Pulmonary Hypertension in 2017

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No disclosures

No off-label uses of medications

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Introduction

- 1. Definition and pathophysiology of pulmonary arterial hypertension
- 2. Prevalence and prognosis of PAH
- 3. Diagnosis of pulmonary arterial hypertension
- 4. Non pharmacologic treatment of pulmonary arterial hypertension

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Definition of PAH

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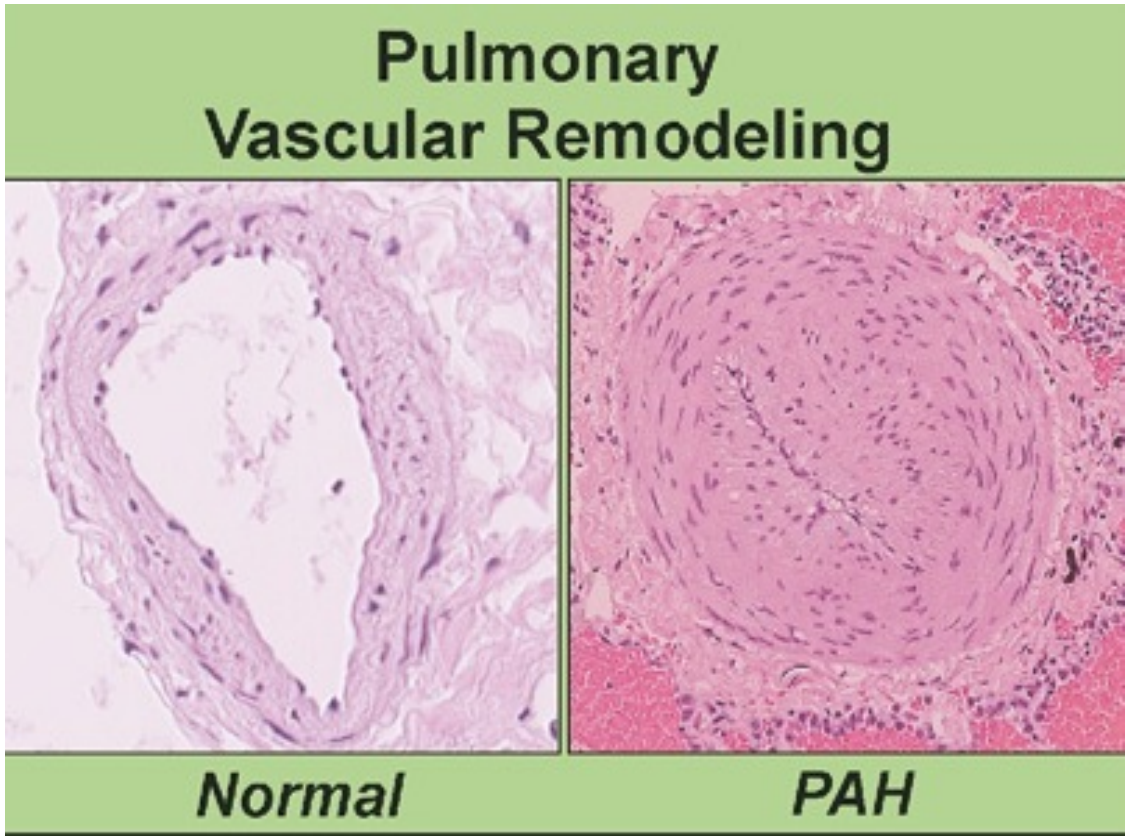
Pulmonary arterial hypertension (PAH) is a syndrome resulting from restricted flow through the pulmonary arterial circulation resulting in increased **pulmonary vascular resistance** and ultimately in right heart failure and death. Multiple pathogenic pathways have been implicated in the development of PAH. The imbalance in the **vasoconstrictor/vasodilator** milieu has served as the basis for current medical therapies, although increasingly it is recognized that PAH also involves an **imbalance of proliferation and apoptosis** (favoring the former).



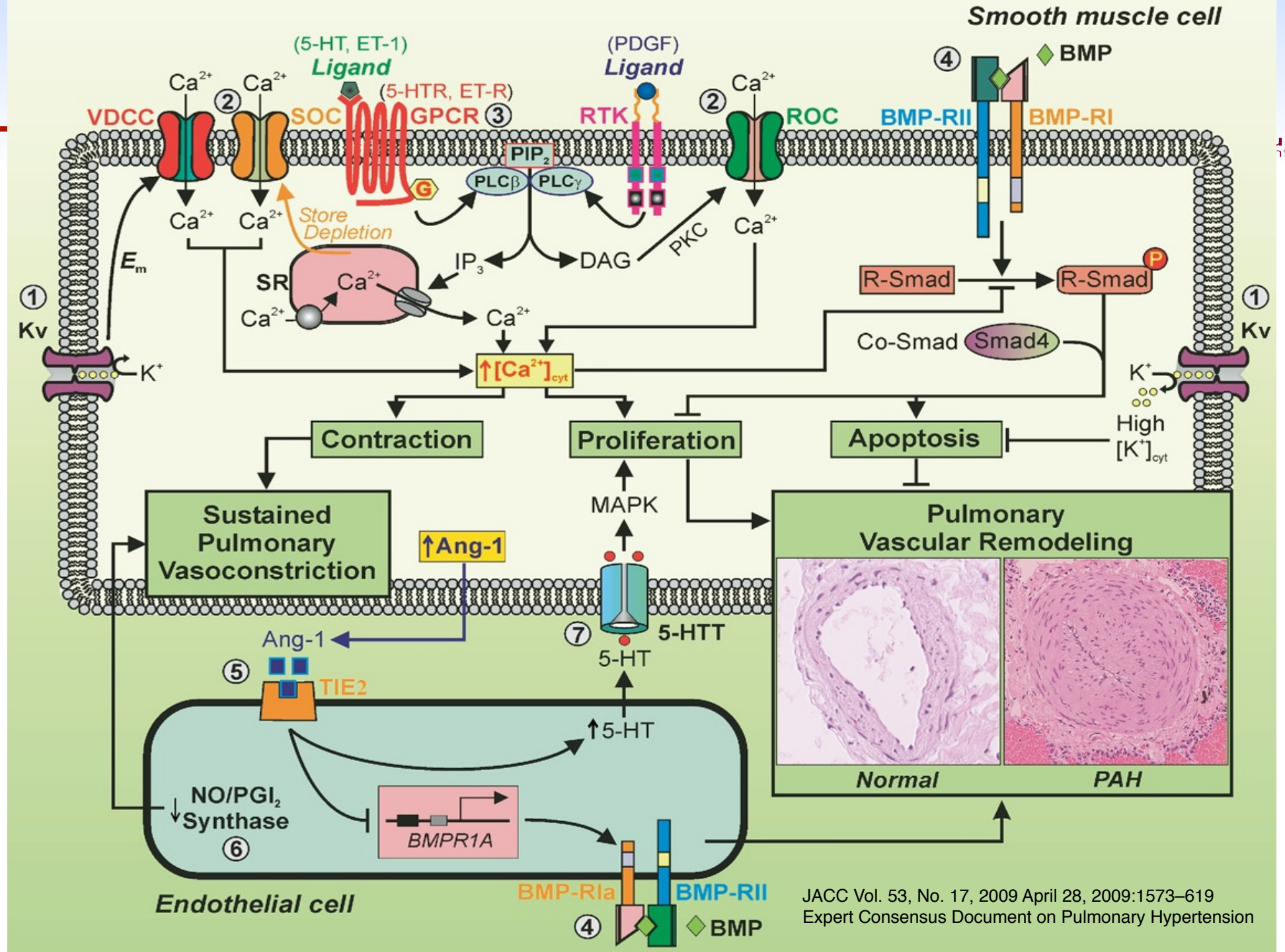
Panvasculopathy (endothelium dysfunction, medial hypertrophy and adventitial proliferation)

Predominant effect on resistance arteries

Thrombosis in situ

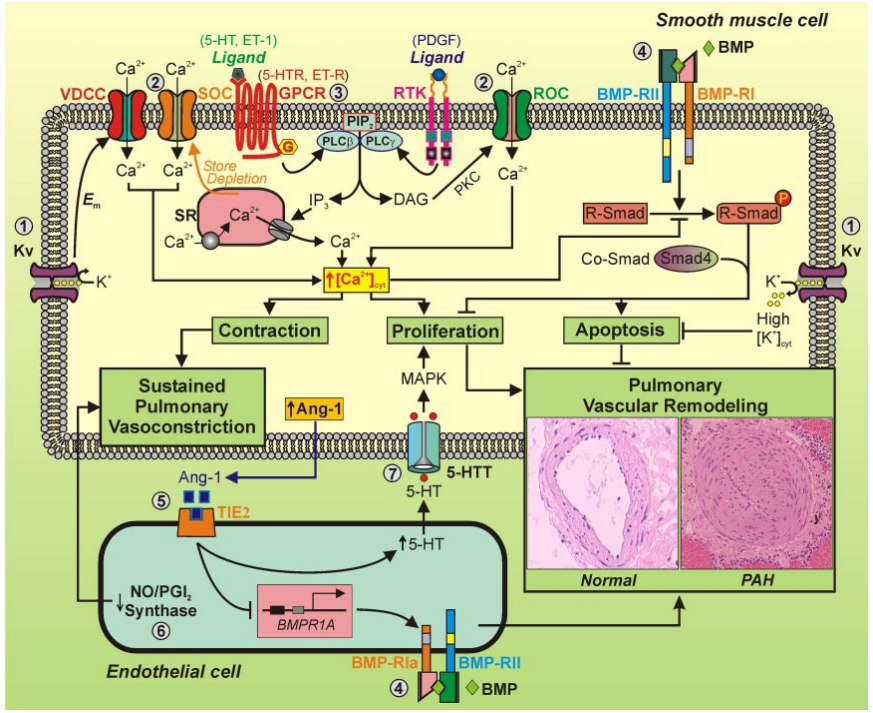
Inflammation

Plexiform lesions



JACC Vol. 53, No. 17, 2009 April 28, 2009:1573–619
Expert Consensus Document on Pulmonary Hypertension

Evolution of PAH: Multiple suspects!



- At smooth muscle cell level:
  - Rise in intracellular calcium due to multiple mechanisms *(such as inactivation of Kv channels and/or Overexpression of Ca++ channels*), resulting in:
    - Contraction/ vasoconstriction
    - Proliferation
  - Dysfunction of Bone Morphogenic Protein receptor *(such as in BMPR mutations)* resulting in:
    - Increased proliferation
    - Reduced apoptosis
- At Endothelial cell level:
  - Reduced Nitric oxide and prostacyclin production resulting in
    - Sustained vasoconstriction
    - Increased inflammation
  - Dysfunction in BMP receptor *(such as in BMPR mutations)* resulting in
    - Increased Angiopoietin production and increased proliferation and angiogenesis.
  - Over-expression of Endothelin receptors (*not in the figure*) resulting in
    - Vasoconstriction
    - Increased inflammation

Yuan JX et al. Circulation 2005

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Epidemiology of PH:

- Prevalence:
  - iPAH and heritable PH are rare: 5-15 per million
  - PAH-HIV: less than 1% of HIV patients)
  - PAH-ACHD: increasingly seen as population with ACHD is rapidly increasing.
  - PAH-CTD: 5-12% of patients with Systemic Sclerosis (SSc) and CREST syndrome. Rare in other CTD (SLE, mixed CTD, RA, dermatomyositis, and Sjo¨gren's syndrome)
  - PoPAH: 1-5% of patients with portal hypertension (with or without cirrhosis)
  - PVOD: Extremely rare. Often associated with pulmonary hemangiomatosis
  - WHO group 2 PH: It is estimated to involve 70-90% of patients left HF
  - WHO group 3, 4, and 5: Prevalence unknown.
- Most common in US: PH-LHD
- Most common worldwide: schistosomiasis-associated PH and high altitude PH

Nazzarino Galie et al. European Heart Journal 2015
Redfield MM et al. JACC 2009

Familial PAH

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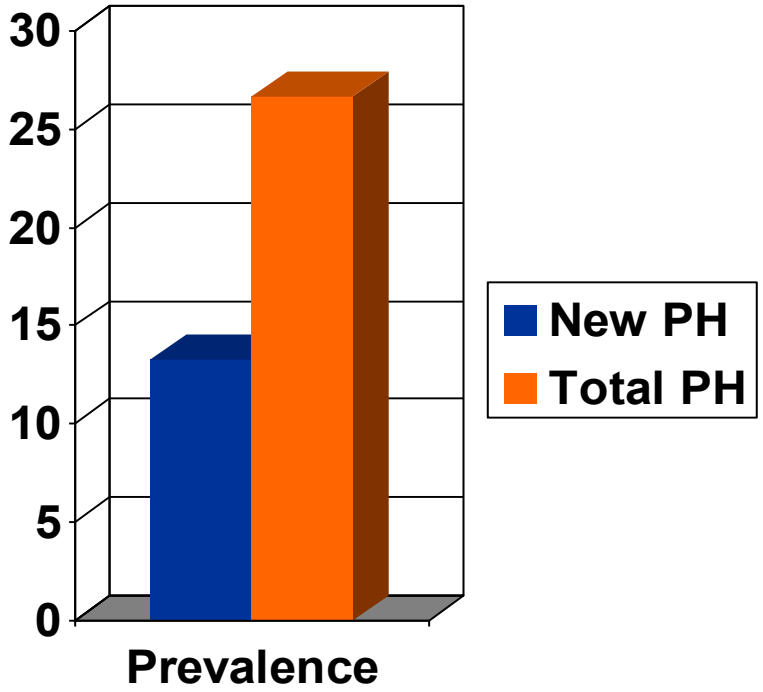
- 6-10% of IPAH patients
- Mutations in BMPR-2, ALK-1 genes which belong to the TGF β superfamily of growth factors
- Two-thirds of FPAH patients have BMPR-2 mutation
- ALK-1 mutation associated with HHT (Osler-Weber-Rendu disease)
- Presence of BMPR-2 mutation confers a 10-20% risk of developing PAH

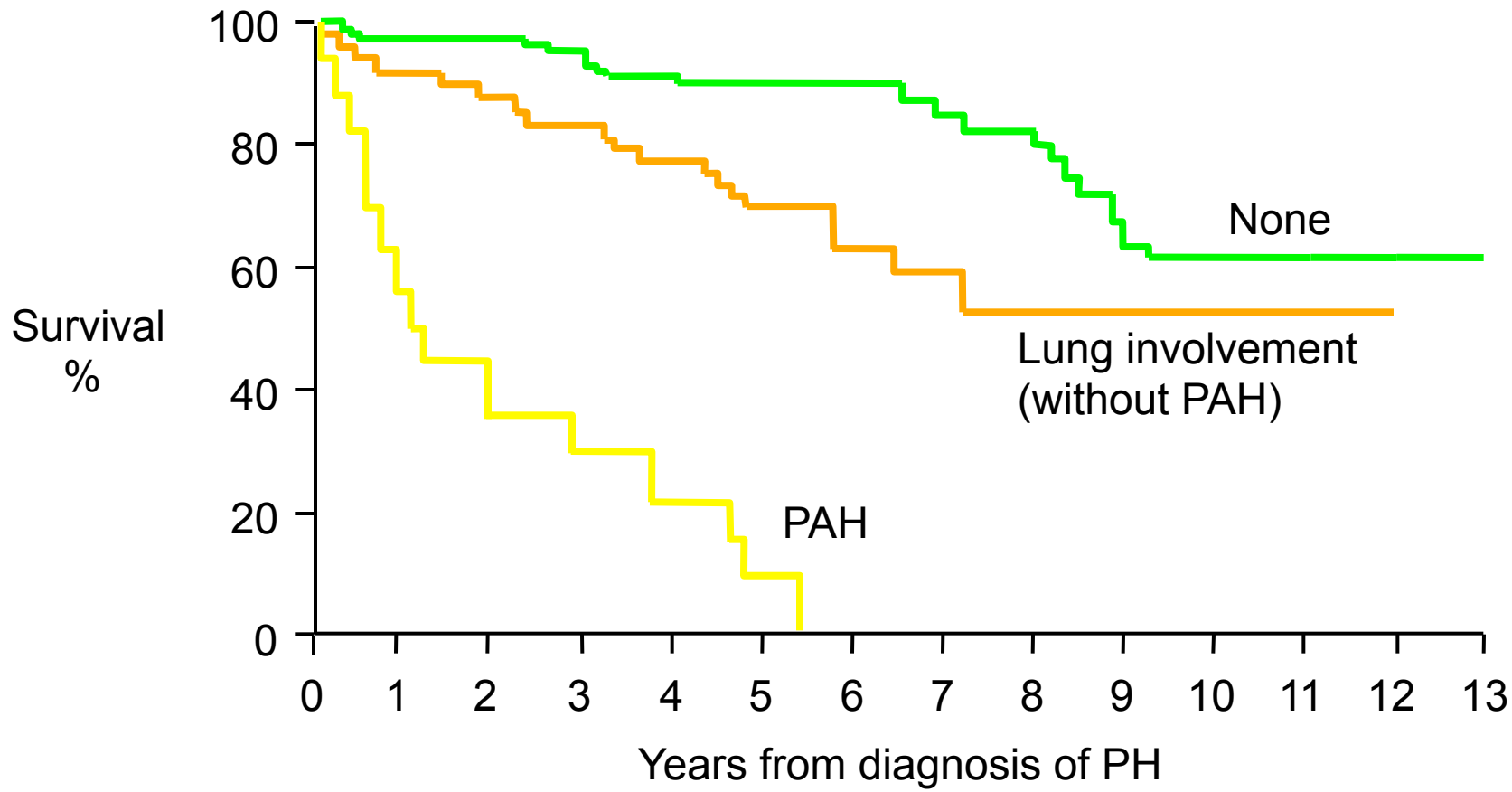
Prevalence of PAH Associated with SSc

- "UNCOVER" study
- Point prevalence of PAH in 50
- community clinics
- Pts with SSc or MCTD without
- known PAH screened with
- ECHO, PFT
- 89/669 (13.3%) had RVSP >40
- mm Hg.
- Total prevalence was 89 (new)
- + 122 (known) = 211/791
- (26.7%)



"New" PAH found in 13% of patients with SSc, MCTD

Survival in Scleroderma Patients With PAH, Lung Involvement, or No Major Organ Involvement



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

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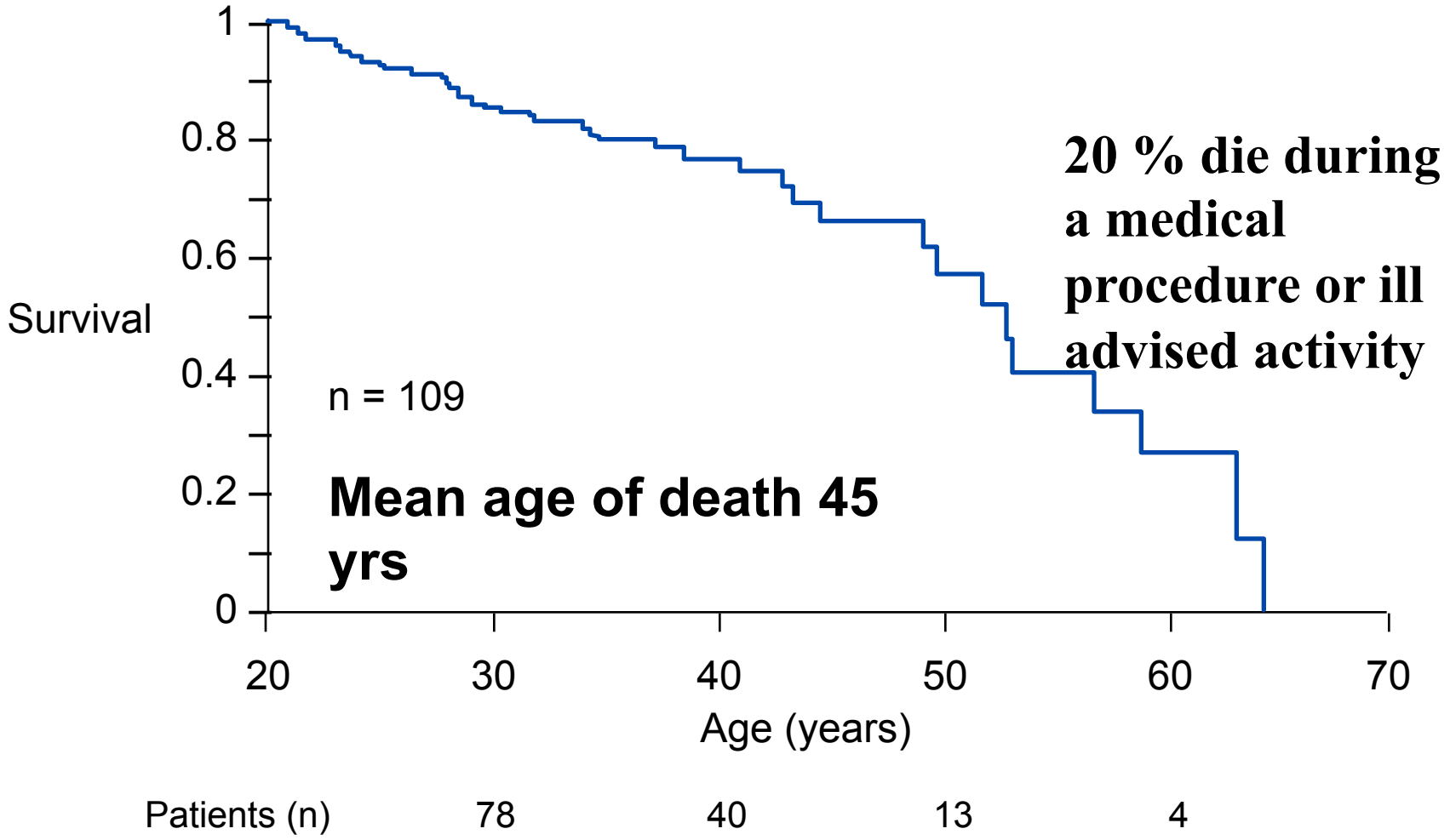
- Left to Right Shunts
- ASD
- VSD
- PDA
- Surgical Shunts

Complex Lesions

- DORV
- Truncus Arteriosus
- TGV/VSD

Survival in Eisenmenger's Syndrome



Vongpatanasin et al. *Ann Intern Med*. 1998; 128: 745-755.

Classification of PH based on etiology:

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

1''. Persistent pulmonary hypertension of the newborn

2. Pulmonary hypertension 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
- 2.5 Congenital /acquired pulmonary veins stenosis

3. Pulmonary hypertension due to lung diseases and/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 disorders
- 3.6 Chronic exposure to high altitude
- 3.7 Developmental lung diseases (Web Table III)

4. Chronic thromboembolic pulmonary hypertension and other pulmonary artery obstructions

- 4.1 Chronic thromboembolic pulmonary hypertension
- 4.2 Other pulmonary artery obstructions
  - 4.2.1 Angiosarcoma
  - 4.2.2 Other intravascular tumors
  - 4.2.3 Arteritis
  - 4.2.4 Congenital pulmonary arteries stenoses
  - 4.2.5 Parasites (hydatidosis)

5. Pulmonary hypertension with unclear and/or multifactorial mechanisms

- 5.1 Haematological disorders: chronic haemolytic anaemia, myeloproliferative disorders, splenectomy
- 5.2 Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis neurofibromatosis
- 5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
- 5.4 Others: pulmonary tumoral thrombothic microangiopathy, fibrosing mediastinitis, chronic renal failure (with/without dialysis), segmental pulmonary hypertension

Nazzarino Galie et al. European Heart Journal 2015

Familial PAH

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- 6-10% of IPAH patients
- Mutations in BMPR-2, ALK-1 genes which belong to the TGF β superfamily of growth factors
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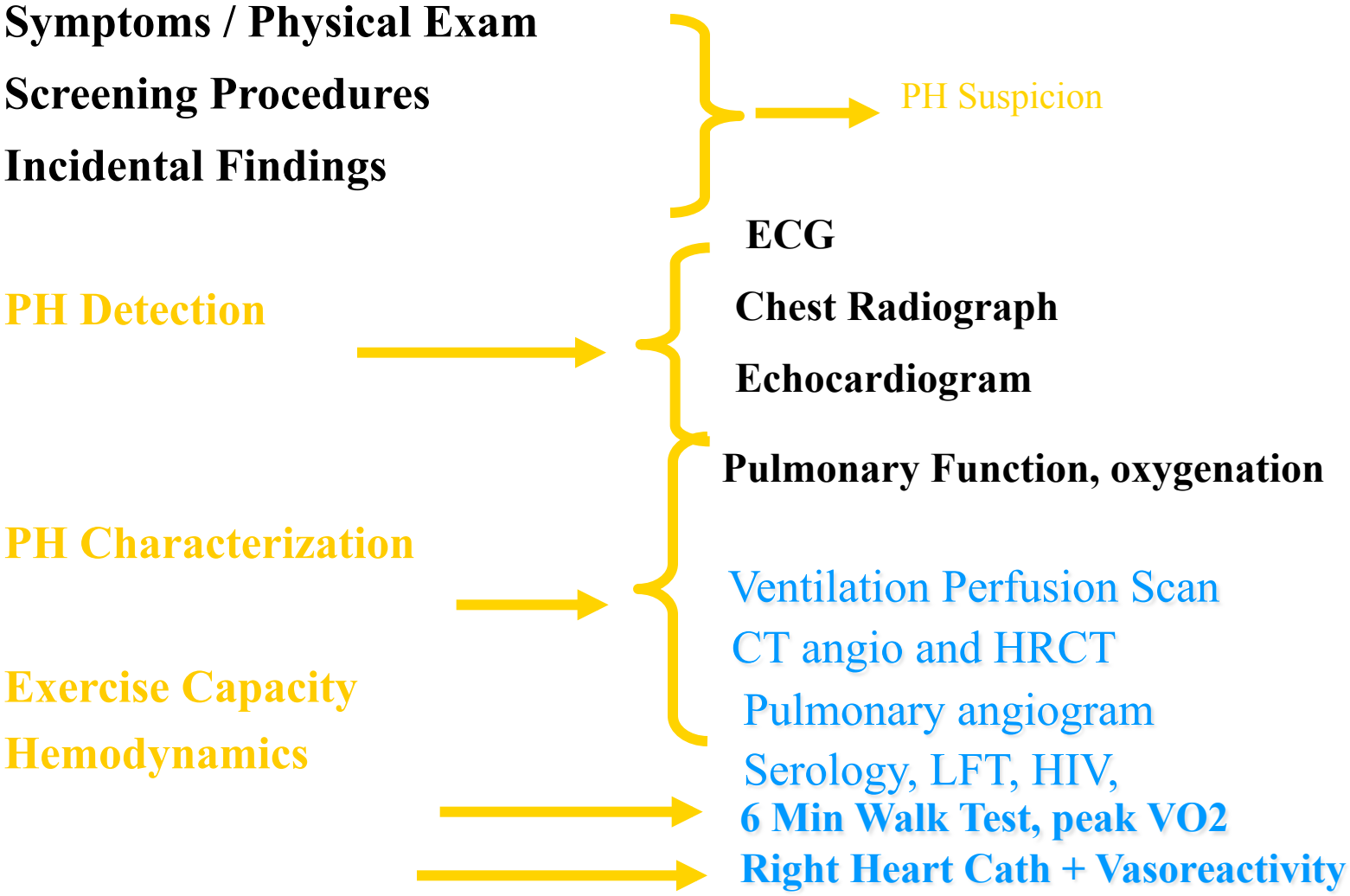
Diagnostic tests for evaluating patients with pulmonary hypertension

- To establish diagnosis:
  - Echocardiogram
  - Right heart catheterization
- To determine prognosis and response to therapy
  - 6MWD
  - Cardiopulmonary exercise testing
  - Laboratory testing: BNP, NT-Pro-BNP, Troponin
  - Cardiac MRI: Assess RV function
- To determine etiology
  - Ventilation/perfusion scan/ CTA/ pulmonary angiogram
  - Pulmonary function testing
  - High resolution CT scan
  - Bronchoscopy/ Lung biopsy
  - Hepatic ultrasound
  - MRI: ACHD, rule out CTEPH in pregnancy, evaluate RV
  - Laboratory testing: HIV serology, Auto-immune testing, hepatitis serology, thrombophilia work up
  - Genetic testing

Clinical Signs of PH:

- Presence of PH
  - Loud P2
  - RV lift
  - Systolic murmur (TR)
  - Diastolic murmur (PR)
  - RV S4
- Presence of RV failure
  - JVD, V wave
  - RV S3
  - Hepatomegaly
  - Edema
  - Ascites

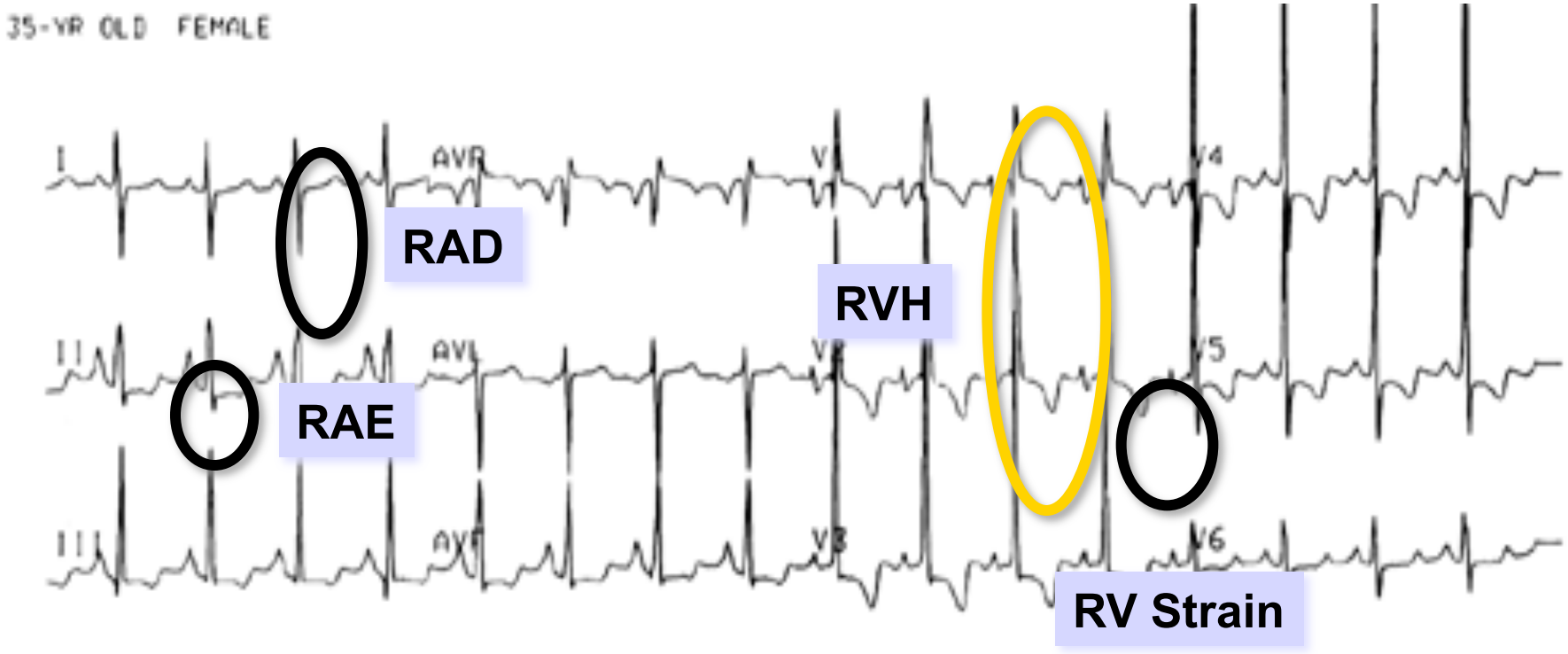
PH: Diagnostic Approach

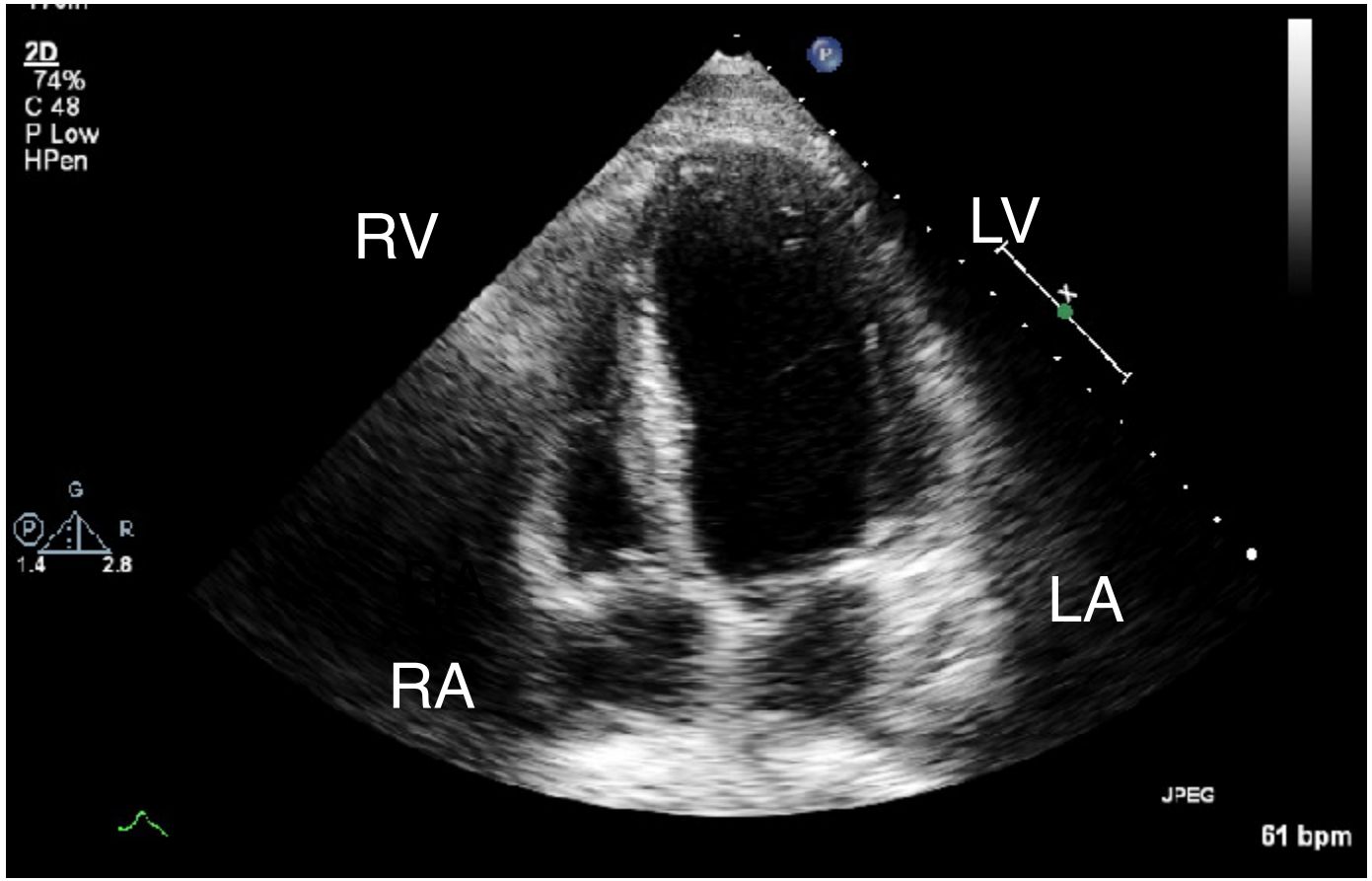


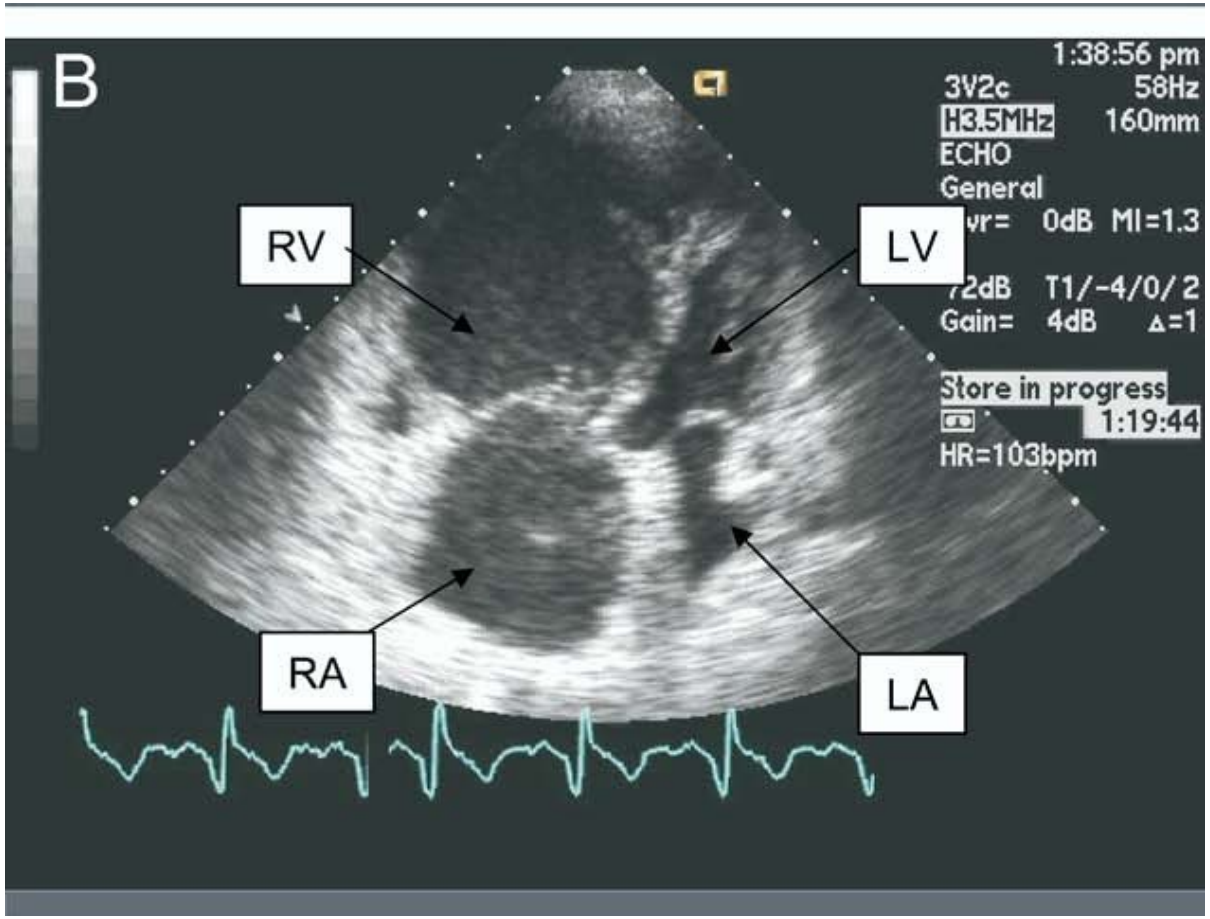
Adapted from: ESC Guidelines. Eur Heart J 2004; 25:2243

EKG in PH:

In IPAH, RAD seen in 79%, and RVH in 87%.
EKG as a screening tool for IPAH: sensitivity 55%, specificity 70%.




2D
74%
C 48
P Low
HPen
RV
LV
LA
RA
G
R
1.4
2.8
JPEG
61 bpm


B
1:38:56 pm
3V2c
58Hz
H3.5MHz
160mm
ECHO
General
0dB MI=1.3
T1/-4/0/2
Gain= 4dB
Store in progress
1:19:44
HR=103bpm
RV
LV
RA
LA

Pulmonary Arterial Hypertension: Diagnosis

- Establish presence and severity
- Echo
- Cath
- ? MRI or CT angio

3

- Establish etiology
- Blood Work to r/o CTD, HIV,
- SSD, CLD
- PFT/CT/X-ray to r/o lung
- disease
- VQ/ CT/PA angiogram to r/o
- CTEPH
- Sleep study
- TTE/TEE/Cath/MRI to r/o
- heart disease

Hemodynamic definition and classification of PH

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]	

Nazzarino Galie et al. European Heart Journal 2015

why is it important to determine cause of pulmonary hypertension?

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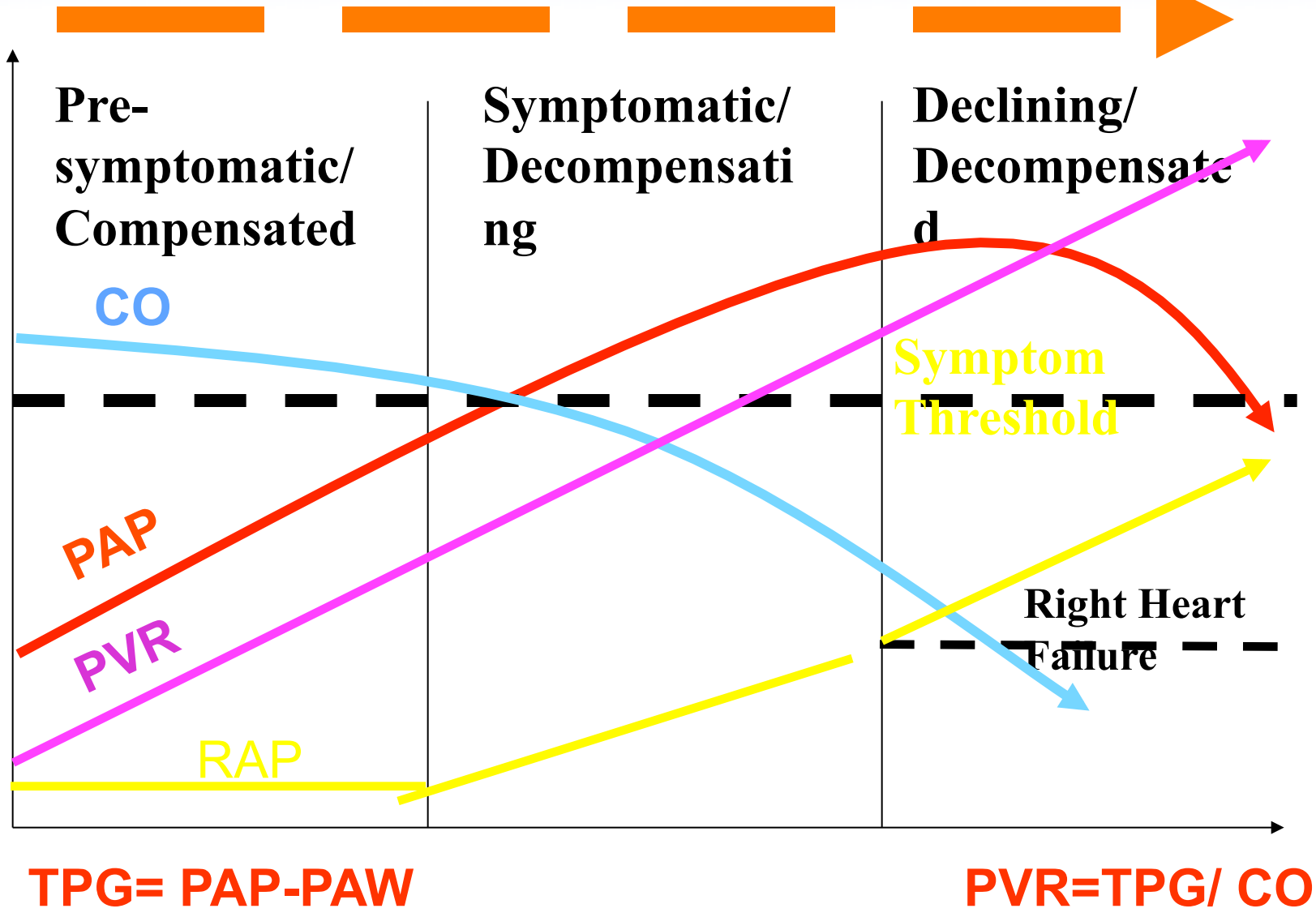
- Patients with pulmonary artery hypertension need treatment, and need it before the right ventricle begins to fail.

- Patients with non Group 1 disease can be treated through titration of medications for Group 2 and possibly evaluation for advanced therapies, evaluation of pulmonary disease for Group 3 patients, treatment of pulmonary emboli (medical vs surgical) for Group 4 patients, and appropriate unusual diagnoses can be made for Group 5 patients.

Hemodynamic Progression of PAH



TPG= PAP-PAW

PVR=TPG/ CO

Predictors of poor prognosis

- 6minute walk < 300 meters
- Presence of a pericardial effusion
- RA pressure > 20 mm hg
- WHO class IV symptoms or syncope
- Elevated BNP

Risk assessment in PAH

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%

Nazzarino Galie et al. European Heart Journal 2015

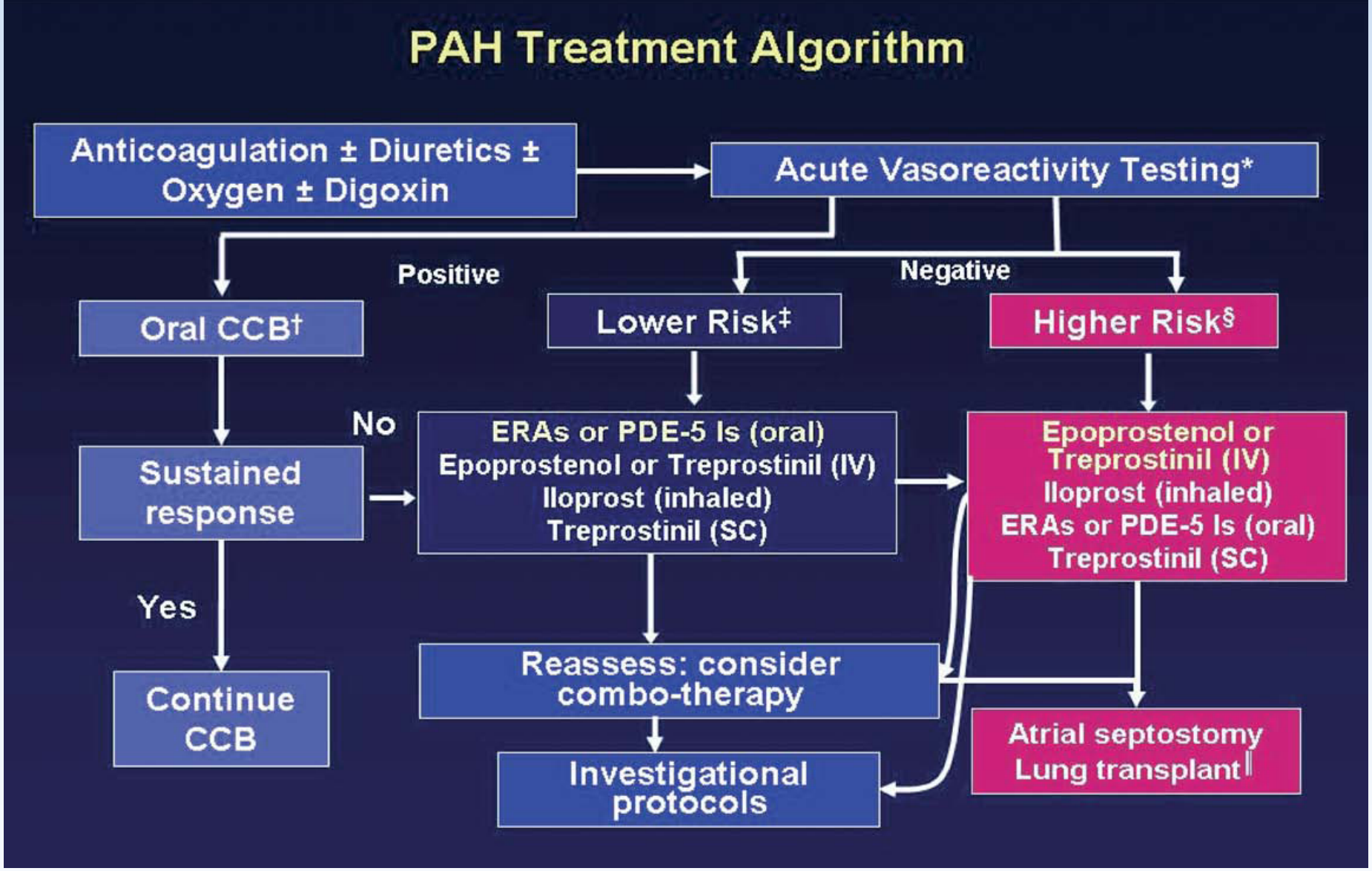
PHCC, Metrohealth Medical Center

- Cardiology run with pulmonary lead
- Direct referral from PCP or through Pulmonary, general cardiology, or heart failure cardiology
- Referral from echo lab
- Referral from inpatient consults.

Right Heart Catheterization and Vaso-reactivity study

- RHC is recommended when:
  - Group 1 PAH is suspected
  - Group 2, with LV failure is being considered for HT
  - When PAH therapy is being considered
  - For follow up to determine response to PAH therapy
- Vaso-reactivity study is recommended when:
  - PAH is suspected (PCWP < 15)
- LHC for LVEDP when:
  - PCWP could not be obtained or confirmed
  - PCWP reading is not consistent with the clinical picture
- Shunt run is recommended when:
  - Suspecting L-R shunt by other imaging or by history
  - PA O2 sat > 75%

Nazzarino Galie et al. European Heart Journal 2015



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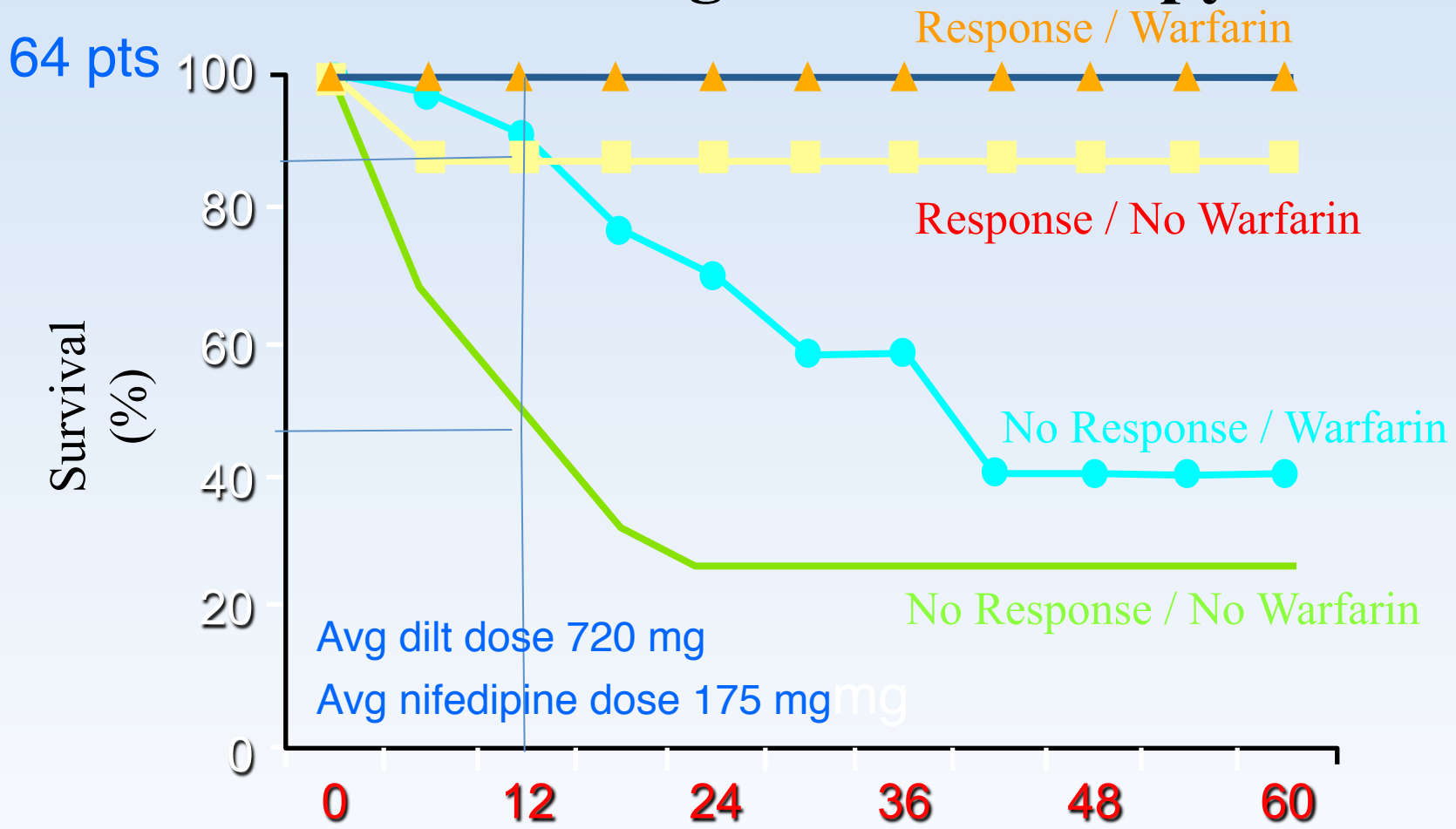
Survival in IPAH with CCB and Anticoagulation Therapy



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Rich et al. NEJM 1992;327:76–81

Survival Curve after 12 weeks Epoprostenol Therapy

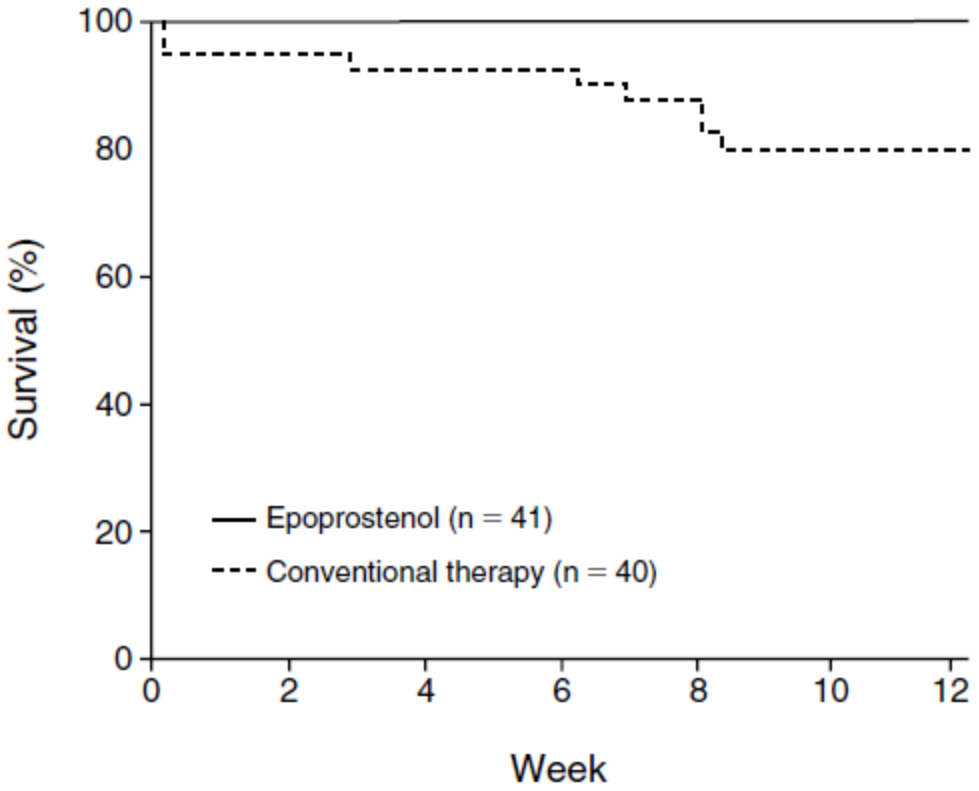
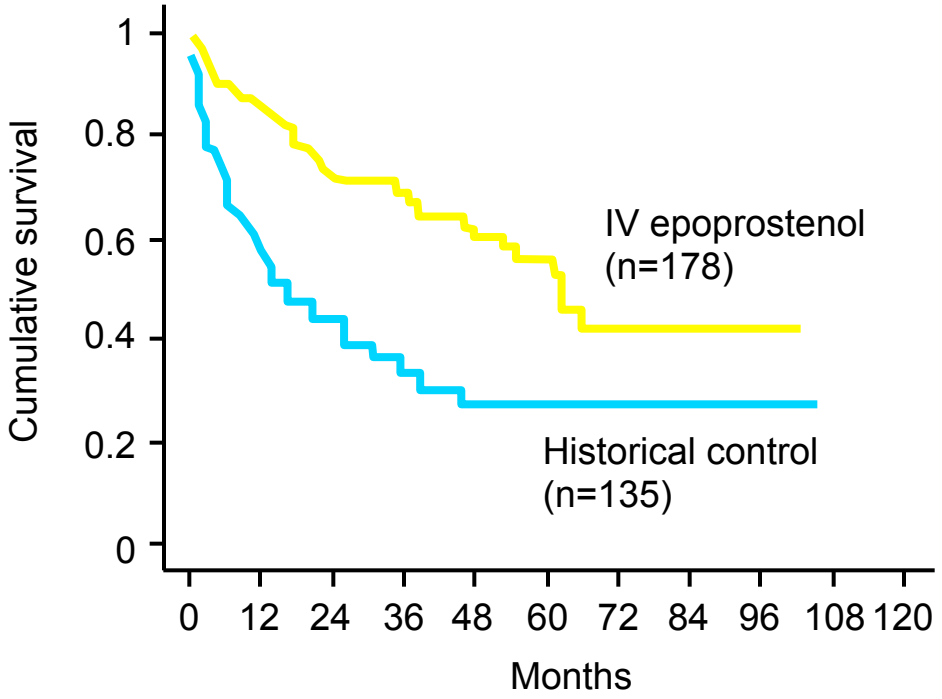


Figure 1. Survival among the 41 Patients Treated with Epoprostenol and the 40 Patients Receiving Conventional Therapy.

Barst, NEJM 1996 Feb 1;334(5):296-302.

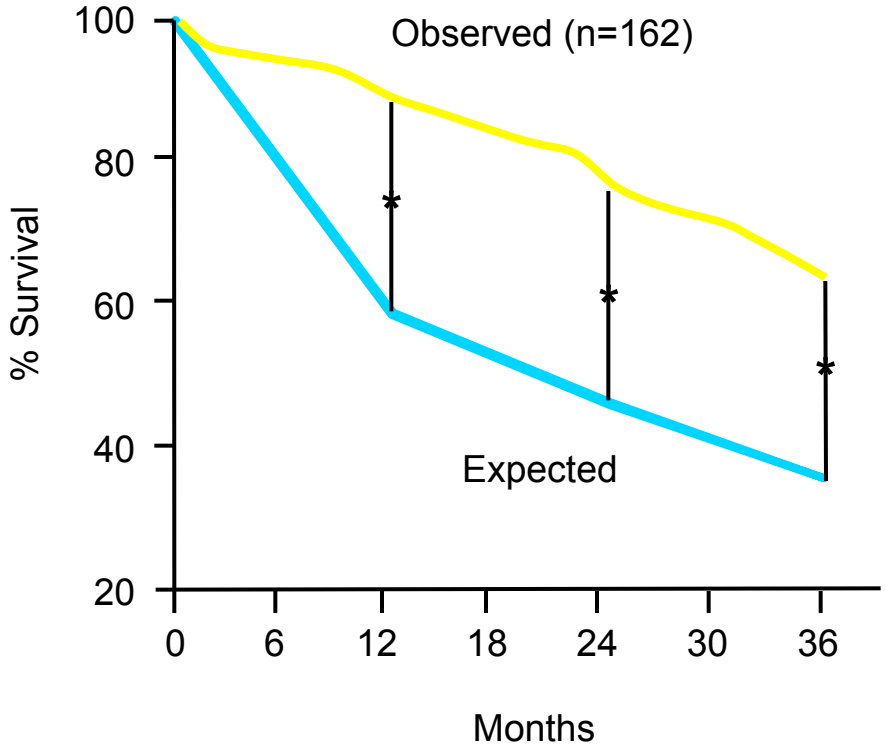
Long-Term Outcome in IPAH With Epoprostenol



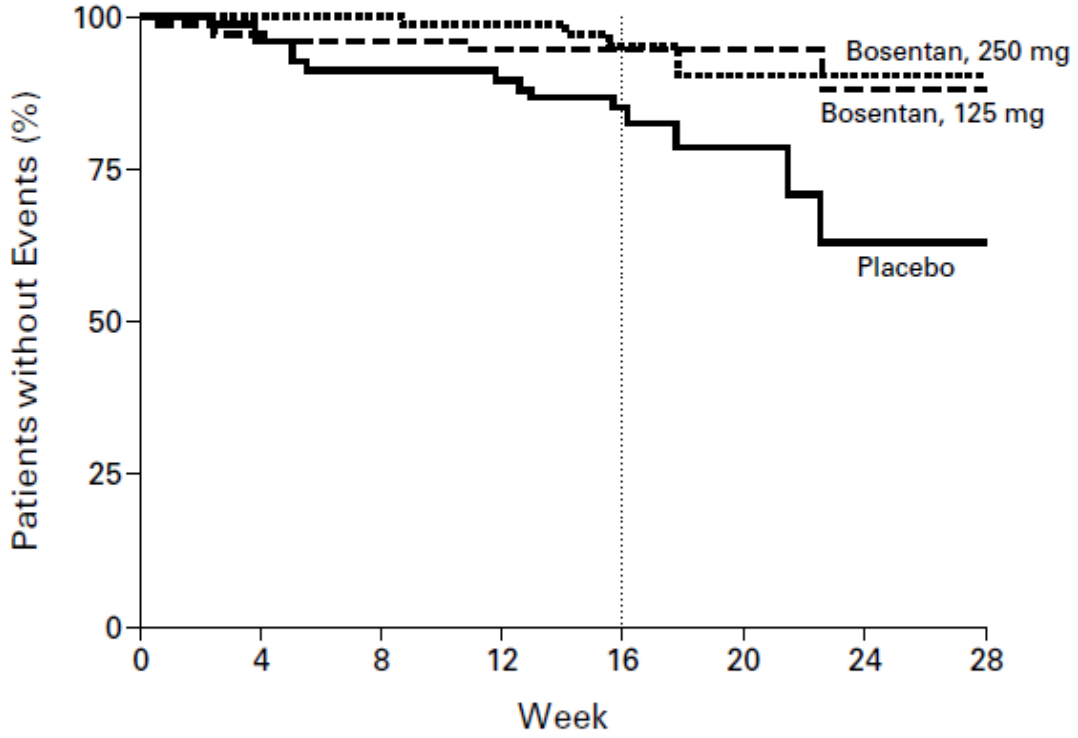
No. at risk

178	129	85	57	36	21	7	3	1	IV epo
135	59	34	20	11	4	2	2	1	Hist. control

Sitbon O et al. *J Am Coll Cardiol.* 2002;40:780-788.



McLaughlin VV et al. *Circulation.* 2002;106:1477-1482.



No. at Risk								
Placebo	69	68	63	62	48	10	7	3
Bosentan, 125 mg	74	72	71	70	55	18	14	7
Bosentan, 250 mg	70	70	70	68	48	13	11	6

Figure 4. Kaplan–Meier Estimates of the Proportion of Patients with Clinical Worsening.

Clinical worsening was defined by the combined end point of death, lung transplantation, hospitalization or discontinuation of the study treatment because of worsening pulmonary arterial hypertension, a need for epoprostenol therapy, or atrial septostomy. $P<0.05$ for the comparison of the bosentan groups with the placebo group at weeks 16 and 28 by the log-rank test. There was no significant difference between the two bosentan groups at weeks 16 and 28 ($P=0.87$).

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Balloon atrial septostomy

- Recommended as palliative therapy or bridge to lung transplant in:
  - Functional class IV patients failing medical therapy
  - RV failure despite maximum medical therapy
  - Recurrent syncope due to severely low cardiac output.
- Contraindicated if:
  - RAP > 20 mmHg
  - Arterial O2 saturation < 85%

Nazzarino Galie et al. European Heart Journal 2015

Other advanced options in severe RV failure:

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- Inotropic support (temporary or home infusion)
- ECMO as a bridge to lung transplant
- RVAD is NOT an option due to high afterload
- Lung transplant

Treatment of pulmonary hypertension

- Optimal management of left sided heart failure
- Optimal management of sleep disordered breathing (OSA)
- Endarterectomy in selected patients with chronic pulmonary emboli
- Oxygen therapy

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Thank you!

Recommendations for general measures

Recommendations	Class[a]	Level[b]	Ref.[c]
It is recommended that PAH patients avoid pregnancy	I	C	160, 161
Immunization of PAH patients against influenza and pneumococcal infection is recommended	I	C	
Psychosocial support is recommended in PAH patients	I	C	168
Supervised exercise training should be considered in physically deconditioned PAH patients under medical therapy	IIa	B	153–157
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	

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Recommendations for supportive therapy

Recommendations	Class[a]	Level[b]	Ref.[c]
Diuretic treatment is recommended in PAH patients with signs of RV failure and fluid retention	I	C	178
Continuous long-term O_2 therapy is recommended in PAH patients when arterial blood O_2 pressure is consistently <8 kPa (60 mmHg)[d]	I	C	179
Oral anticoagulant treatment may be considered in patients with IPAH, HPAH and PAH due to use of anorexigens	IIb	C	84,171, 175–177
Correction of anaemia and/or iron status may be considered in PAH patients	IIb	C	184
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	

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PAH-specific drugs: Mono-therapy

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	-	-

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Combination therapy

Measure/ treatment	Class[a]-Level[b]						Ref.[c]
	WHO-FC II		WHO-FC III		WHO-FC IV		
Ambrisentan + tadalafil[d]	I	B	I	B	IIb	C	247
Other ERA + PDE-5i	IIa	C	IIa	C	IIb	C	-
Bosentan + sildenafil + i.v. epoprostenol	-	-	IIa	C	IIa	C	246
Bosentan + i.v. epoprostenol	-	-	IIa	C	IIa	C	198, 245
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	-

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PAH-specific drugs: Sequential therapy

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

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Management of PAH-ACHD

- Exclude PH secondary to LV dysfunction or associated lung disease.
- Start PAH medications early
- Closure of L-R shunt if indicated
- Other management aspects:
  - Oxygen, hydration
  - Anticoagulation in absence of hemoptysis
  - Avoid Ca++ blockers
  - IV filters to prevent paradoxical emboli

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PAH associated with connective tissue disease (PAH-CTD)

- Screening asymptomatic patients **is recommended** in SSc with annual echocardiogram, DLCO and biomarkers.
- Evaluate for group 2 (due to diastolic dysfunction) and group 3 (due to ILD)
- Start PAH medications early

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PAH associated with portal hypertension (PoPH)

- Patients tend to have higher CI and lower PVR
- Screening for PoPAH is recommended prior to listing for liver transplant.
- Associated with high mortality post liver transplant:
  - 100% for mPAP > 50
  - 50% for mPAP 35-50 mmHg
- Supportive measures:
  - Avoid anticoagulation
  - Avoid beta blockers (often used for E varices)
  - Avoid ERAs, especially Bosentan

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PAH associated with HIV infection:

- Screening asymptomatic patients is **not recommended** due to low incidence.
- Rule out
  - PoPAH
  - drug-induced PAH
  - group 2 (due to LHD)
  - group 3 (ILD)
  - group 4 (CTEPH)
- Be aware of interaction between ERA and HIV medications

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PVOD/PCH

- Very rare
- Suspect when:
  - Chronic pulmonary edema with hypoxia, clubbing, DOE
  - Hemodynamics consistent with PAH, but with high PCWP
  - Severe reduction in DLCO
  - Characteristic findings on HRCT:
    - Sub-pleural thickened septal lines
    - ground-glass opacities
    - mediastinal lymphadenopathy
    - occult alveolar hemorrhage on Bronchoscopy
    - Exaggerated rise in PCWP during reversibility study
- Gold standard is lung biopsy but often not necessary
- Therapy:
  - Diuretics, Oxygen
  - Slow introduction of PAH medications (often not tolerated)
  - Experimental use of angiogenesis inhibitors such as INF alpha2
  - Lung transplant

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PH-LHD (group 2 PH)

- Treat underlying LV dysfunction or valvular disease
- PDE-5 inhibitors have been used in patients awaiting HT and resulted in reduction of PVR
- Ongoing trials for the use of PDE-5 and ERA in these patients.
  - Sildenafil: *SilHF (NCT01616381)*
  - Macitentan: *Melody-1 (NCT02070991)*

PH due to lung disease and/or hypoxia (Group 3 PH)

- Most commonly seen in COPD, ILD, IPF.
- Rarely seen in OSA without left heart disease
- Usually mild to moderate. If severe, look for other causes
- No correlation between severity of lung disease and severity of PH
- Mechanism is thought to be hypoxia-induced chronic vasoconstriction
- O2 therapy can slow down progression of disease
- PAH medications are not recommended unless mixed etiology (groups 1,3) is suspected (as in scleroderma
- Vasodilators and PAH meds, if used, may worsen hypoxia

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Chronic thromboembolic PH (CTPH)
Group 4 PH

- Majority are diagnosed in patient with no prior clinical history of PE
- Lifelong anticoagulation
- Always assess candidacy for pulmonary endarterectomy
- Start PAH medications early on even after surgery if PH does not resolve

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PH due to unclear and/or multifactorial mechanisms
Group 5 PH

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5. Pulmonary hypertension with unclear and/or multifactorial mechanisms

5.1 Haematological disorders: chronic haemolytic anaemia, myeloproliferative disorders, splenectomy
5.2 Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis neurofibromatosis
5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
5.4 Others: pulmonary tumoral thrombothic microangiopathy, fibrosing mediastinitis, chronic renal failure (with/without dialysis), segmental pulmonary hypertension

- Heterogeneous group with poorly understood mechanisms including:
  - pulmonary vasoconstriction
  - proliferative vasculopathy
  - extrinsic compression (Histoplasmosis/ fibrosing mediastinitis, hydated cysts)
  - intrinsic occlusion (PV stenosis after PVI)
  - high-output cardiac failure (chronic anemia especially hemolytic anemia, AV-shunts)
- Treatment is targeting the underlying cause

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