Clinical Advances in Pulmonary Arterial Hypertension

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Faculty

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Disclosures

- **Franck Rahaghi, MD, MHS, FCCP** serves as a consultant, lecturer and reseacrher for Actelion, Bayer, Gilead, United Therapeutics and Lung Biotech.

Learning Objectives

1. Discuss the pathophysiology of pulmonary arterial hypertension (PAH)
2. Recognize signs and symptoms suggestive of PAH and the appropriate diagnostic strategy
3. Describe how to monitor patients with PAH for disease progression
4. Review current and emerging treatments for patients with PAH

Pulmonary Hypertension

- Is an imprecise term!
- One interpretation can be Increased Pulmonary Pressure which happens in multiple conditions and is not a disease but a manifestation of disease: An echo cardiogram shows Pulmonary Hypertension
- A Set of diseases which manifest with increased pulmonary pressure
- Incorrectly and interchangeably used as Pulmonary Arterial Hypertension

What Is Pulmonary Arterial Hypertension?

Chronic, progressive, cardiopulmonary condition associated with:

- Progressive exertional shortness of breath
- Decreased endurance related to physical activity
- Syncope, chest pain or fatigue

Hemodynamically defined as:

- Abnormal increase in pulmonary artery pressure
- Normal pulmonary capillary wedge pressure
- Increased pulmonary vascular resistance

Pulmonary hypertension results in right ventricular pressure/volume overload leading to right heart failure and death

Echocardiographic Estimation of Pulmonary Hypertension in Clinical Practice

- An estimated RVSP ≥35 mm Hg should raise concern, especially when accompanied by evidence of right heart pressure overload
  - Right atrial enlargement
  - Right ventricular enlargement, hypertrophy or dysfunction
  - Significant tricuspid regurgitation
- American College of Cardiology / American Heart Association expert consensus recommends further evaluation of patient with dyspnea and an estimated RVSP >40 mm Hg

Rudski LG, et al. *J Am Soc Echocardiogr*. 2010;23:685-713.
McLaughlin VV, et al. *Circulation*. 2009:119:2250-2294.

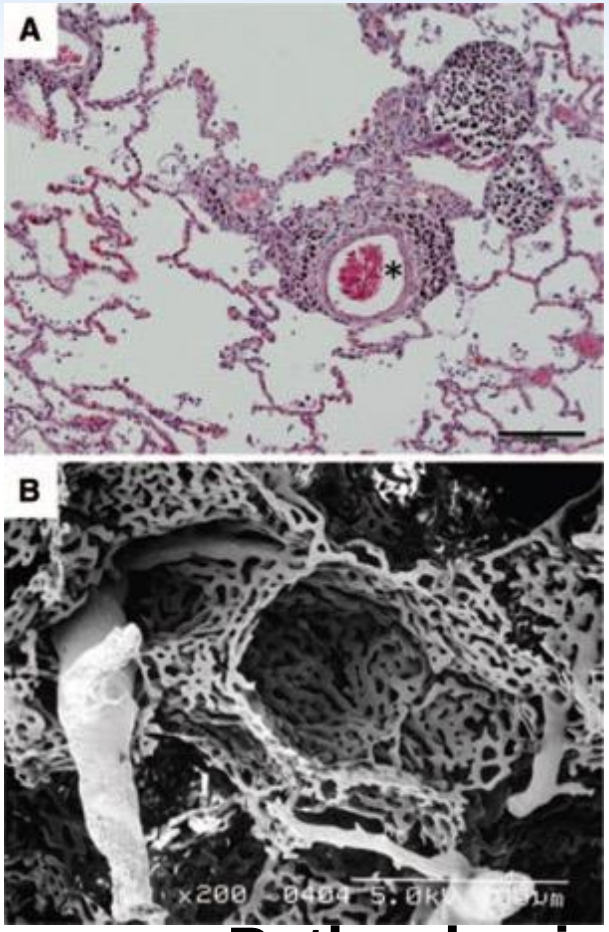
Fifth World Symposium on Pulmonary Hypertension: Diagnostic Definition of PAH

Pulmonary Arterial Hypertension	
Mean pulmonary artery pressure (mPAP)	≥25 mm Hg
And	
Mean pulmonary artery wedge pressure (PAWP)	≤15 mm Hg
With	
Pulmonary vascular resistance (PVR) **As measured by right-heart catheterization.**	>3 Wood units

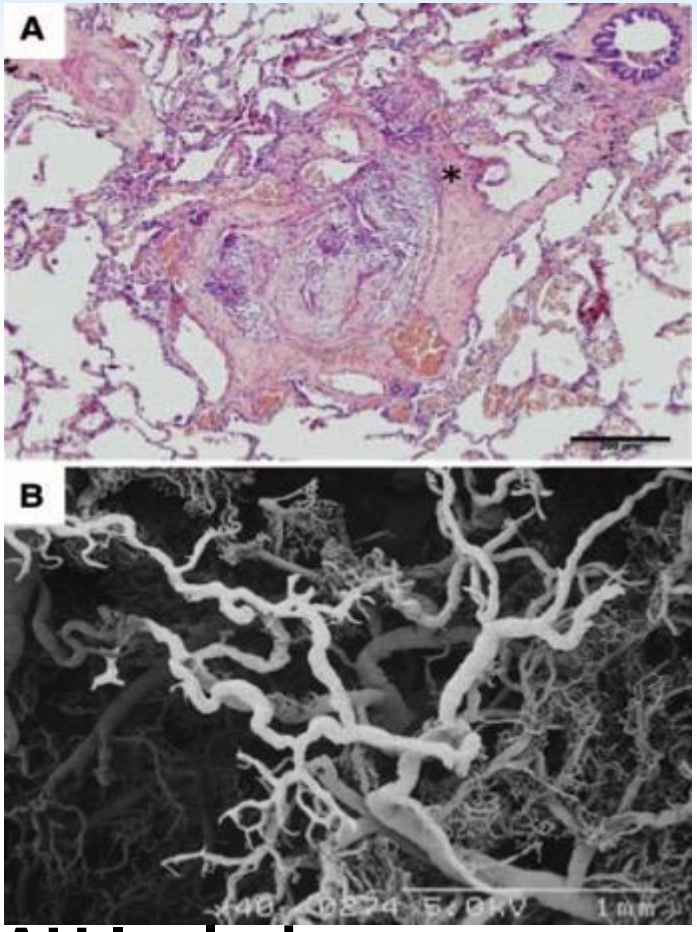
Hoeper MM, et al. J Am Coll Cardiol. 2013;62:D42-50.

Pulmonary Vascular Pathology

Normal Pulmonary Artery



Pulmonary Arterial Hypertension



Pathophysiology of PAH Includes: Vasoconstriction, Vasoproliferation, and Eventual Right Heart Failure

Miura A, et al. Circulation 2010;121:2151

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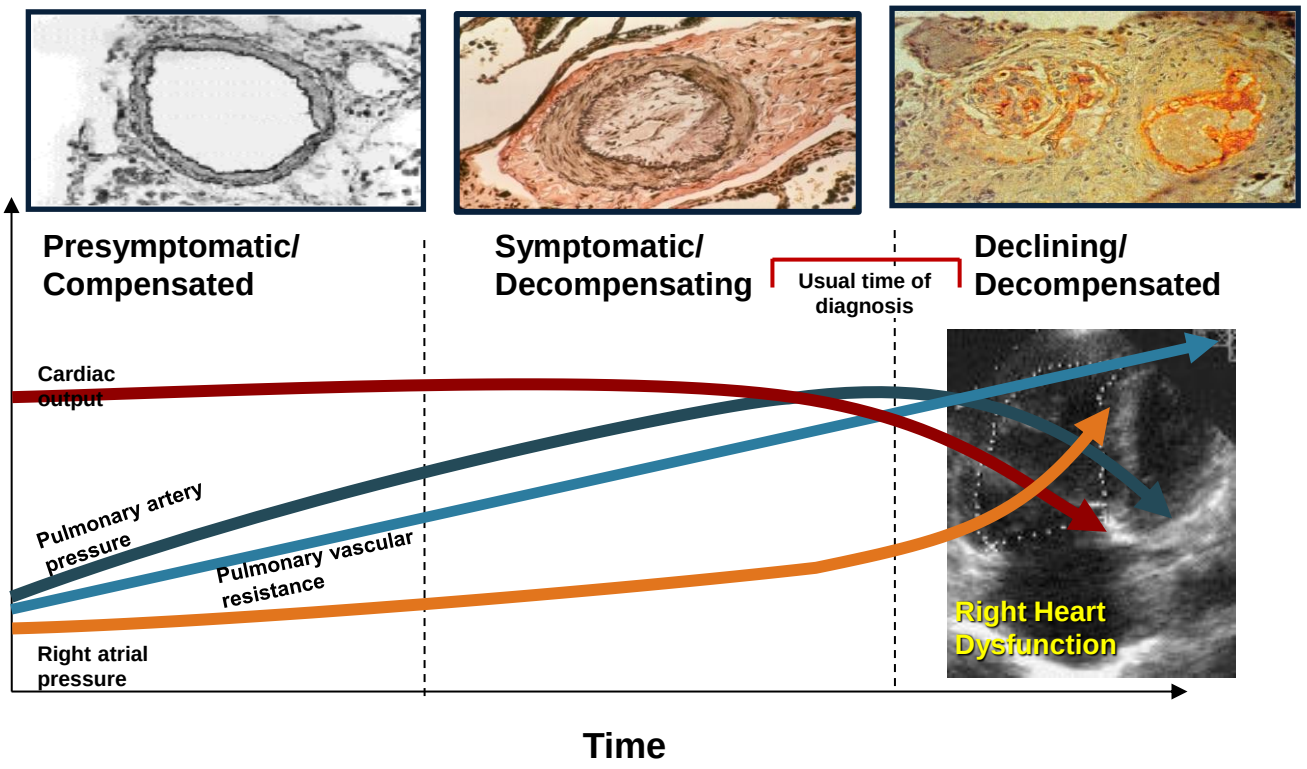
Schematic Progression of PAH



Adapted from: Hill NS. *Pulmonary Hypertension Therapy*. Summit Communications, LLC; 2006:9.

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Presentations of Dyspnea

Sudden onset

- ✓ Pulmonary embolism, pneumonia, myocardial infarction

Slowly progressive conditions

- ✓ COPD, interstitial lung disease, cardiomyopathy, pulmonary vascular disease

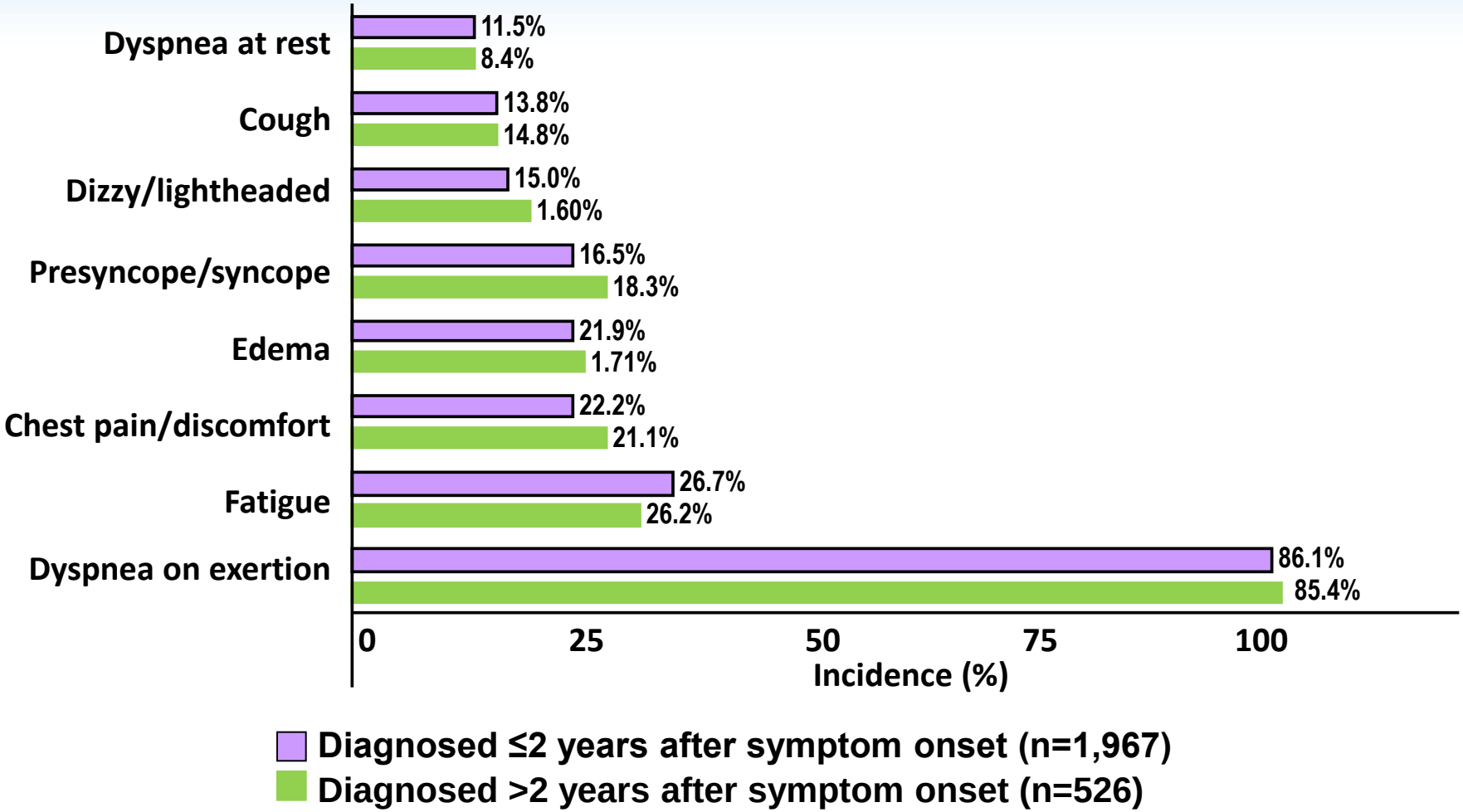
Dyspnea with chronic cough

- ✓ Airway disease, interstitial lung disease, GERD

Nocturnal symptoms

- ✓ Asthma, COPD, GERD, cardiomyopathy, neuromuscular conditions

REVEAL:
Most Frequent PAH Presenting Symptoms



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

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NYHA/WHO Functional Classification for PAH (Disease Severity)

Class I	No limitation of physical activity. Ordinary physical activity does not cause undue dyspnea, fatigue, chest pain, or near syncope.
Class II	Slight limitation of physical activity; no discomfort at rest. Ordinary activity causes undue dyspnea, fatigue, chest pain, or near syncope.
Class III	Marked limitation of physical activity; no discomfort at rest. Less than ordinary physical activity causes undue dyspnea, fatigue, chest pain, or near syncope.
Class IV	Inability to perform any physical activity without symptoms; signs of right ventricular failure or syncope; dyspnea and/or fatigue may be present at rest; discomfort is increased by any physical activity.

Taichman, et al. *Clin Chest Med*. 2007;28:1-22.

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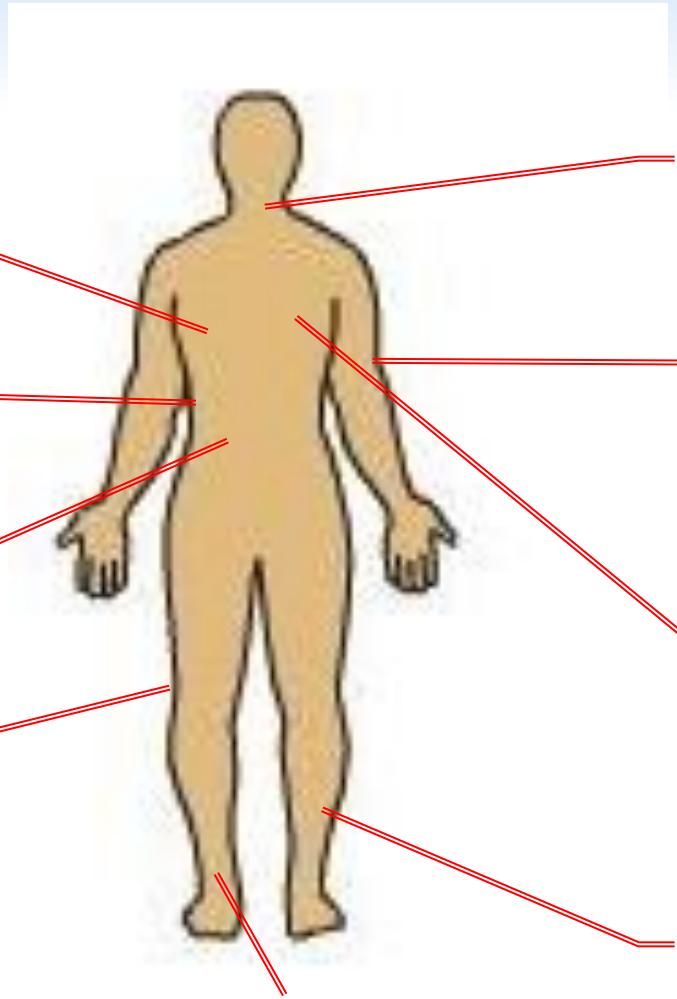
Examination Findings Suggestive of PH/PAH



Lungs: CTA w/o wheeze / crackles

Liver: Hepatomegaly Pulsatile liver

Abdomen: Ascites

Joint: Changes c/w CTD

Neck: HJR, JVD

Skin: Changes c/w CTD

Heart: Heave, RRR, Increased P2, TR SM

Extremities: Edema

Digits: Cool, Cyanotic

McGoon M, et al. Chest. 2004;126(suppl 1):14S-34S.

Classification: 5 Groups

1. PAH
- Idiopathic
- Heritable
- Drug and toxin induced
- Persistent PH of newborn
- Associated with
  - CTD
  - HIV
  - Portal HTN
  - Congenital HD
  - Schistosomiasis
- 1' PVOD and PCH
- 1" PPH of the newborn

2. PH due to Left Heart Disease
- Systolic Dysfunction
- Diastolic Dysfunction
- Valvular Disease

3. PH owing to Lung Disease and/or Hypoxia
- COPD
- ILD
- Sleep disordered breathing
- Alveolar hypoventilation syndromes
- Chronic exposure to high altitude
- Developmental abnormalities

4. Chronic ThromboEmbolic PH
- Other pulmonary artery obstruction

5. PH with unclear mechanisms
- Chronic hemolytic anemias / Splenectomy
- Sarcoidosis
- Pulm LCH / LAM
- Metabolic disorders
- Others – Chronic renal failure, tumoral obstruction, fibrosing mediastinitis

Classification of Pulmonary Arterial Hypertension by Etiology

Group 1-- Pulmonary Arterial Hypertension (PAH):

- Idiopathic (IPAH)
- Heritable (HPAH)
  - BMPR2
  - ALK-1, endoglin, SMAD9, CAV1, KCNK3
  - Unknown
- Drugs and toxins induced
- Associated with:
  - Connective Tissue Diseases
  - HIV Infection
  - Portal Hypertension
  - Congenital Heart Diseases
  - Schistosomiasis

- Group 1' Pulmonary Veno Occlusive Disease (PVOD) and/or Pulmonary Capillary Hemangiomatosis (PCH)
- Group 1" Persistent pulmonary hypertension of the newborn (PPHN)

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

Clinical Classification of Other Forms of Pulmonary Hypertension

Group 2 -- Pulmonary Hypertension Due to Left Heart Disease *(Most common)*

- Left ventricular systolic dysfunction
- Left ventricular diastolic dysfunction
- Valvular disease
- Congenital / acquired left heart inflow / outflow tract obstruction

Clinical Classification of Other Forms of Pulmonary Hypertension

Group 3 -- Pulmonary Hypertension Due to Lung Diseases and/or Hypoxemia *(Common)*

- Chronic obstructive pulmonary disease
- Interstitial lung disease
- Other pulmonary diseases with mixed restrictive and obstructive pattern
- Sleep-disordered breathing
- Alveolar hypoventilation disorders
- Chronic exposure to high altitude

Clinical Classification of Other Forms of Pulmonary Hypertension

Group 4 -- Chronic Thromboembolic Pulmonary Hypertension (CTEPH)

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

Clinical Classification of Other Forms of Pulmonary Hypertension

Group 5 -- Pulmonary Hypertension with Unclear Multifactorial Mechanisms

- Hematologic disorders: chronic hemolytic anemias, myeloproliferative disorders, splenectomy
- Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis, lymphangioleiomyomatosis, neurofibromatosis, vasculitis
- Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
- Others: tumor obstruction, fibrosing mediastinitis, chronic renal failure

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

Elevated Pulmonary Artery Pressures Are Seen in Wide Range of Conditions

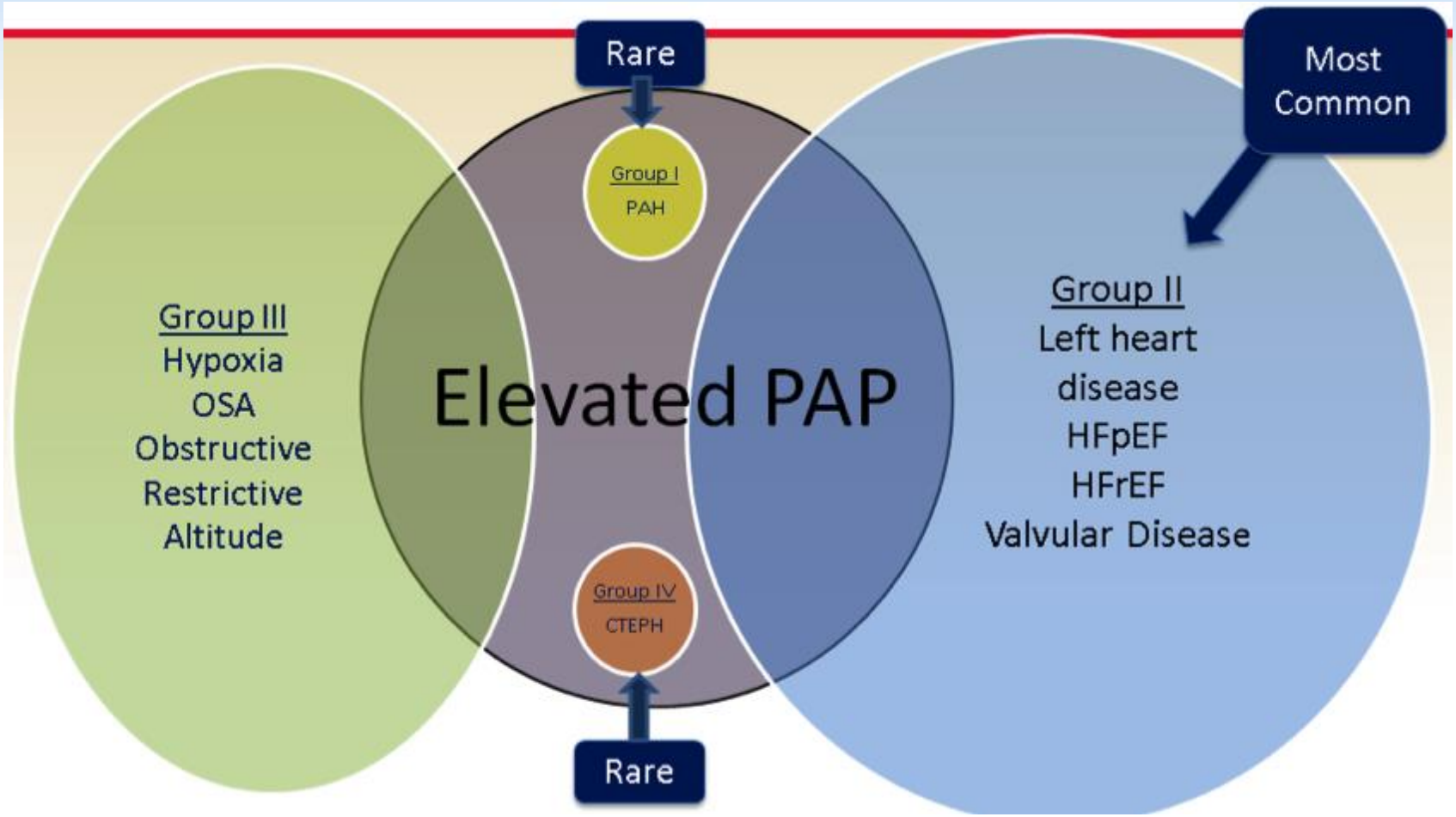


Image courtesy of Jean Elwing, MD

Prevalence of Pulmonary Hypertension

Condition	Prevalence of PH
Reduced EF heart failure	12 -14 % of pts with HF
Preserved EF heart failure	12 % of pts with HF
COPD	20 - 50 % of pts with advanced lung disease
Obstructive sleep apnea	20 %
Chronic thromboembolic	0.5 - 3.8 % pts with acute pulmonary embolism

Prevalence of PAH in associated conditions

Associated condition	Prevalence of PAH
Systemic sclerosis	7 - 12 %
Portal hypertension	2 - 6 %
Congenital heart disease Eisenmenger's syndrome	1 - 12 % with systemic to pulmonary shunts 25 - 50 %
HIV infection	0.5 %
Schistosomiasis	4.6 % with hepatic involvement

Diagnosing PAH: Assessment of Patients Presenting With Unexplained Dyspnea

- History including risk factors
- Physical examination
- Chest X-ray
- ECG
- PFT including DLCO
- Echocardiogram
- Chest CT
- Serology: HIV, Hepatitis B & C, ANA
- Ventilation-perfusion scan
- Right heart catheterization

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

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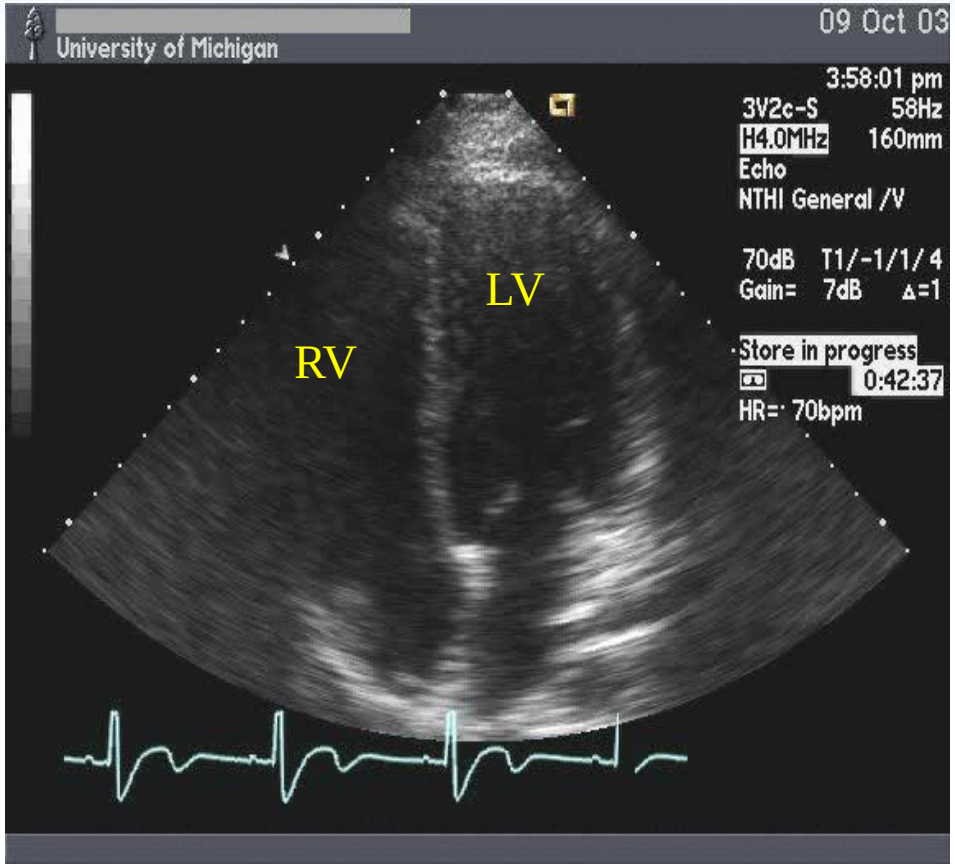
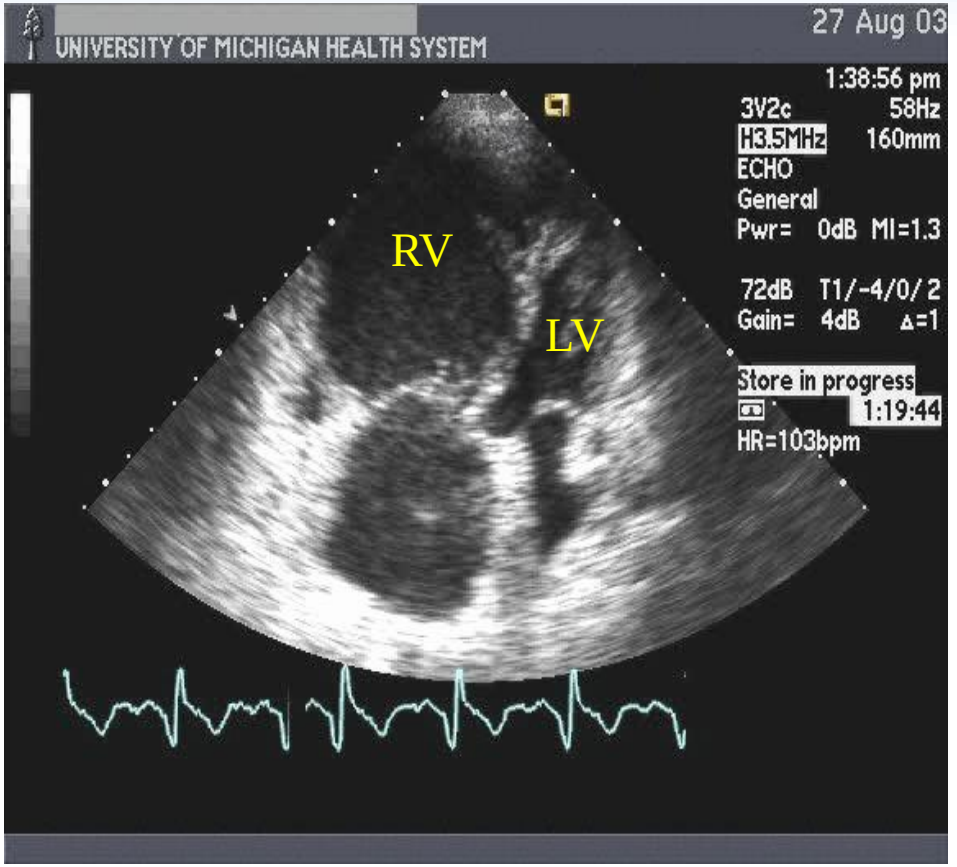
Echocardiogram: Apical Four Chamber



Normal structure and function

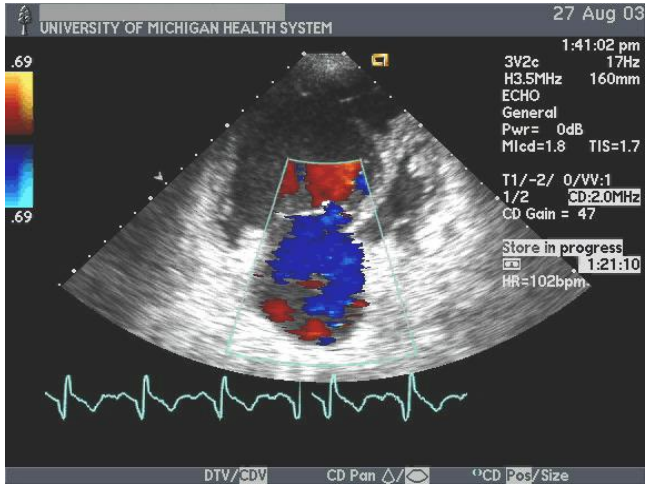


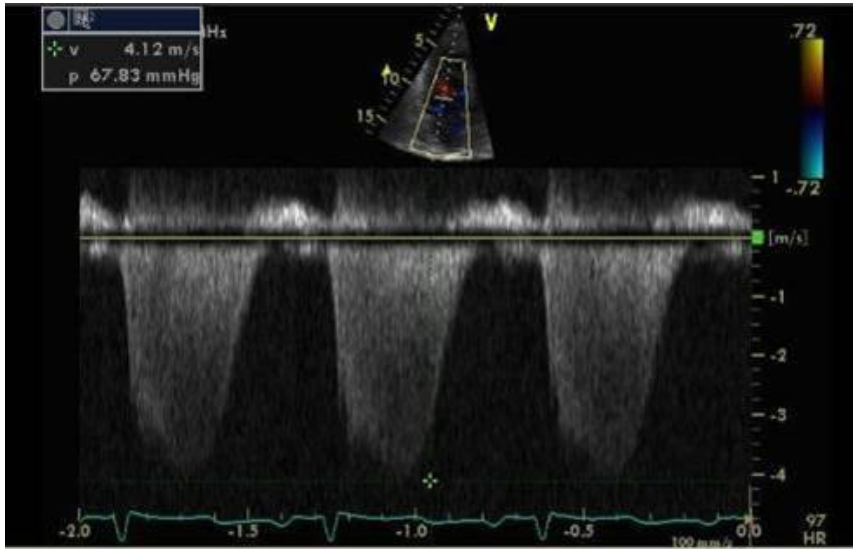
Abnormal structure and function

Image courtesy of Vallerie McLaughlin, MD

Echocardiography: Tricuspid Regurgitation

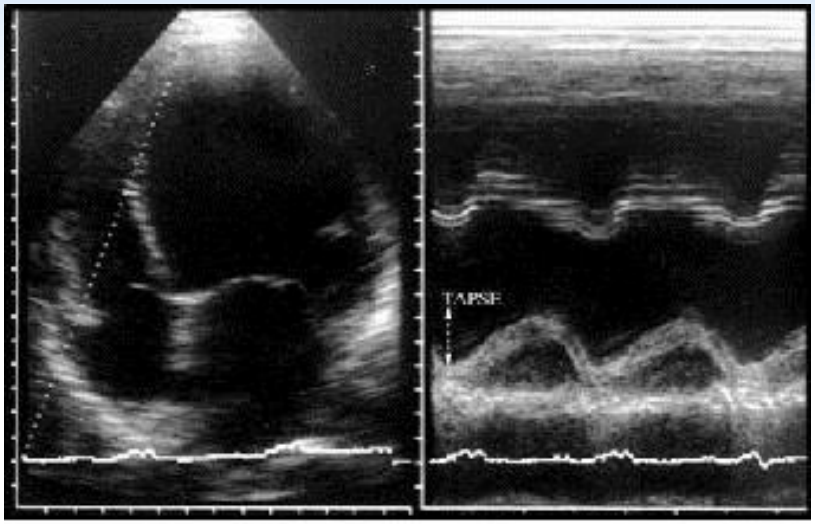
Modified Bernoulli's Equation:
$4 \times (V)^2 + RAP = RVSP\ (PASP)$



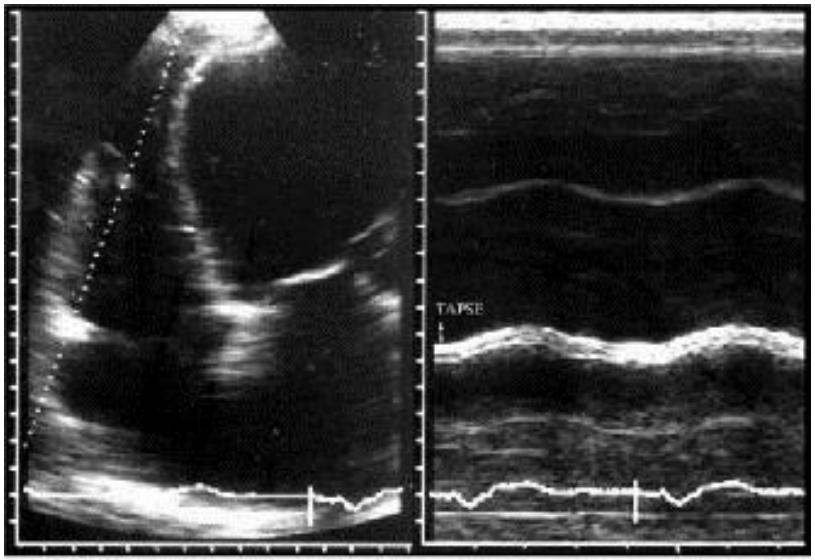


V=tricuspid jet velocity (m/s); RAP= right atrial pressure; RVSP=right ventricular systolic pressure; PASP=pulmonary artery systolic pressure.

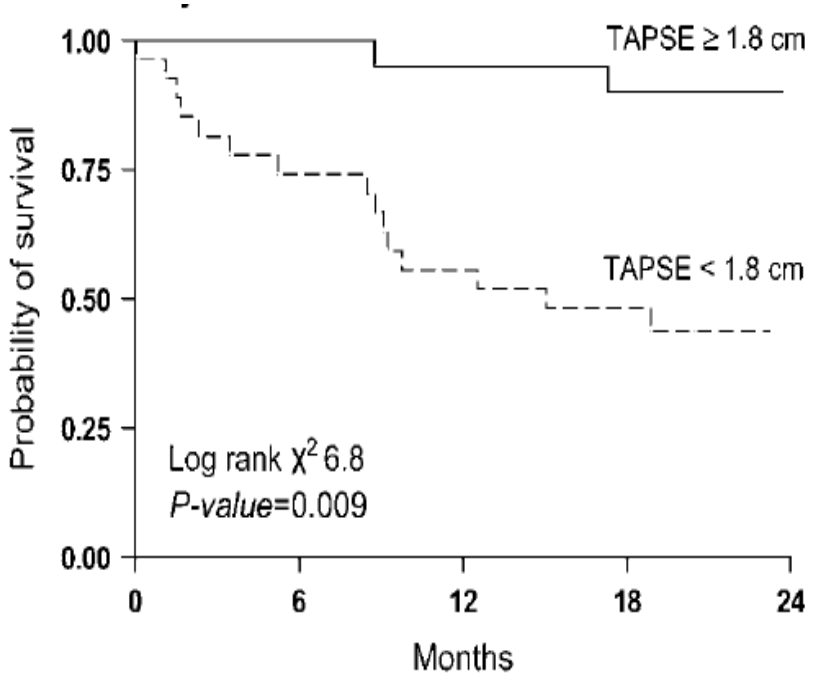
Tricuspid Annular Plane Systolic Excursion (TAPSE)



Normal TAPSE



Reduced TAPSE



Forfia et al AJRCCM 2006; 174:1034-1041

Echocardiogram in Pulmonary Hypertension

Echocardiogram findings in pulmonary hypertension (PH)

- RA/RV
  - Right atrial enlargement (RAE), RV dilation
  - RV dysfunction
  - Decreased tricuspid annular plane excursion (TAPSE)
  - Elevated pulmonary artery pressure (PAP)

Echocardiogram findings in PH associated with left heart disease

- Left atrial enlargement (LAE), LVH, LV dilation
- LV systolic dysfunction
- Grade II/III diastolic dysfunction
- Mitral/aortic valvular disease

Echocardiographic Estimation of Pulmonary Hypertension in Clinical Practice

- In the echo lab a commonly measured and reported value is systolic pulmonary artery pressure or RVSP

Normal resting values defined as peak systolic pressure of 35 or 36 mmHg

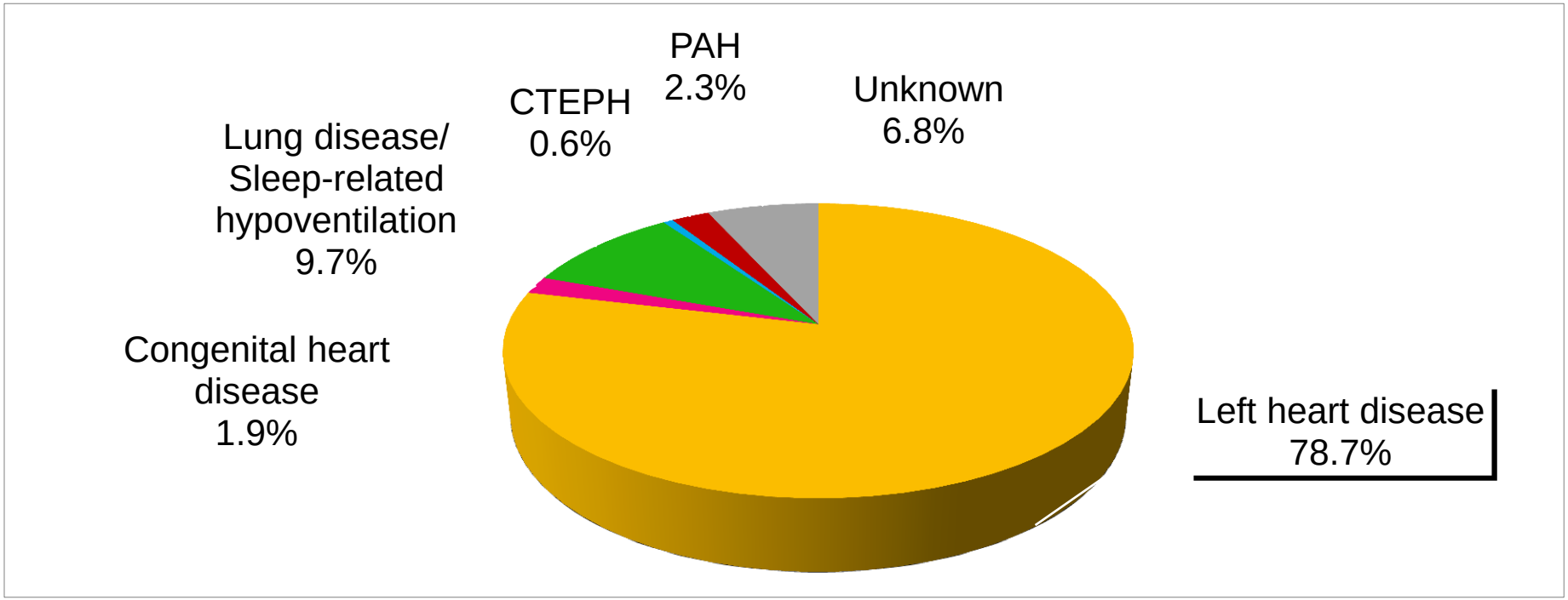
- American College of Cardiology / American Heart Association expert consensus recommends further evaluation of patient with dyspnea and an estimated RVSP >40 mm Hg

- Echo-derived reports of PH are not considered diagnostic
- **Further work-up is required**

Rudski LG, et al. J Am Soc Echocardiogr. 2010;23:685-713.
McLaughlin VV, et al. Circulation. 2009:119:2250-2294.

PH by Echo ≠ PAH

- Single echo lab/Australian community of 160,000
- Etiology of PH noted on echocardiogram

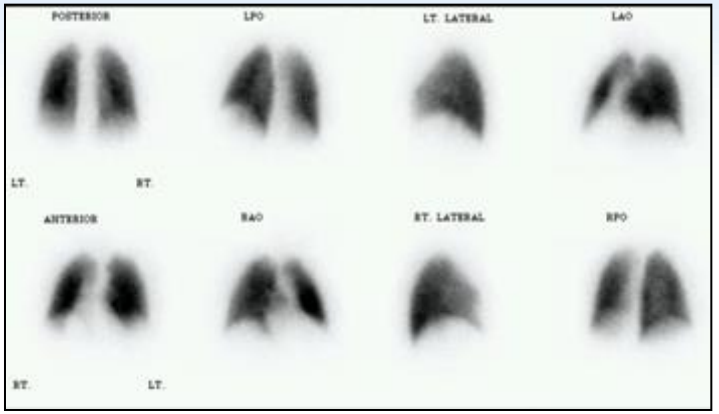


N=483 of 4579 patients with echo PASP >40 mm Hg.
Gabby E. *Am J Respir Crit Care Med*. 2007;175:A713.

Diagnostic Testing Results Frequently Found with PAH

Pulmonary function testing

- Preserved pulmonary mechanics
- Isolated low DLco
- Example: FEV1 88%, FVC 86%, DLco 42%

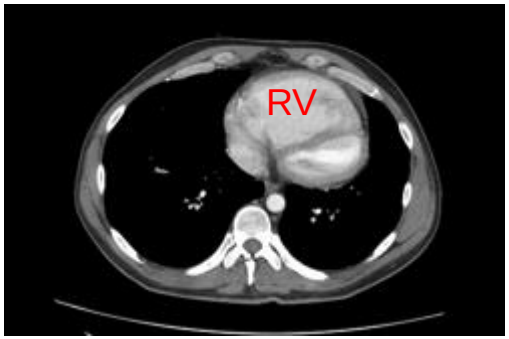


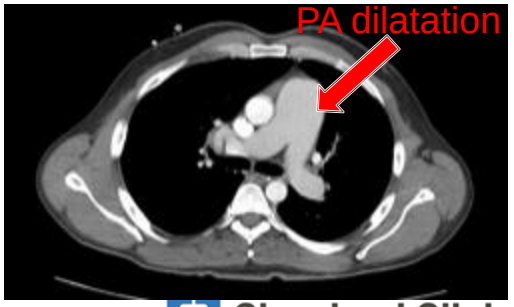
V/Q

- No evidence of acute or chronic PE

CT chest

- Lack of significant parenchymal disease
- Enlarged PA/RA/RV





Overnight pulse oximetry

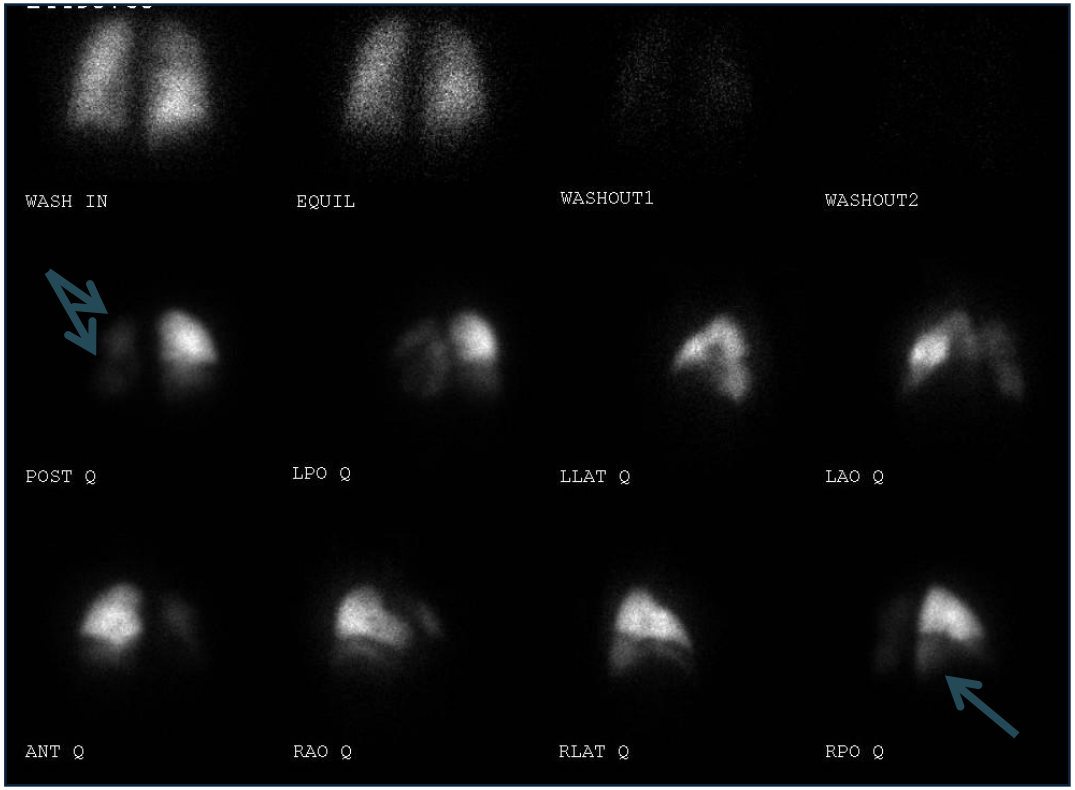
- Normal or mild hypoxemia

Polysomnogram

- Normal or controlled OSA

CT Chest with enlarged PA, RA, RV

Ventilation Perfusion (V/Q) Scintigraphy in CTEPH



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

Blue Arrows:
Hypo-perfused regions representing perfusion defects

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

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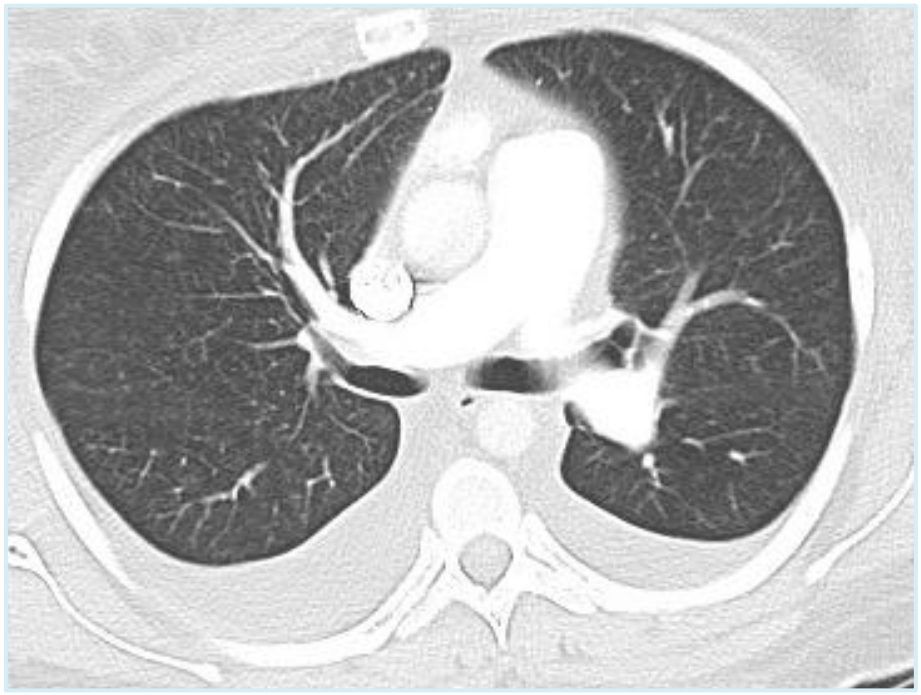
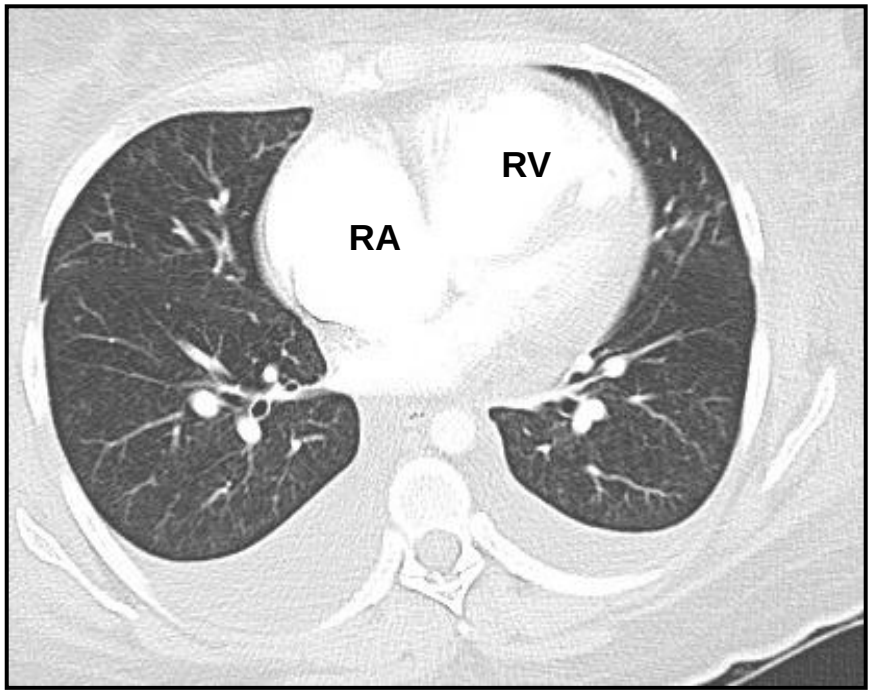
CT Findings Suggestive of PH

- Ratio of diameters of main pulmonary artery to ascending aorta (PA/Ao) ≥1.0 should prompt investigation for PH
  - Sensitivity 75%, specificity 92%, positive predictive value 95%, negative predictive value 64%
- RV/LV ratio ≥1.20 measured on the axial view or PA/Ao ≥1.0
  - Sensitivity 94%, specificity 80%, positive predictive value 91%, negative predictive value 87%

Spruijt O, et al. *Int J Cardiovasc Imaging.* 2015;31:871-879.

CT-Chest: RA, RV, PA Enlargement





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

Image courtesy of Jean Elwing, MD

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V/Q Scan More Sensitive Than CTA

	V/Q High-Probability Scans	CTPA
Sensitivity	96.2%	51.3%
Specificity	94.6%	99.3%
Accuracy	95.2%	82.8%
Negative Predictive Value	97.9%	79.7%
Positive Predictive Value	90.3%	97.6%

N=227 single center.

Tunariu N, et al. *J Nucl Med.* 2007;48:680-684.

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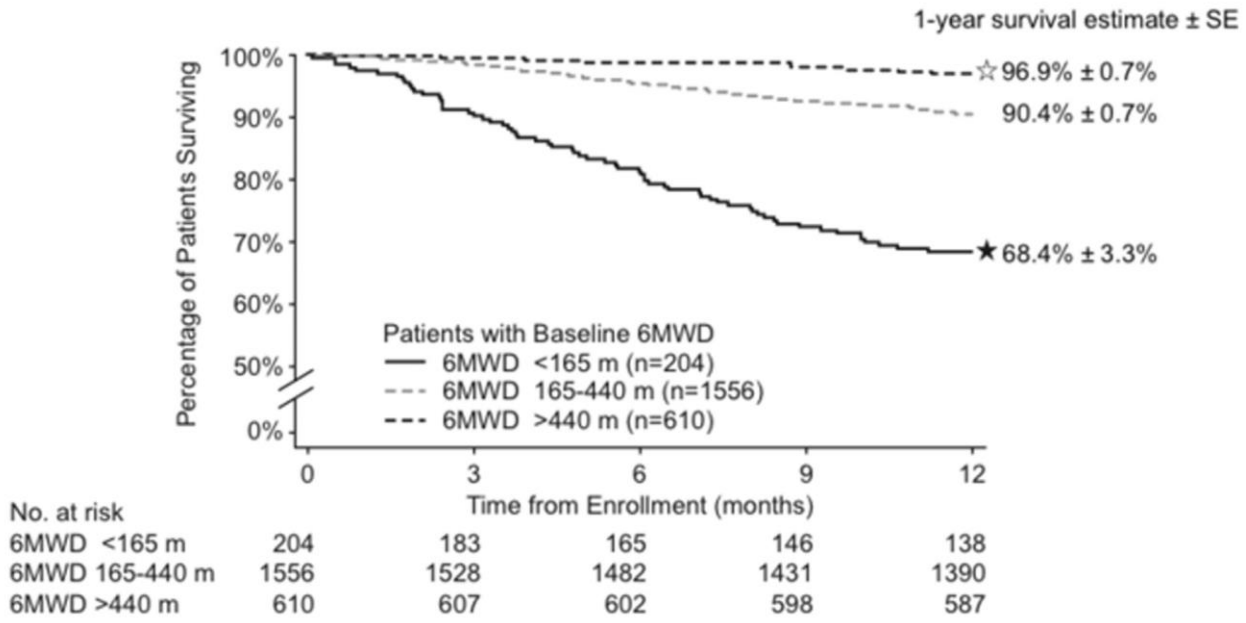
6MWT



Baseline 6MWD and survival at 1 year

REVEAL Registry data - Farber HW: 2015 JHLT 34

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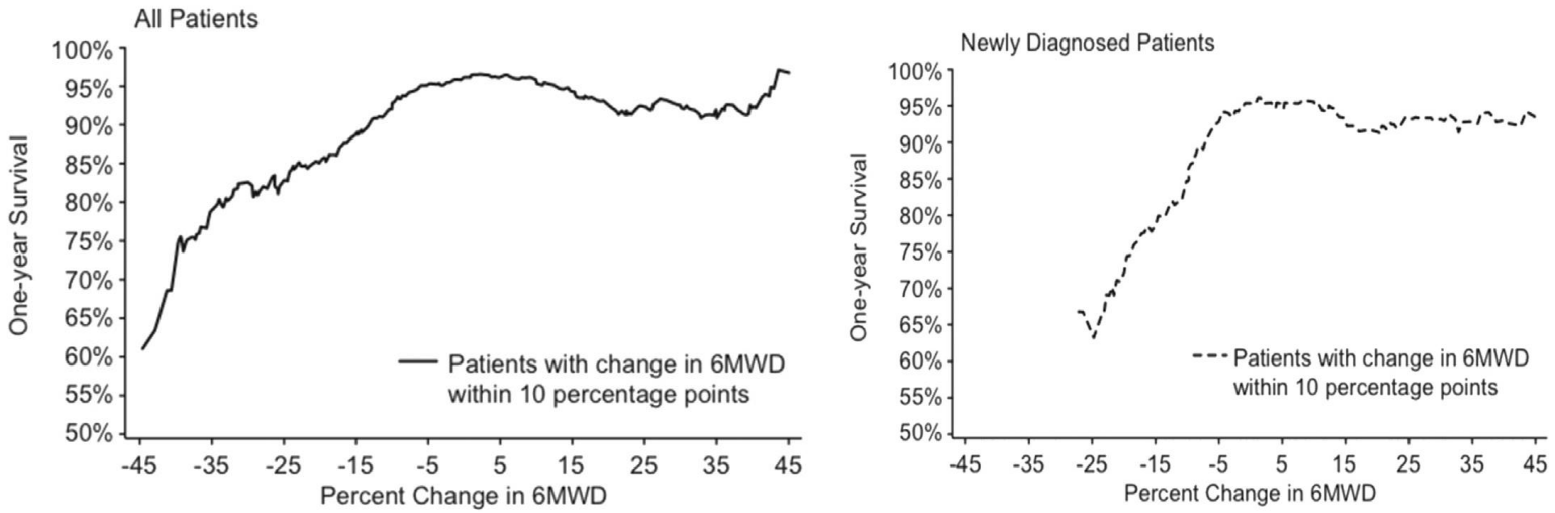
6MWT



Percent Change in 6MWD and survival at 1 year

REVEAL Registry data - Farber HW: 2015 JHLT 34

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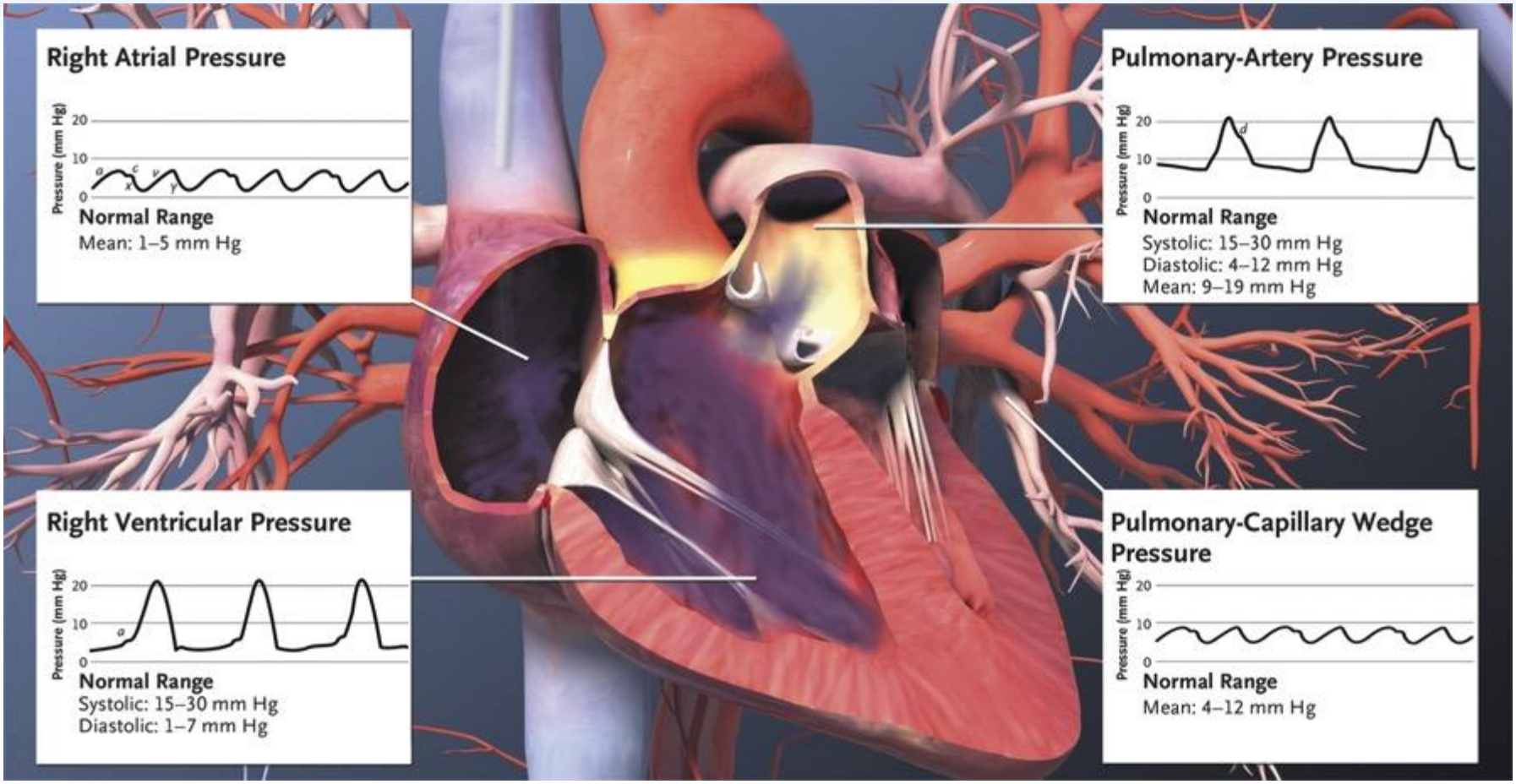
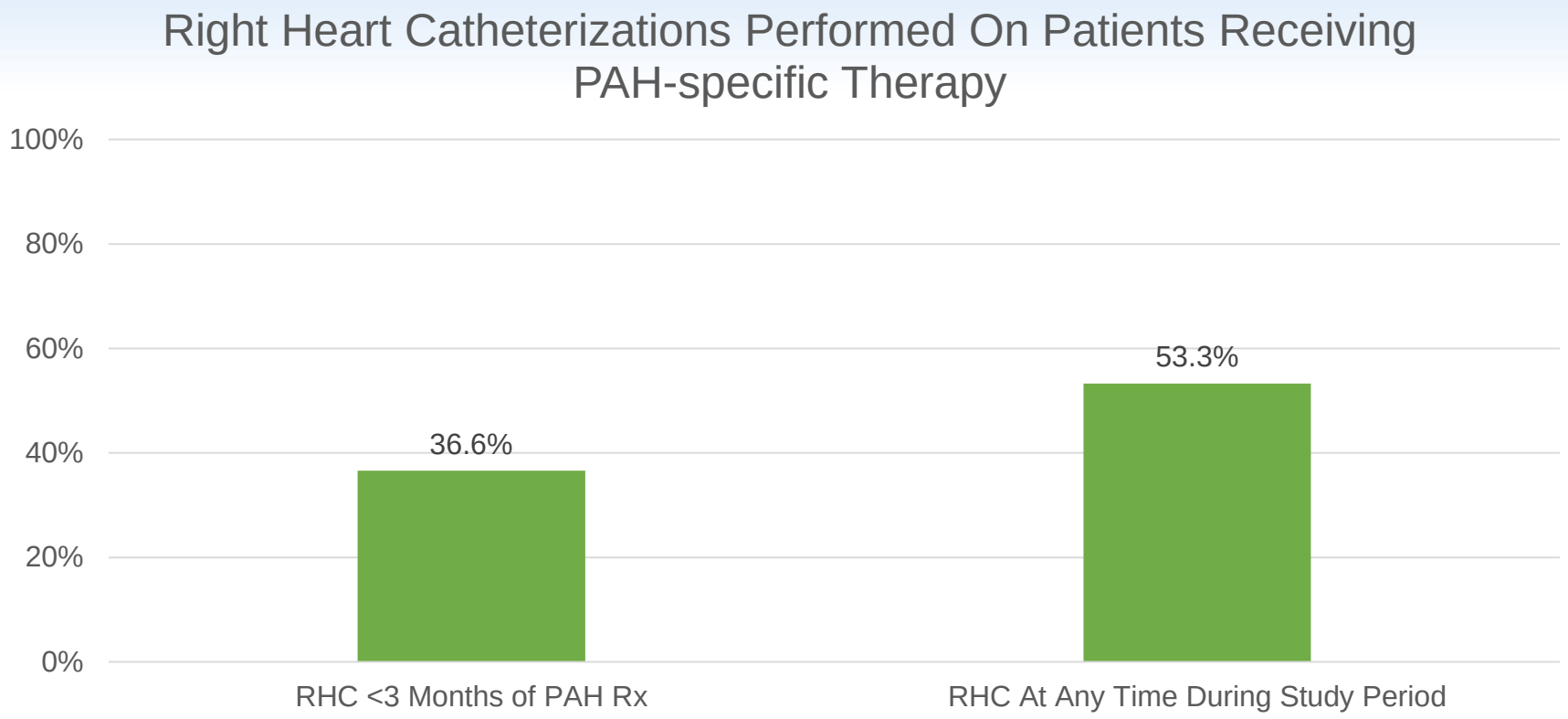
Right heart catheterization is necessary to establish cause of pulmonary hypertension



Low Use of Right Heart Catheterization Prior to Initiation of PAH-specific Medications



N=1,159 patients receiving PAH-specific medications from national (US) private insurance database. Patients were enrolled continuously for 27 months (12 months prior and 15 months after initial office visit for PH).

Duarte AG, Lin Y, Sharma G. Am J Respir Crit Care Med. 191;2015:A4802.

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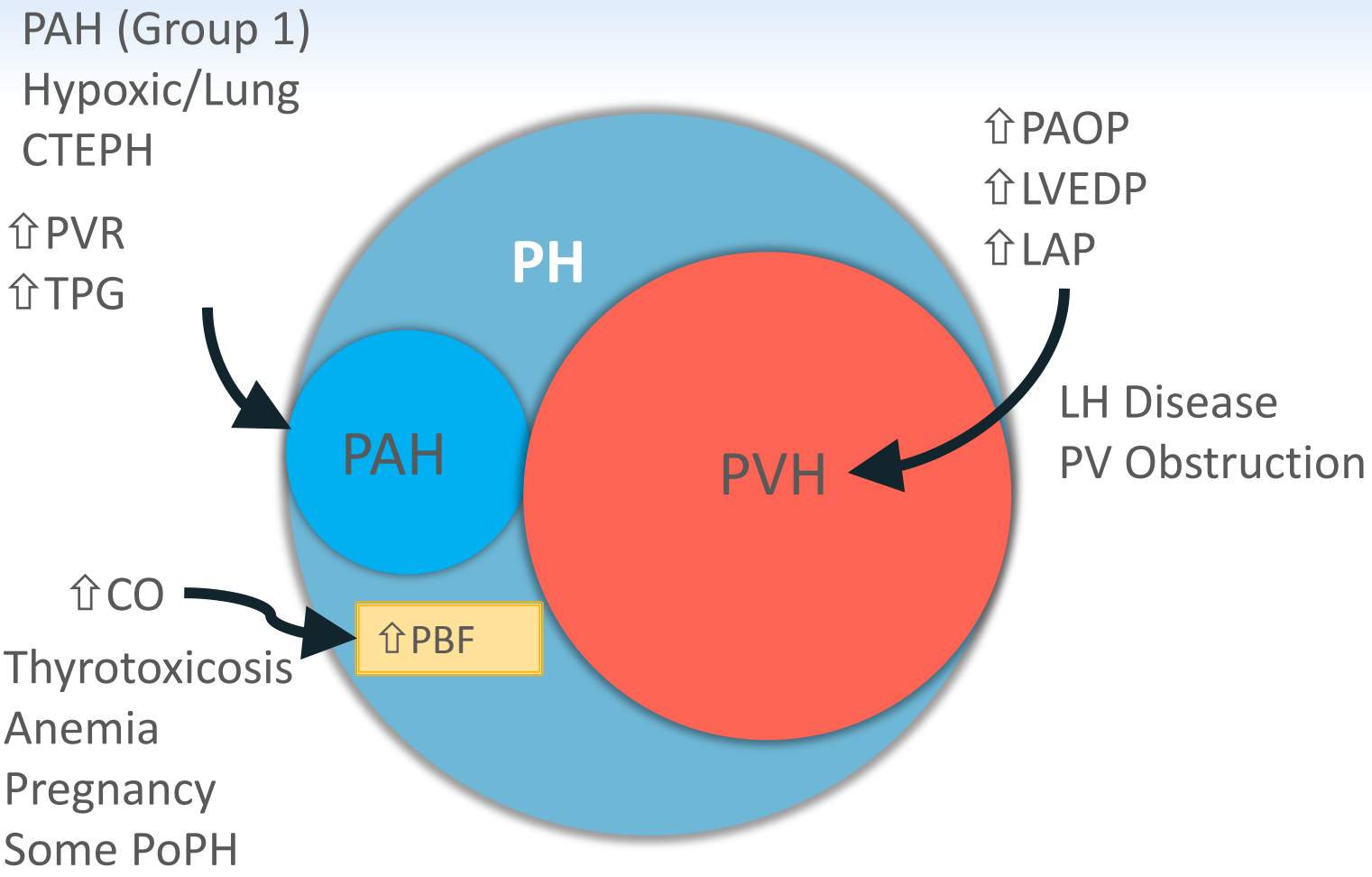

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Right Heart Catheterization

Which hemodynamic profile is associated with PAH?

1. RAP 13, PAP 70/25 (40), wedge 25, CO 5, PVR 3
2. RAP 15, PAP 80/42 (55), wedge 10, CO 3.5, PVR 13
3. RAP 11, PAP 60/18 (32), wedge 15, CO 10, PVR 1.7
4. None of the above

RAP - Right atrial pressure (mmHg)
PAP – Pulmonary artery pressure (mmHg)
Wedge – pulmonary capillary wedge pressure (mmHg)
CO – Cardiac output L/min
CI – Cardiac index L/min/m^2
PVR = mPAP – wedge / CO

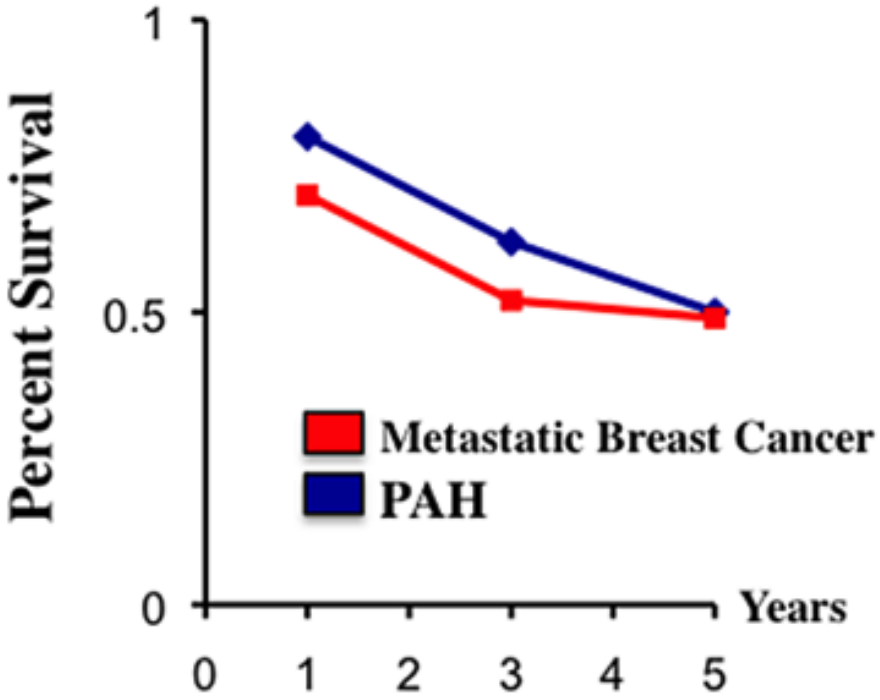
What RHC's Will and Will Not Show Us

- If there is Group II disease through elevated Wedge pressure
- Show severity of disease through PVR and CO and RA and pressures
- If PH is present and NOT group II,
  - The RHC will NOT tell us if the PH is PAH, Group III or Group IV (CTEPH)

Facts About Pulmonary Hypertension

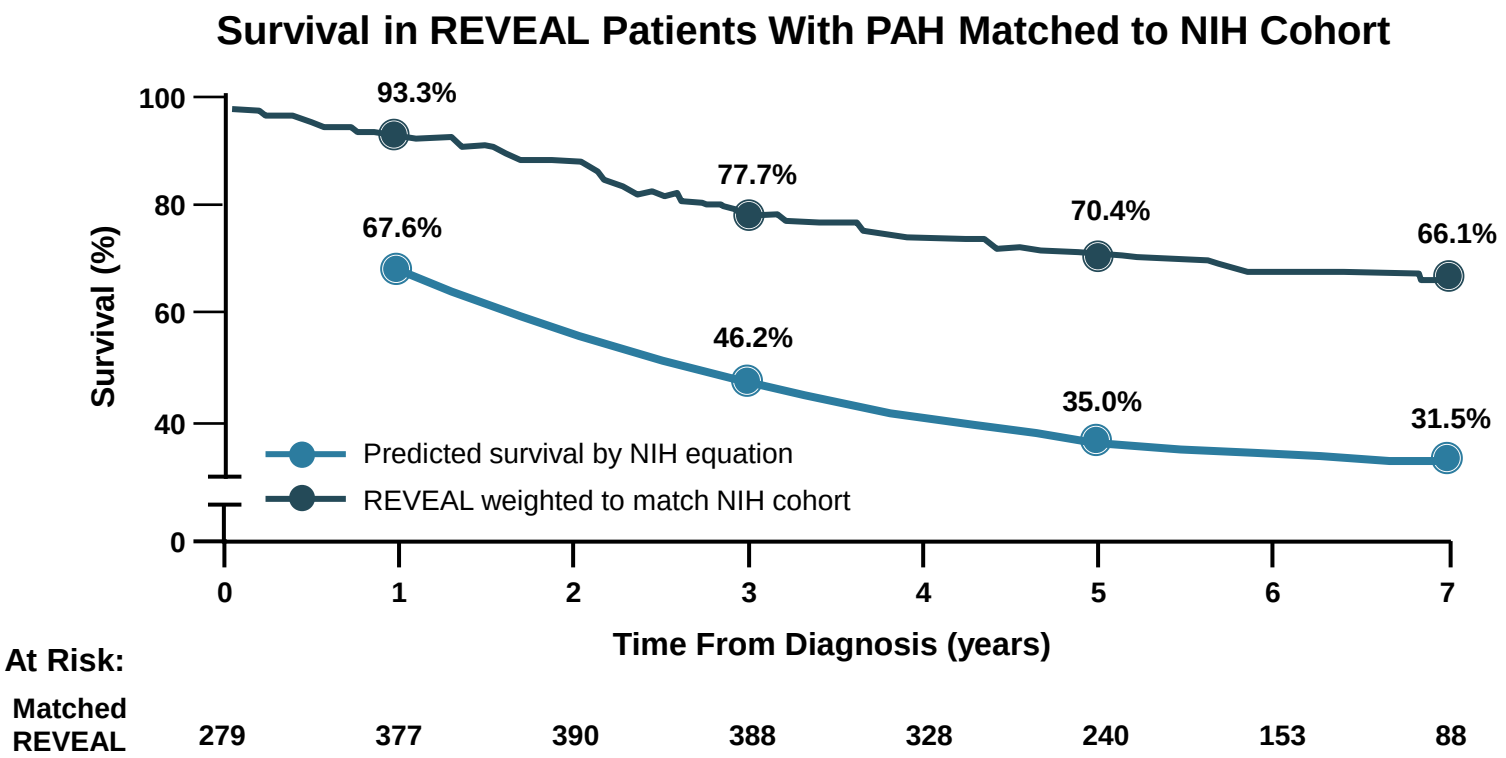
- Pulmonary Hypertension represents a group of diseases that manifest themselves in increased pressures in the pulmonary arteries
- The group that has been subject of the most attention has been Pulmonary Arterial Hypertension (disease in the vasculature of the lungs)
- It is of outmost importance to ask these questions face with the statement: “Patient has Pulmonary Hypertension”
  - Verify if the patient truly has PH and What kind of pulmonary hypertension?
  - Why does the patient have it?
  - How severe is the disease?

Survival in PAH phenotypes is decreased and similar to metastatic breast cancer



Michelakis ED. Circ Res. 2014;115:109

Long-term Survival From Time of Diagnosis of PAH in the REVEAL Registry



Benza RL, et al. *Chest*. 2012;142:448-456.

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2015 ESC/ERS Guidelines: Disease Progression Risk Factors in PAH

Determination of prognosis (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	Repeated syncope
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
Hemodynamics	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%

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

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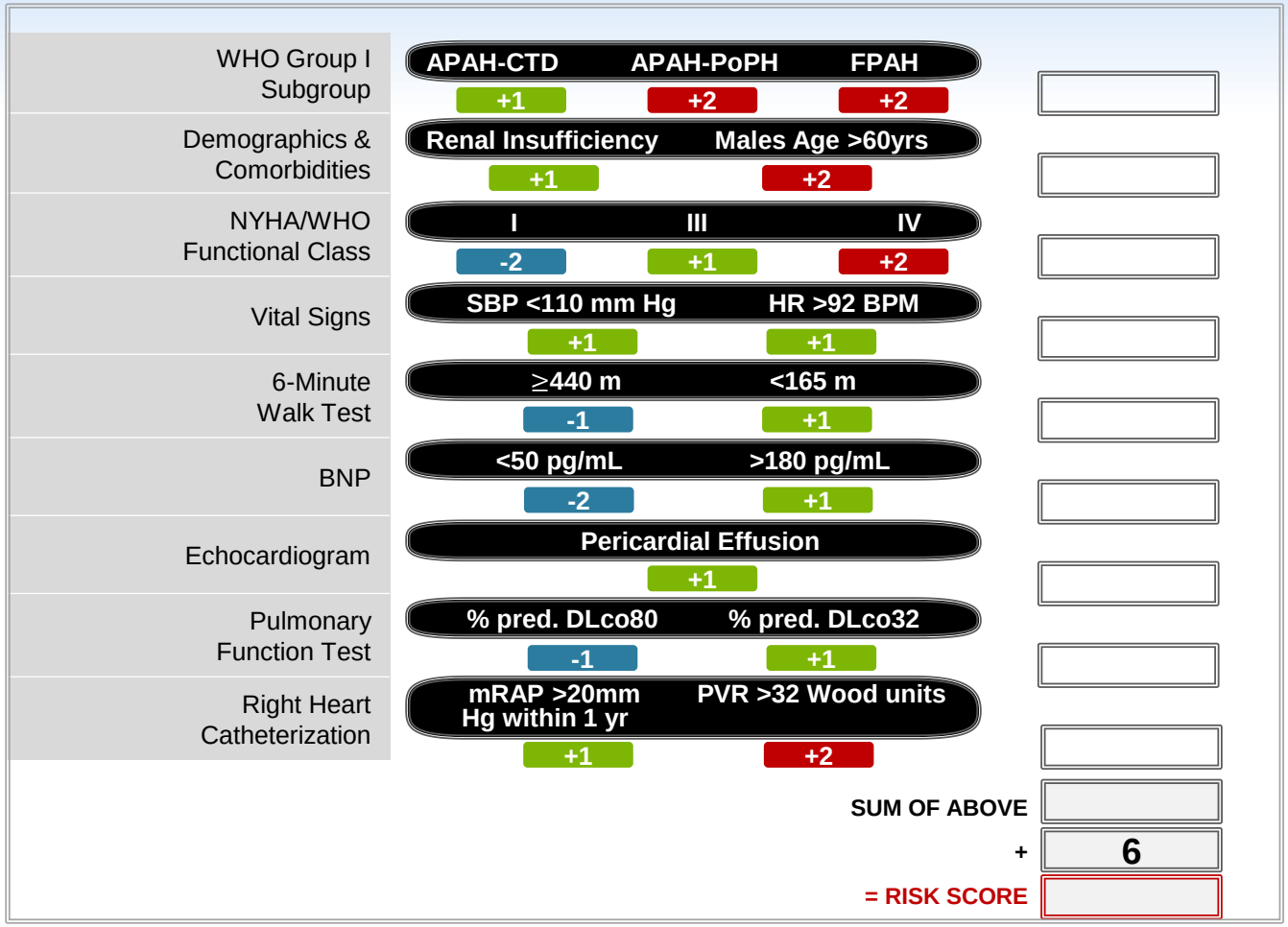
REVEAL Risk Score Calculator



Calculated risk scores can range from 0 (lowest risk) to 22 (highest risk). If N-terminal proBNP is available and BNP is not, listed cut points are replaced with < 300 pg/mL and > 1500 pg/mL.

Benza R. *Chest*. 2012;141:354-362.

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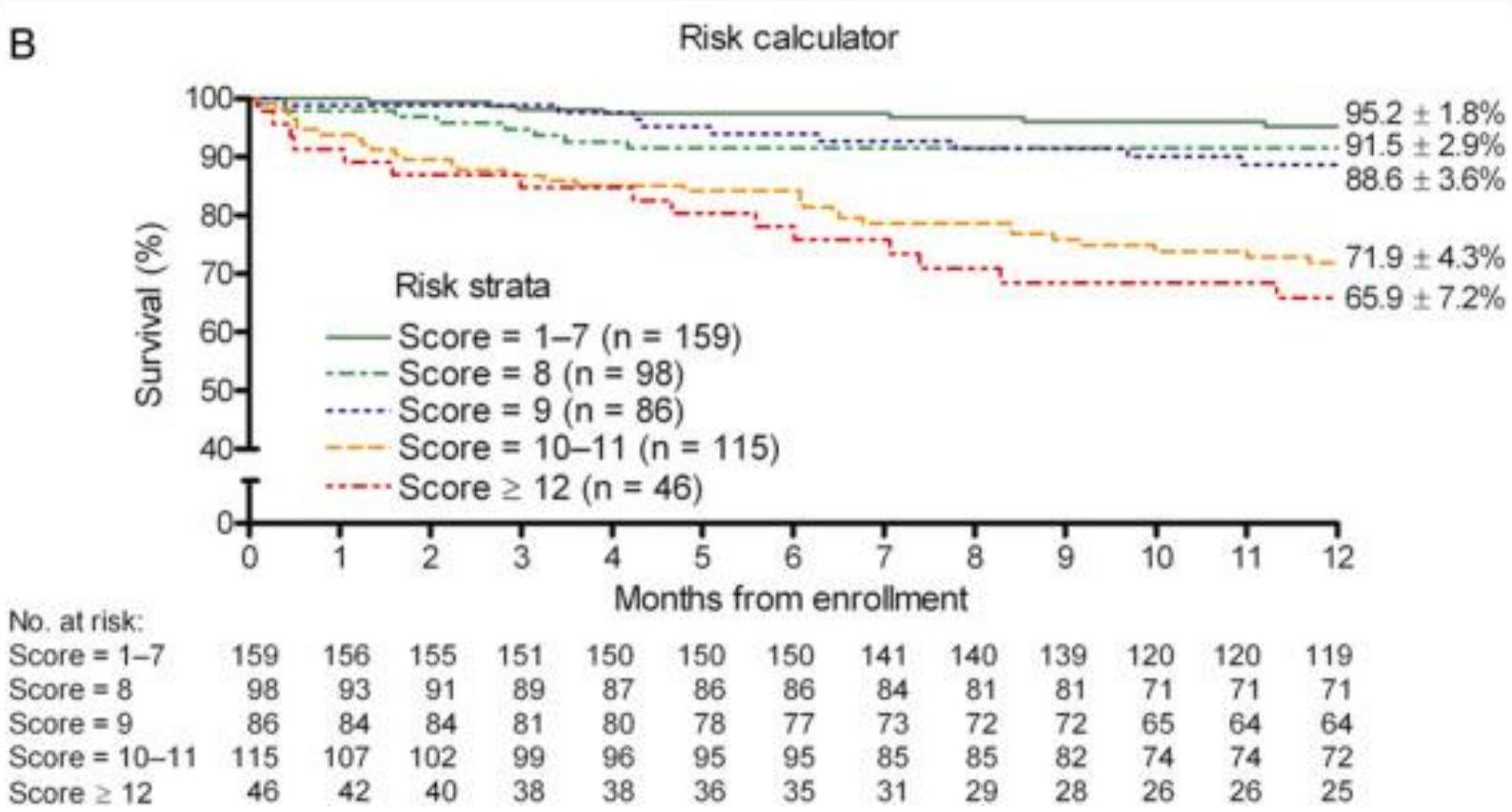
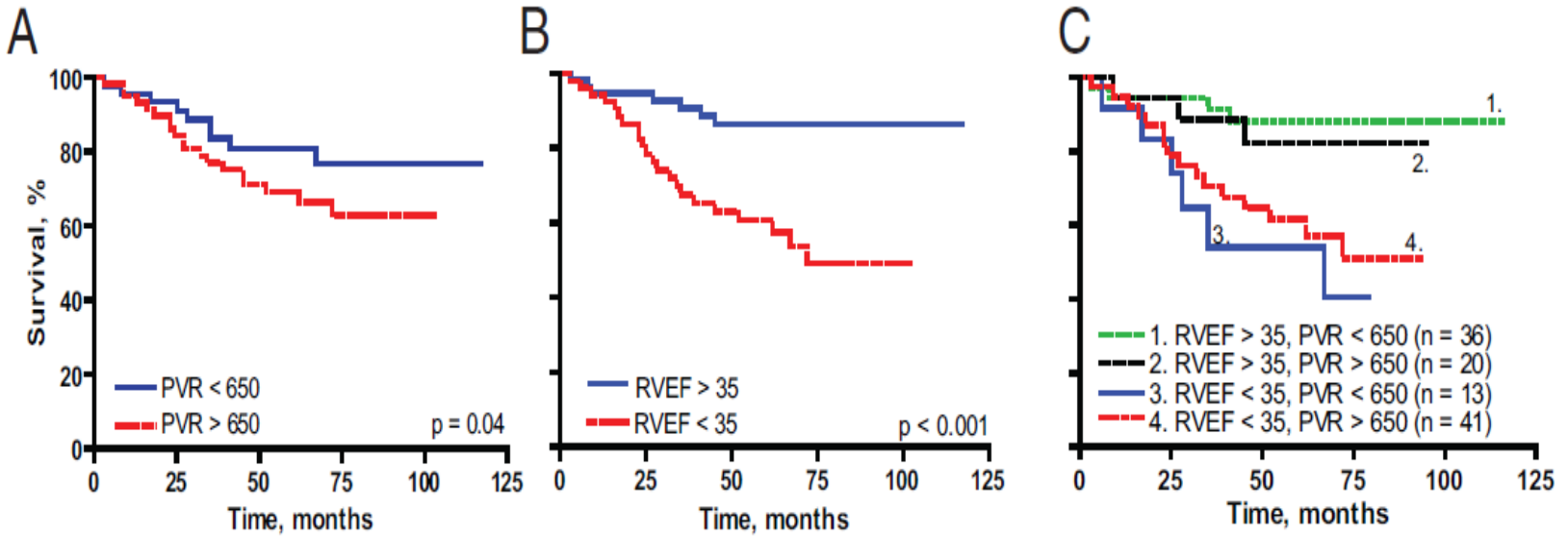
Survival Based on Reveal Score



Chest, Volume 141, Issue 2, February 2012, Pages 354-362

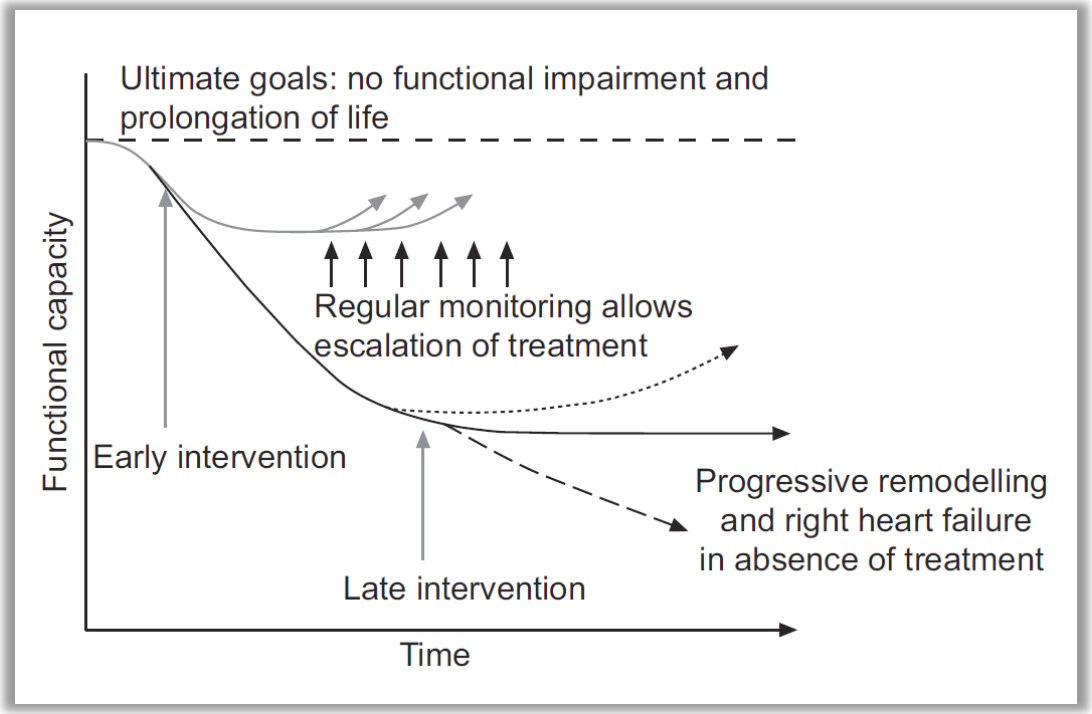
Right Ventricle Matters MORE



(A) Patients with pulmonary vascular resistance (PVR) 650 dyne·s·cm5 showed better survival rates than patients with PVR 650 (p 0.04).
(B) Patients with right ventricular ejection fraction (RVEF) 35% showed better survival rates compared with with RVEF 35% (p 0.001).
(C) Survival rates based on the coupling of PVR and RVEF. PAH pulmonary arterial hypertension.

van de Veerdonk et al. J Am Coll Cardiol 2011;58:2511–9

Treatment Goals



Sitbon O & Galie N: 2010 Eur Res Rev 19: 118

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PAH-specific FDA-approved Therapies for Use in the US

Endothelin Receptor Antagonists	NO-cGMP Pathway	Prostanoids – Prostacyclin Analogs	Prostacyclin Agonists
Bosentan (PO) FDA Approved: 2001	**Sildenafil (PO)** FDA Approved: June 2005	**Epoprostenol (IV)** FDA Approved: September 1995 FDA Approved: June 2008	**Selexipag (PO)** FDA Approved: December 2015
Ambrisentan (PO) FDA Approved: June 2007	**Tadalafil (PO)** FDA Approved: May 2009	**Treprostinil (IV, SC, PO, and inhaled)** First (SC formulation) FDA Approved: July 2002	
Macitentan (PO) FDA Approved: October 2013	**Riociguat (PO)** FDA Approved: October 2013	**Iloprost (inhaled)** FDA Approved: December 2004	

http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Search_Drug_Name. Accessed November 1, 2013.

Initial Therapy with Approved PAH Drugs—Recommendations

INITIAL THERAPY WITH APPROVED PAH DRUGS		
RED: Clinical trials supporting approval utilized mortality and morbidity endpoints in randomized controlled studies or reduced all-cause mortality. Level of evidence is based on the WHO FC and the majority of patients in supportive trials.		
WHO FC II	**WHO FC III**	**WHO FC IV**
Ambrisentan **Bosentan** **Macitentan** **Riociguat** **Sildenafil** **Tadalafil** **Selexipag****	**Ambrisentan** **Bosentan** **Macitentan** **Riociguat** **Sildenafil** **Tadalafil** **Treprostinil (SC or inhaled)** **Iloprost (inhaled)** **Epoprostenol** **Selexipag**** **Iloprost (IV)** **Treprostinil (IV) (oral*)**	**Epoprostenol (IV)** **Ambrisentan** **Bosentan** **Macitentan** **Riociguat** **Sildenafil** **Tadalafil** **Treprostinil (SC, IV, inhaled) (oral*)**
	Beraprost*	

Calcium Channel Blockers:

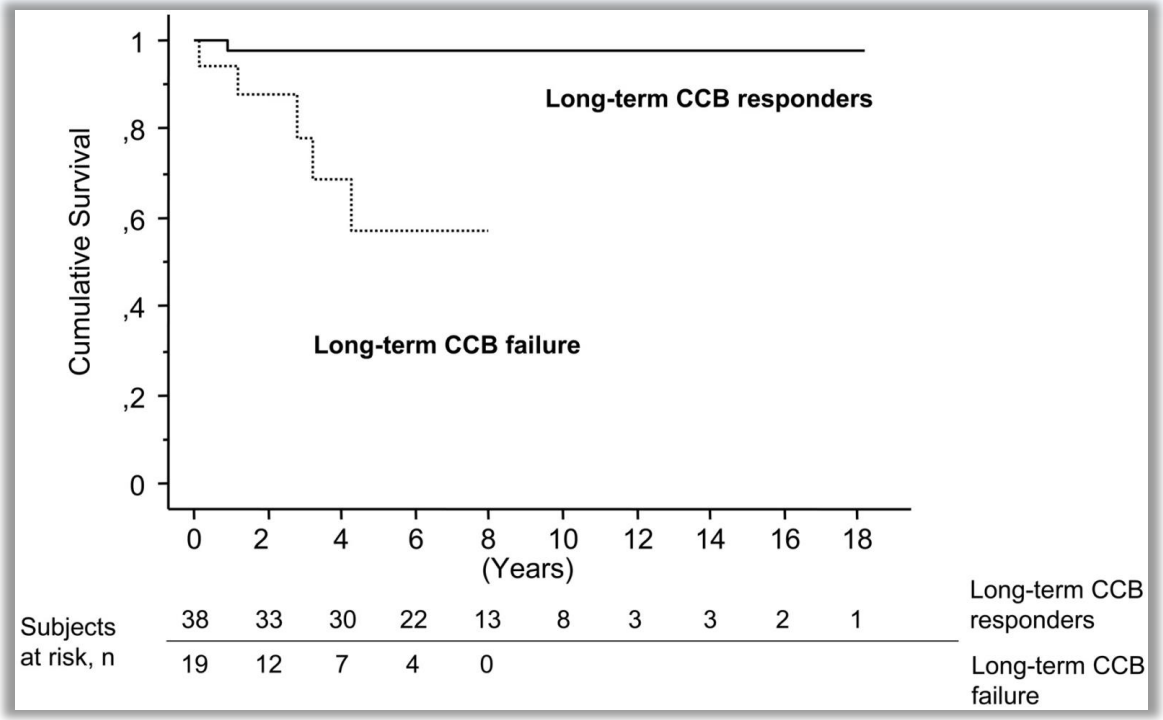
-Only to be used on a patients that had a right heart catheterization and had a response to vasodilators;

AND NO ONE ELSE!

*Oral treprostinil was approved by the FDA in December 2013, for treatment of WHO Group I patients to improve exercise capacity.
**Selexipag was approved by the US FDA in December 2015.
***Beraprost approved in Japan, not in the US.

Adapted from Galiè N, et al. *JACC.* 2013;62(25 suppl D):D60-D72.

CCB Therapy



Both groups showed acute vasoreactivity to either epoprostenol or NO

Acute vasoreactivity (iNO / iloprost / adenosine)

Decrease in mPAP by > 10 and to < 40 mm Hg with an unchanged / improved CO

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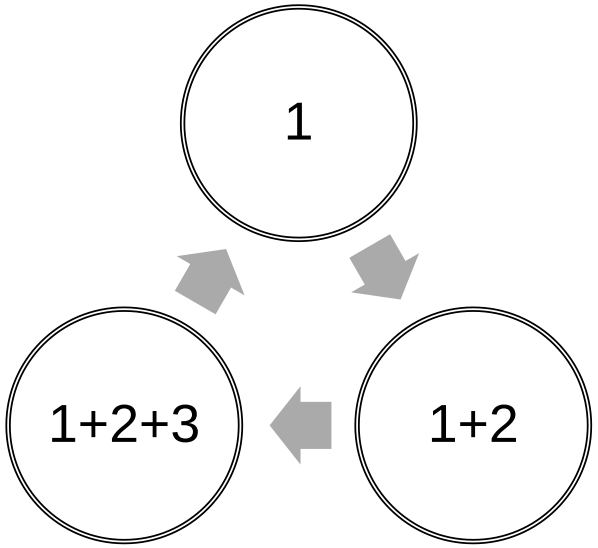
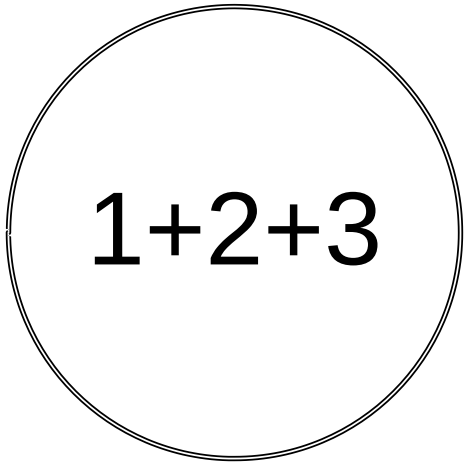
Combination Therapy

Sequential / Add on



Upfront



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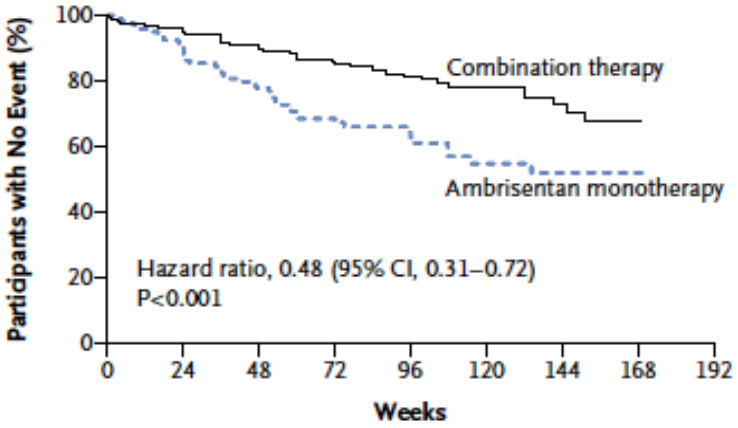
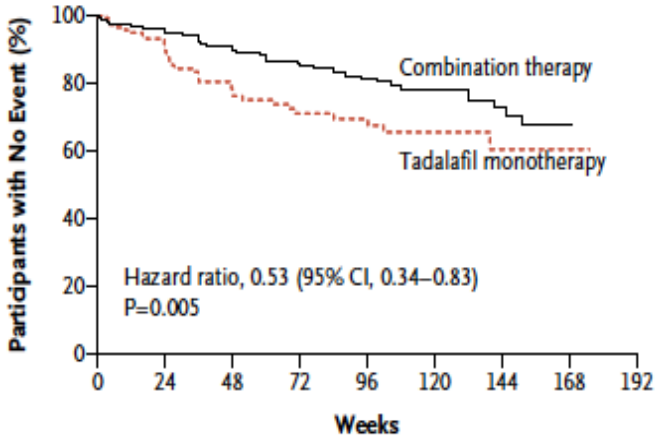
Combination Therapy Reduces Risk of Events Compared to Ambrisentan or Tadalafil Monotherapy

Combination vs. Ambrisentan Monotherapy



No. at Risk								
Combination therapy	253	229	186	145	106	71	36	4
Ambrisentan monotherapy	126	104	81	57	39	23	14	3

Combination vs. Tadalafil Monotherapy

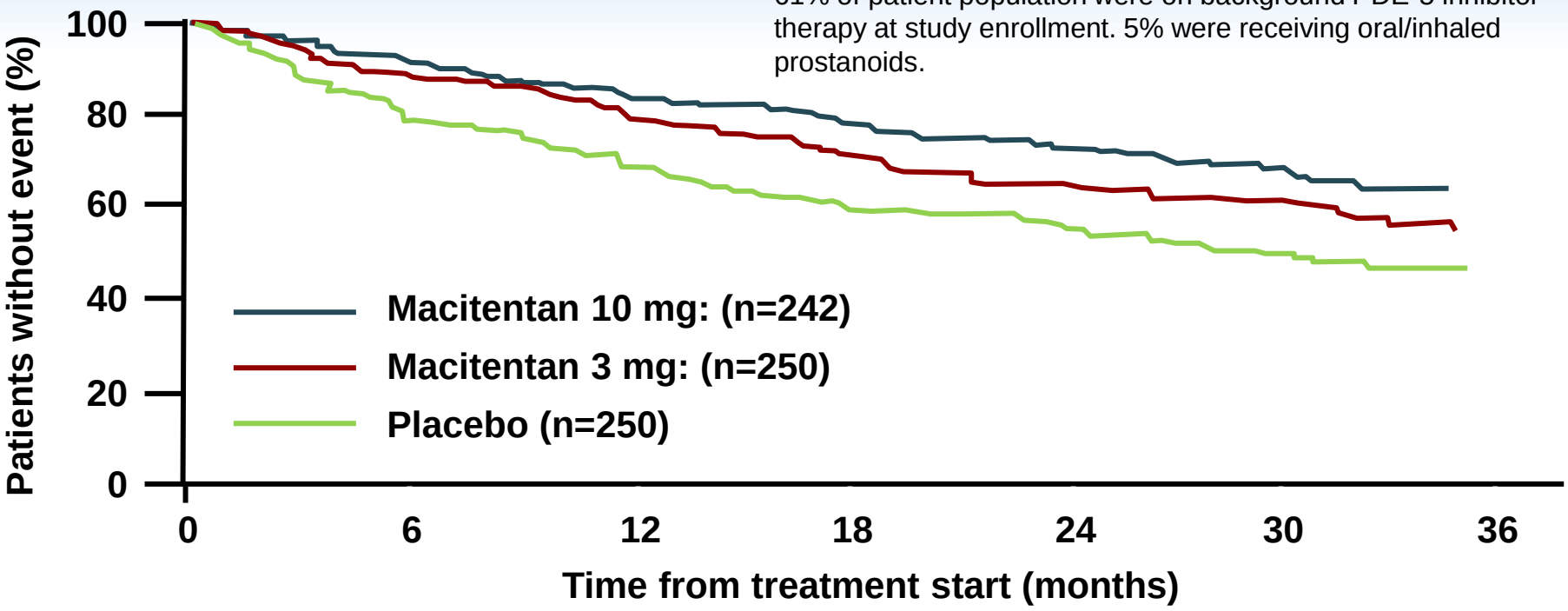


No. at Risk								
Combination therapy	253	229	186	145	106	71	36	4
Tadalafil monotherapy	121	105	74	51	38	26	11	2

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

SERAPHIN: Macitentan, Monotherapy or Sequential Combination Therapy

61% of patient population were on background PDE-5 inhibitor therapy at study enrollment. 5% were receiving oral/inhaled prostanoids.



Macitentan 10 mg: **Hazard ratio=0.55; log rank *P*<0.001**
Macitentan 3 mg: **Hazard ratio=0.70; log-rank *P*=0.01**

N=742. Double-blind, placebo-controlled Phase III study. Primary endpoint was time to first event related to PAH [worsening of PAH, initiation of IV or SC prostanoids, lung transplantation, or atrial septostomy] or all-cause death.

Pulido T, et al. *N Engl J Med*. 2013;369-808-813.

Guidelines

Measure/ treatment	Class[a]-Level[b]					
	WHO-FC II		WHO-FC III		WHO-FC IV	
Ambrisentan + tadalafil[d]	I	B	I	B	IIb	C
Other ERA + PDE-5i	IIa	C	IIa	C	IIb	C
Bosentan + sildenafil + i.v. epoprostenol	-	-	IIa	C	IIa	C
Bosentan + i.v. epoprostenol	-	-	IIa	C	IIa	C
Other ERA or PDE-5i + s.c. treprostinil			IIb	C	IIb	C
Other ERA or PDE-5i + other i.v. prostacyclin analogues			IIb	C	IIb	C

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

Measure/ treatment	Class[a]-Level[b]					
	WHO-FC II		WHO-FC III		WHO-FC IV	
Macitentan added to sildenafil[d]	I	B	I	B	IIa	C
Riociguat added to bosentan	I	B	I	B	IIa	C
Selexipag[e] added to ERA and/or PDE-5i[d]	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

2015 ESC/ERS Guidelines for the Diagnosis and Treatment of Pulmonary Hypertension

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General PAH Care

Anticoagulation	• In general, IPAH patients receive anticoagulant therapy • Anticoagulation therapy should be considered for patients with secondary PAH
Oxygen	• Hypoxia is a potent vasoconstrictor and can elevate PA pressure
Fluid/ volume control	• Diuretics • Fluid restriction • Low salt diet

IPAH=idiopathic pulmonary arterial hypertension; PA=pulmonary artery; PAH=pulmonary arterial hypertension.
Galiè N et al. *J Am Coll Cardiol.* 2013;62 (25 Suppl):D60-D72. Barst RJ et al. *J Am Coll Cardiol.* 2009;54(1 Suppl):S78-S84.
McLaughlin VV et al. *Circulation.* 2009;119:2250-2294.

A Problem

- 15 to 30% of patients self-discontinue medications, with adverse effects and lack of perceived benefits being the most common reasons.

Psychiatr Serv. 2014;66(5):455-62
BJU Int. 2010;105(9):1276-82
Personal Communication with Marketing and sales of Advanced Lung Disease related Pharmaceutical Companies

The “ Side Effect” Problem

- Lack of Communication Regarding Adverse Events
  - Lack of understanding by the patients
  - Lack of clear/ contextual vocabulary
  - Lack of adequate explanation/ contextualization by providers
- Lack of Guidance on prevention and management of adverse events

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Adverse Events (AE)

- An adverse event (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a drug, without any judgment about causality or relationship to the drug.
- An adverse event can arise from any use of the drug (e.g., off-label use, use in combination with another drug) and from any route of administration, formulation, or dose, including an overdose.

ICH E6 Section 1.2

FDA

- The FDA recommends classifying adverse events on the basis of “seriousness, severity, frequency, and strength of causal relationship.” Serious adverse effects, such as those resulting in hospitalization or death, are classified as ‘boxed warnings’ and receive detailed description.
- Common adverse effects are defined as those “occurring at a rate of 10 percent or greater.”
- The FDA further recommends avoiding “exhaustive lists of every reported adverse event, including those that are infrequent or minor” claiming that such lists are “not informative and tend to obscure the more clinically meaningful information.”

www.fda.gov

AE Management Interventions

Example: Nausea with Orenitram

- Non Pharmacological
  - Take meds with Caloric Food
- Pharmacological
  - First Line
    - Ondansetron (Zofran™)
    - PPI's
  - Second Line
    - Prochlorperazine (Compazine™-Oral/ Suppository)
    - Oral Promethazine (Phenergan™)
- Dose Down Titration/ Holiday/ (followed by possible Re-Uptitration)

Rahaghi et al, Pulm Circ 2017 Jul-Sep;7(3):702-711.

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Suggested Follow-up

	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]

ECS/ERS Guidelines 2015 European Heart Journal doi:10.1093/eurheartj/ehv317

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