPH: 2%-6%[5,6]
  - HIV: 0.5%[7]

1. Simonneau et al. *J Am Coll Cardiol*. 2009;54(1 suppl S):S43-S54. 2. Hachulla et al. *Arthritis Rheum*. 2009;60:1831-1839. 3. Mukerjee et al. *Ann Rheum Dis*. 2003;62:1088-1093. 4. Landzberg. *Clin Chest Med*. 2007;28:243-253. 5. Hadengue et al. *Gastroenterology*. 1991;100:520-528. 6. Krowka et al. *Hepatology*. 2006;44:1502-1510. 7. Sitbon et al. *Am J Respir Crit Care Med*. 2008;177:108-113. 8. Humbert et al. *Am J Respir Crit Care Med*. 2006;173:1023-1030.

PATHOPHYSIOLOGY/NATURAL HISTORY

Progression of Pulmonary Vascular Disease



Consequences of PAH

↑ PVR

↓

↑ RV afterload

↓

↓ RV ejection (CO) and PBF

↓

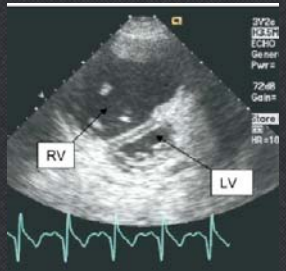
RV hypertrophy and dilation

↓

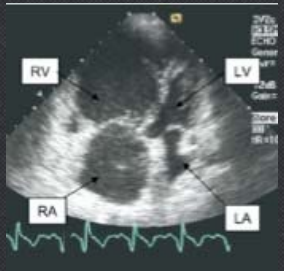
Death

Echocardiographic Characteristics of PAH

Parasternal view

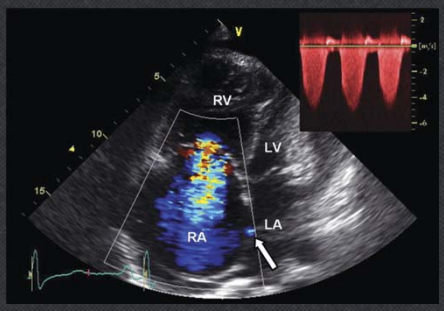


Apical 4-chamber view

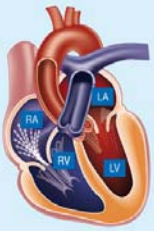


Echocardiography provides estimated RV systolic pressure and morphologic cardiac abnormalities

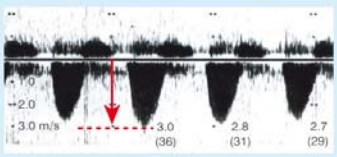
Tricuspid Regurgitation



Echocardiography in PAH



Tricuspid regurgitation (TR)



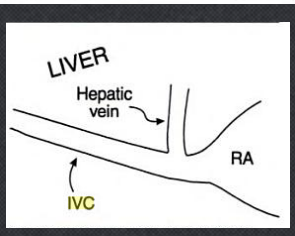
TR jet velocity (v)

Syst PAP= Right Ventricular Systolic Pressure
(in absence of pulmonary outflow obstruction)
$RVSP = 4v^2 + RAP^*$

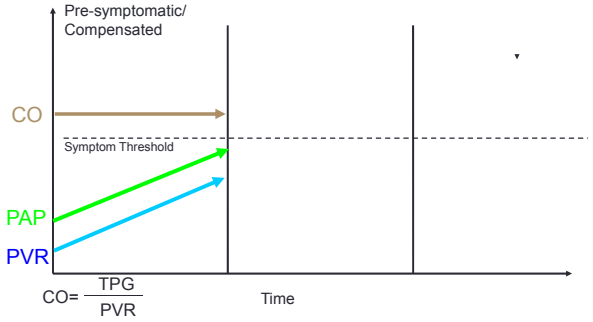
*ESC guidelines. Eur Heart J 2004 Dec;25(24):2243–78.

Estimation of RAP

Findings	Estimated RAP
Small & collapse	0–5 mmHg
Normal & normal ↓ size	5–10 mmHg
Normal & abnormal ↓ size	10–15 mmHg
Dilated & abnormal ↓ size	15–20 mmHg
Dilated & no change in size	>20 mmHg

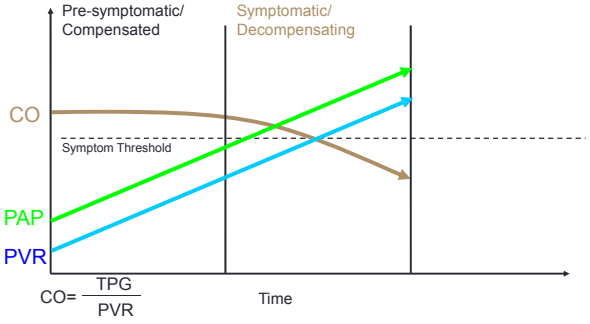


Schematic Progression of PAH



PAP=pulmonary artery pressure; PVR=pulmonary vascular resistance; TPG=transpulmonary gradient.
Courtesy of: Vallerie V. McLaughlin, MD.

Schematic Progression of PAH



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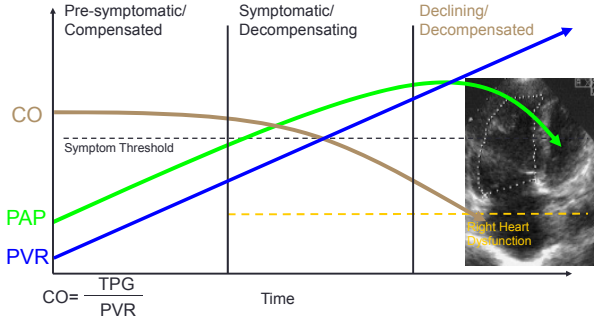
Schematic Progression of PAH



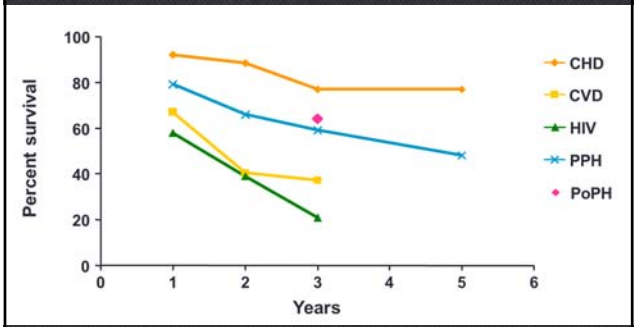
PAP=pulmonary artery pressure; PVR=pulmonary vascular resistance; TPG=transpulmonary gradient.
Courtesy of: Vallerie V. McLaughlin, MD.

PAH Determinants of Risk

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	Rapid
Syncope	No	Occasional syncope[b]	Repeated syncope [c]
WHO functional class	I, II	III	IV
6MWD	>440 m	165–440 m	<165 m
Cardiopulmonary exercise testing	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	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)	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	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%

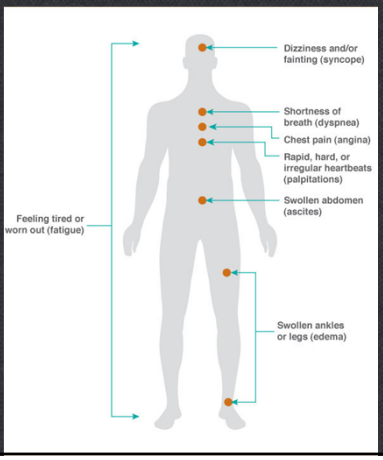
European Heart Journal, Volume 37, Issue 1, 1 January 2016, Pages 67–119,https://doi.org/10.1093/eurheartj/ehv317 - Table 1

Survival by PAH Etiology

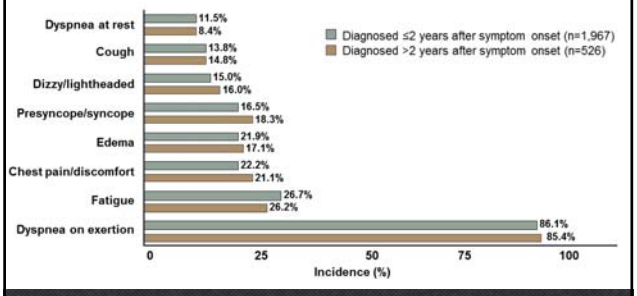


McLaughlin and McGoon. *Circulation*. 2006;114:1417-1431. 2. McLaughlin et al. *Chest*. 2004;126:78S-92S.

SIGNS, SYMPTOMS & DIAGNOSIS



REVEAL: Most Frequent PAH Presenting Symptoms



Elliott EG, et al. *Chest.* 2007;132(suppl 4):631S.

NYHA Functional Classification

NYHA	Definition
Class I	• No symptoms with ordinary physical activity
Class II	• Some symptoms with ordinary activity. Slight limitation of activity
Class III	• Symptoms with less than ordinary activity. Marked limitation of activity
Class IV	• Symptoms with any activity or even at rest

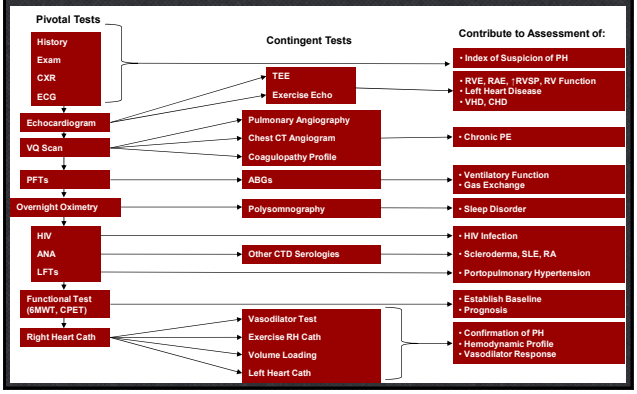
WHO Functional Classification

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

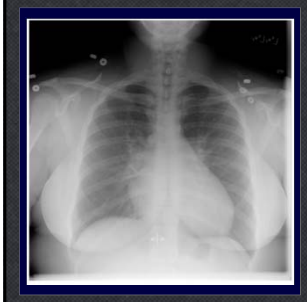
Diagnosis of PAH

Diagnostic	Outcomes
History and physical[b]	• Evaluate signs and symptoms, family history, associated diseases, ANA
Chest x-ray[b]	• Assess for RV enlargement, peripheral hypovascularity (pruning), and prominent pulmonary arteries
Echocardiogram	• Assess for RV and RA enlargement, RV dysfunction, TR velocity to measure RVSP
Electrocardiogram	• Evaluate for right heart enlargement and strain, cardiac rhythm
Cardiac catheterization[b]	• Evaluate for CHD; measure wedge pressure or LVEDP; establish severity and prognosis; test vasodilator therapy
PFTs with DLCO	• Assess obstructive and restrictive airway disease
VQ scan	• Rule out thromboembolic disease

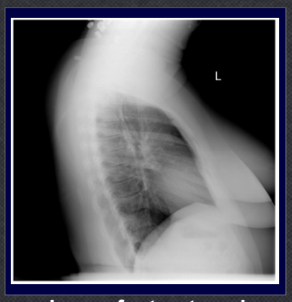
PAH Diagnostic Testing



Chest X-Ray Consistent With PH

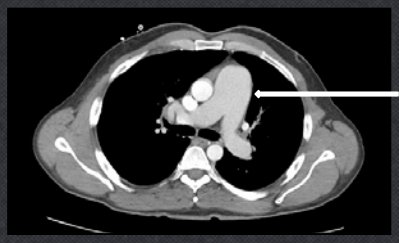


RA enlargement, prominent PA



Loss of retrosternal airspace RV enlargement

CT-Chest: Pulmonary Dilation



PA Dilation 3.9cm

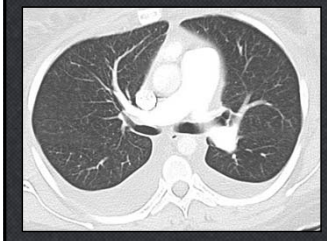
PA size and ratio vary by patient size and sex
Sex-specific cutoff values
- Men 29 mm
- Women 27 mm

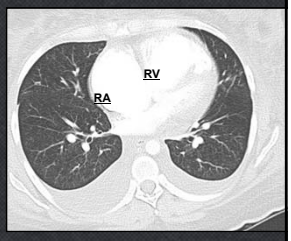
Normal PA:aortic ratio = 0.9

Dilated Pulmonary Artery

Ng CS, et al. *J Thorac Imaging*. 1999;14:270-278.

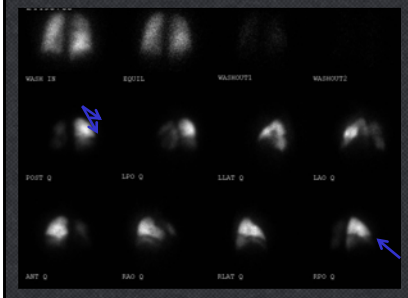
CT-Chest: RA, RV, PA Enlargement





Enlarged PA, RV, RA, Pleural Effusions
Lack of Significant Parenchymal Disease

Ventilation Perfusion (V/Q) Scintigraphy in CTEPH



Case Example: Perfusion is intact primarily to the right upper lobe

Hypo-perfused regions representing perfusion defects

Auger WR, et al. *Clin Chest Med.* 2010;31:741-758.

Pulmonary Hypertension

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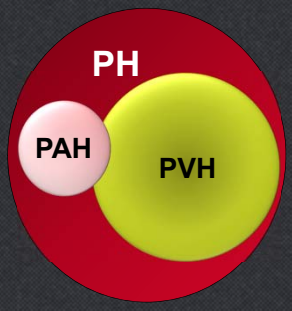
RIGHT HEART CATHETERIZATION

Right Heart Catheterization

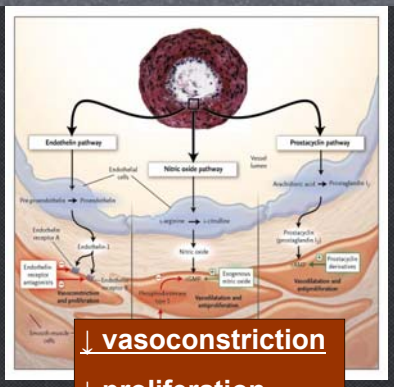
- Confirm diagnosis
  - Gold standard
- Evaluate severity of PAH
- Assess congenital heart defects
- Exclude left-sided heart disease
- Assess response to vasodilator challenge
- Assess key hemodynamic parameters

Importance of Right Heart Catheterization

- Vast majority of PH cases are non–WHO group 1
- PAH characterized by
  - ↑PVR
  - ↑TPG
  - Normal left-sided filling pressures
- PVH characterized by
  - ↑PCWP
  - ↑LVEDP
  - ↑LAP



PAH Disease Pathways



↓ vasoconstriction

↓ proliferation

PAH Disease Pathways

- Soluble GC Stimulator
  - Enhancing the sensitivity of sGC to nitric oxide NO
  - Direct sGC stimulator that will activate sGC to synthesize cGMP in the absence of NO
- Nitric Oxide Deficiency
  - PDE-5 inhibitors block the activity of PDE-5, restoring vasodilation through an increase in cGMP
- Prostacyclin
  - Supplement the deficiency in PGI2, resulting in vasodilation and inhibition of platelet aggregation.
- Endothelin Receptor Antagonists
  - Block the binding of ET-1 to its receptors, preventing a vasoconstriction effectB

TREATMENT OF PULMONARY ARTERIAL HYPERTENSION

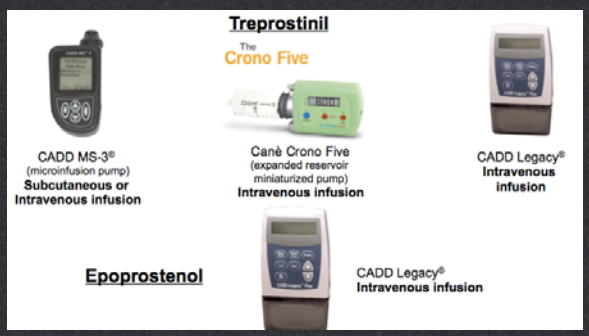
PAH Treatment Goals

- Improve quality of life and survival
- Improve to FC I or II
- Improve 6MWD to ≥380 m
- Improve hemodynamics
- Alleviate symptoms

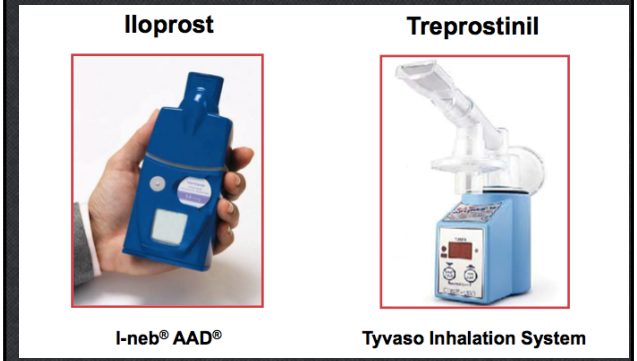
PAH Treatment

- Endothelin Receptor Antagonists
  - Bosentan
  - Ambrisentan
  - Macitentan
- Phosphodiesterase Inhibitors
  - Sildenafil
  - Tadalafil
- Soluble GC Stimulator
  - Riociguat
- Prostanoids
  - Epoprostenol (IV)
  - Treprostinil (IV, SQ, inhaled, oral)
  - Iloprost (inhaled)
  - Selexipeg (oral)
- Calcium Channel Blockers

Prostanoids - Infused



Prostanoids -- Inhaled



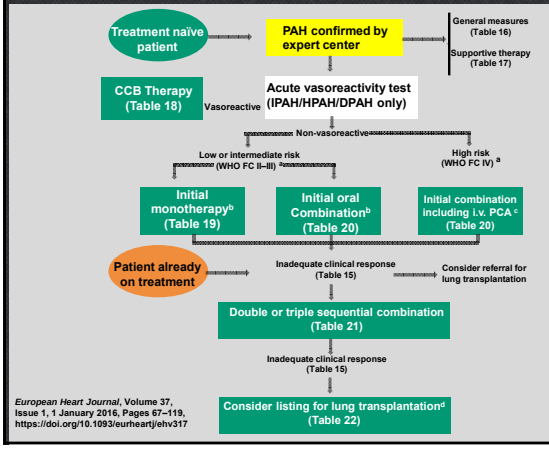
Calcium Channel Blocker Therapy

- Used for patients with IPAH who respond to acute vasodilator[a] testing at the time of cardiac catheterization
  - Response defined by reduction in mPAP ≥10 mm Hg to a mPAP ≤40 mm Hg, with an unchanged or increased CO[1]
- Approximately 13% of patients with IPAH respond to acute vasodilator testing[2]
  - Only 6.8% had a favorable clinical response to chronic CCB therapy at 1 year
- Other PAH treatments should be evaluated if patient does not improve to FC I or II

1. Badesch et al. *Chest*. 2007;131:1917-1928. 2. Sitbon et al. *Circulation*. 2005;111:3105-3111.

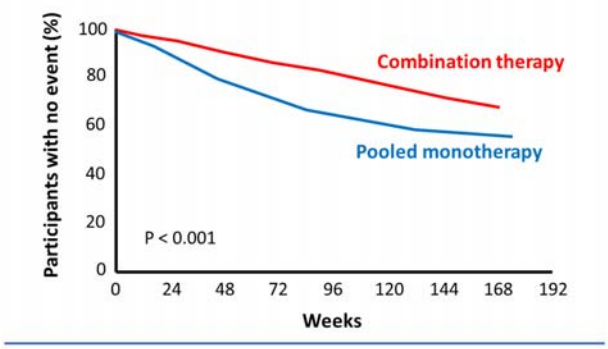
PAH MANAGEMENT TRENDS & OUTCOMES

Treatment Algorithm for PAH



European Heart Journal, Volume 37, Issue 1, 1 January 2016, Pages 67–119, https://doi.org/10.1093/eurheartj/ehv317

Ambition: upfront combination of Tadalafil + Letairis



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

MORTALITY IN PATIENTS WITH PAH IN THE MODERN ERA: DATA FROM THE QUALITY ENHANCEMENT RESEARCH INITIATIVE (QUERI)

QuERI Methods

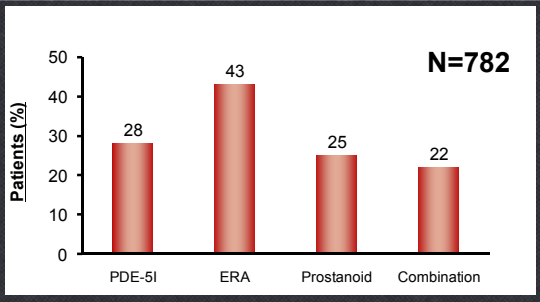
- Despite advances in PAH therapy, patient mortality remains unacceptably high
- Although ACCP guidelines have been developed to assist clinicians in managing patients with PAH, the effectiveness of these guidelines is unclear
- Database was designed to collect information regarding medical management of patients with PAH initiated in 2005. Newly and previously diagnosed patients were enrolled (N=782)
  - Patients were enrolled from PAH centers and community centers
- Study determined whether ACCP guidelines were followed, including RHC for diagnosis

QuERI: Patient Demographics and Baseline Characteristics[1,2]

	All cases (N=782)
Disease subtype, %	
Idiopathic	38
Familial	3
Connective tissue diseases	30
Congenital heart diseases	7
Portal hypertension	4
Drug exposure	7
HIV infection	4
WHO functional class, %	
I	9
II	39
III	48
IV	5

1. McLaughlin et al. Am J Respir Crit Care Med. 2009;179:A1043. 2. Mathier et al. Am J Respir Crit Care Med. 2009;179:A2658.

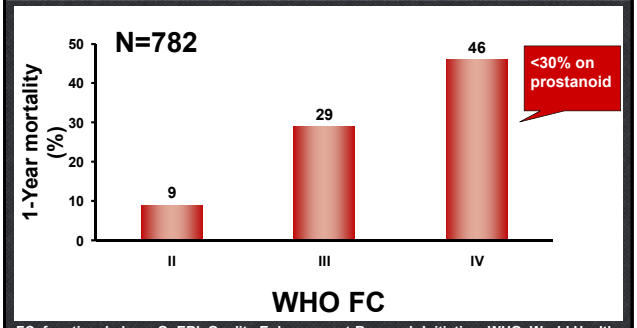
QuERI: Overall PAH Therapy Use in Enrolled Population[1,2]



ERA, endothelin receptor antagonist; PDE-5I, phosphodiesterase type 5 inhibitor; QuERI, Quality Enhancement Research Initiative.

1. McLaughlin et al. *Am J Respir Crit Care Med*. 2009;179:A1043. 2. Mathier et al. *Am J Respir Crit Care Med*. 2009:179:A2658.

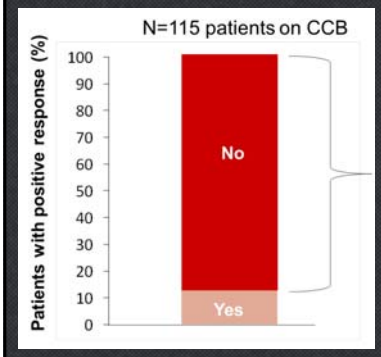
QuERI: 1-Year Mortality Remains High in FC IV Patients[1,2]



FC, functional class; QuERI, Quality Enhancement Research Initiative; WHO, World Health Organization.

1. McLaughlin et al. *Am J Respir Crit Care Med*. 2009;179:A1043. 2. Mathier et al. *Am J Respir Crit Care Med*. 2009:179:A2658.

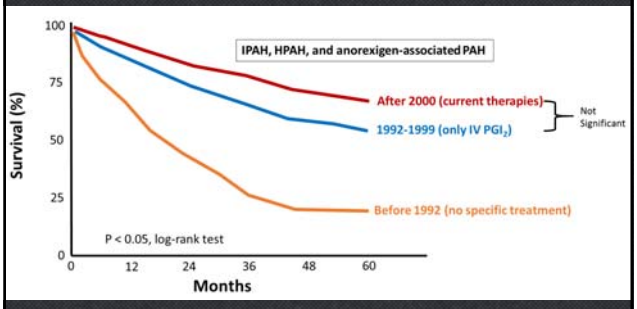
QuERI: Current Use of CCB Therapy



- 87% of patients receiving CCB did not respond to acute vasoreactivity testing
- ~10% were receiving PAH therapy without RHC-confirmed diagnosis

McLaughlin et al. *Am J Respir Crit Care Med*. 2009;179:A1043.

Has Survival Meaningfully Improved With Modern Therapies?



Sitbon et al. European Respiratory Society; September 16-18, 2007; Stockholm, Sweden.

Conclusions

- PAH is a rare disease associated with very high mortality if untreated.
- PAH is a diagnosis of exclusion and diagnosis requires a comprehensive cardiopulmonary evaluation as well as a right heart catheterization
- Current guidelines recommend use of upfront combination therapy, if tolerated.
- Patients with advanced PAH and right heart failure, should be treated with parental prostacyclins alone or in combination with other oral specific PAH vasodilators.
- Goals of care: functional capacity class I or II and normal right ventricular function