Pulmonary Hypertension

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- Research Support – United Therapeutics, Novartis, Novo Nordisk
- CSL Behring – Safety review committee for Phase 1 clinical trial of hemopexin for SCD
- Novo Nordisk – Advisory Board/Consultant - End Organ Complications of SCD
- Pfizer – Consultant – End organ complications of SCD

Case

45 yr old female with DM, prior bariatric surgery (BMI now 29), and Fe deficiency anemia who presents to clinic for annual exam.

Notes worsening dyspnea over the past year. Now is short of breath with climbing one flight of stairs. She is short of breath on walking 5 blocks. She notes some dizziness with stairs but no syncope. Denies chest pain, PND, orthopnea, LE edema

Physical Exam – Not hypoxic, VS otherwise unremarkable
Neck – Elevated JVP
Lungs – Clear to auscultation
COR- RRR, normal S1, loud split S2, III/VI systolic murmur at LSB, no RV heave, no S3, no edema

Symptoms and Signs of Pulmonary HTN

- Progressive dyspnea on exertion
- Chest pain/dizziness/syncope with exertion
- Right sided CHF – increased abd girth, LE edema
- PND, orthopnea

Exam – 1) Can by hypoxic with exertion but does not have to be

2) Elevated JVP

3) Lungs can be clear if no co-existent lung/heart disease

4) Cardiac exam – loud P2 with fixed split, RV heave, palpable PA, TR murmur/pulsatile liver, LE edema, ascites

5) Look for connective tissue disease tip offs.

Echocardiogram

Normal LV size, and systolic function; LVEF 61%. No WMA.

Mildly increased LV wall thickness with Grade 2 Diastolic dysfunction

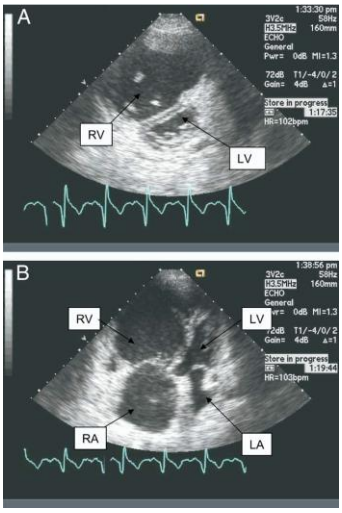
Normal LA and RA

Normal RV size and function

2+ MR, 2+ TR

PASP 57 mmHg; normal IVC size and respirophasic variation. No pericardial effusion.

Echo in Pulmonary HTN



Reliability of Echocardiography in Assessing PH

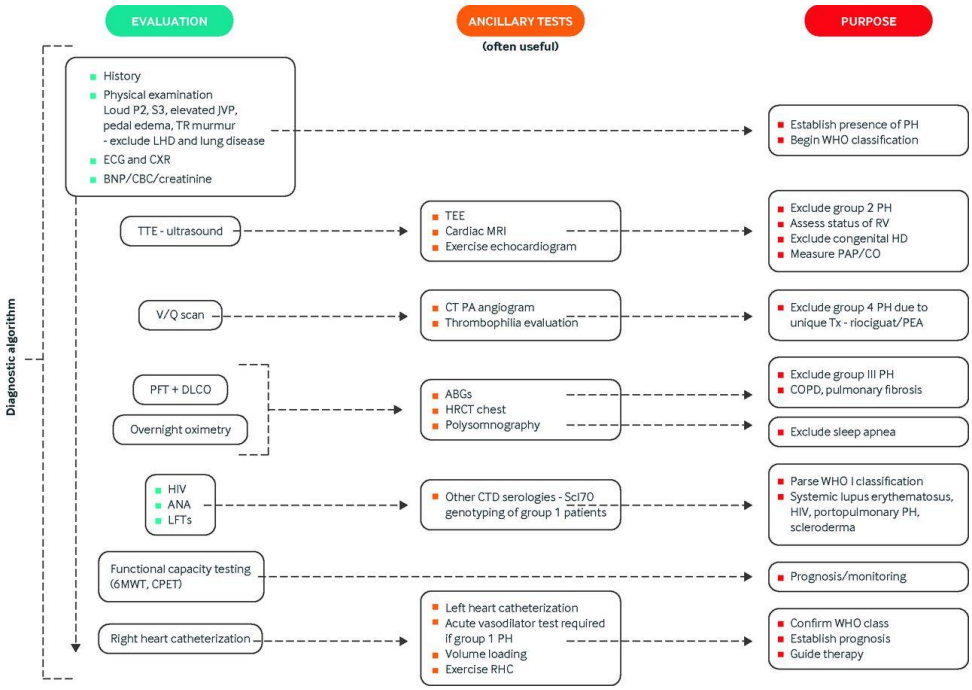
- Relies on Bernoulli equation – takes into account TRV and RAP
- Right atrial pressure – estimation based on IVC collapsibility
- TRV can be over-estimated or under-estimated

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

Peak tricuspid regurgitation velocity (m/s)	Presence of other echo 'PH signs'[a]	Echocardiographic probability of pulmonary hypertension
≤2.8 or not measurable	No	Low
≤2.8 or not measurable	Yes	Intermediate
2.9–3.4	No	
2.9–3.4	Yes	High
>3.4	Not required	

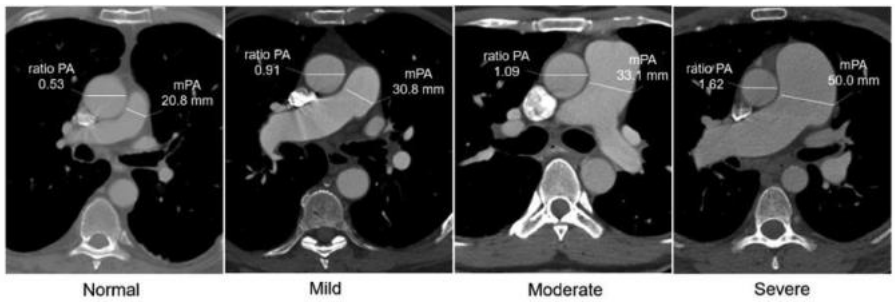
Galie N, et al. *European Heart Journal*, 2016; 37:67–119

Patient referred to pulmonary HTN clinic



CT Scanning in PH Evaluation

- Increased PA diameter (≥29 mm) – Severe (>34 mm) most specific
- Pulmonary artery:ascending aorta diameter ratio (≥1.0) - >1.1 most specific



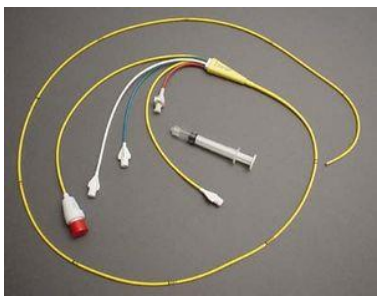
Truong QA, et al. J Cardiovasc Computed Tomography 2018; 12:60-66

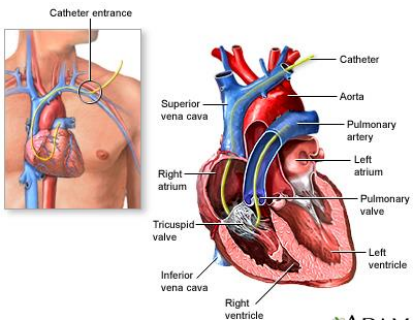
Rest of PH Workup

- ANA + 1:640, HIV neg, anti-Scl-70 positive, dsDNA neg, Sm Ab neg
- Negative V/Q scan
- PFTs and CT scan – no ILD
- Diagnosed with Sine scleroderma (scleroderma without skin disease)

Pulmonary Hypertension: Changing Definition as of 2019

- Defined hemodynamically by right heart catheterization
- Mean pulmonary artery pressure (PAP) >20 mm Hg at rest



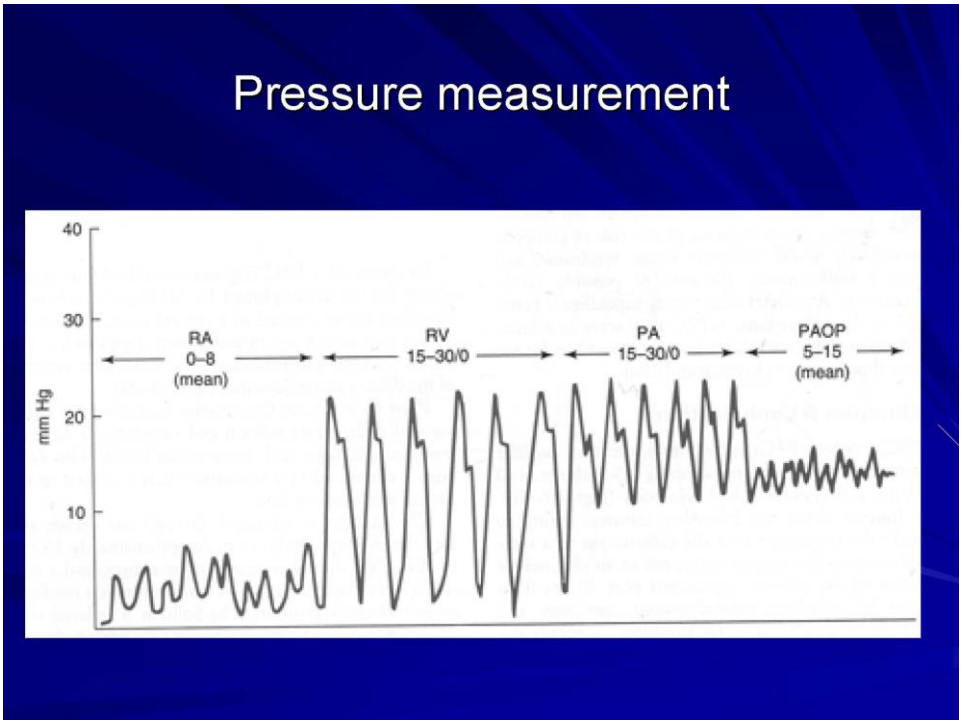


Defining Pre- and Post-Capillary PH

Definitions	Characteristics	Clinical groups[#]
Pre-capillary PH	mPAP >20 mmHg	1, 3, 4 and 5
	PAWP ≤15 mmHg	
	PVR ≥3 WU	
Isolated post-capillary PH (IpcPH)	mPAP >20 mmHg	2 and 5
	PAWP >15 mmHg	
	PVR <3 WU	
Combined pre- and post-capillary PH (CpcPH)	mPAP >20 mmHg	2 and 5
	PAWP >15 mmHg	
	PVR ≥3 WU	

PVR = mPAP-PAWP/CO (Wood units)
If you multiple by 80: dynes·sec/cm^5

Simonneau G, et al. Eur Respir J 2019; 53(1): 1801913.



Right Heart Catheterization

RA: 10/8 (6)

RV: 57/1, 12

PAP: 57/18 (35)

PAWP: 14

PA sat 63%

CO/CI (TD): 7.7/3.5

CO/CI (Fick): 7.5/3.8

PVR (Fick): 320

WHO Classification of PH

- Group I – Pulmonary Arterial Hypertension
- Group II – Pulmonary Hypertension Due to Left-Sided Heart Disease
- Group III – PH Assoc. with Chronic Lung Disease/Hypoxia
- Group IV – PH due to PA Obstructions – CTEPH, PA tumors
- Group V – PH with unclear multi-factorial mechanisms – Sarcoidosis, Sickle Cell Disease, Chronic renal failure

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

Classification: Group 1 PAH

1 PAH

- 1.1 Idiopathic PAH
- 1.2 Heritable PAH
- 1.3 Drug- and toxin-induced PAH (table 3)
- 1.4 PAH associated with:
  - 1.4.1 Connective tissue disease
  - 1.4.2 HIV infection
  - 1.4.3 Portal hypertension
  - 1.4.4 Congenital heart disease
  - 1.4.5 Schistosomiasis
- 1.5 PAH long-term responders to calcium channel blockers (table 4)
- 1.6 PAH with overt features of venous/capillaries (PVOD/PCH) involvement (table 5)
- 1.7 Persistent PH of the newborn syndrome

Simonneau G, et al. Eur Respir J 2019; 53(1): 1801913

Classification: Group 2-5 PH

2 PH due to left heart disease

- 2.1 PH due to heart failure with preserved LVEF
- 2.2 PH due to heart failure with reduced LVEF
- 2.3 Valvular heart disease
- 2.4 Congenital/acquired cardiovascular conditions leading to post-capilla

3 PH due to lung diseases and/or hypoxia

- 3.1 Obstructive lung disease
- 3.2 Restrictive lung disease
- 3.3 Other lung disease with mixed restrictive/obstructive pattern
- 3.4 Hypoxia without lung disease
- 3.5 Developmental lung disorders

4 PH due to pulmonary artery obstructions (table 6)

- 4.1 Chronic thromboembolic PH
- 4.2 Other pulmonary artery obstructions

5 PH with unclear and/or multifactorial mechanisms (table 7)

- 5.1 Haematological disorders
- 5.2 Systemic and metabolic disorders
- 5.3 Others
- 5.4 Complex congenital heart disease

Simonneau G, et al. Eur Respir J 2019; 53(1): 1801913

Group 5 PH

TABLE 7

Pulmonary hypertension with unclear and/or multifactorial mechanisms

5.1 Haematological disorders	Chronic haemolytic anaemia
	Myeloproliferative disorders
5.2 Systemic and metabolic disorders	Pulmonary Langerhans cell histiocytosis
	Gaucher disease
	Glycogen storage disease
	Neurofibromatosis
	Sarcoidosis
5.3 Others	Chronic renal failure with or without haemodialysis
	Fibrosing mediastinitis
5.4 Complex congenital heart disease	See the Task Force article by ROSENZWEIG *et al.* [31] in this issue of the *European Respiratory Journal*

Simonneau G, et al. Eur Respir J 2019; 53(1): 1801913

Pulmonary Arterial Hypertension due to Connective Tissue Disease

Pulmonary Arterial Hypertension

- Prevalence of 15-50 cases/million adults
- Historically, most frequent in 35-50 yr olds, now older
- Generally more common in women, survival worse in men
- Mean survival without treatment 2.8 yrs

Group I - PAH

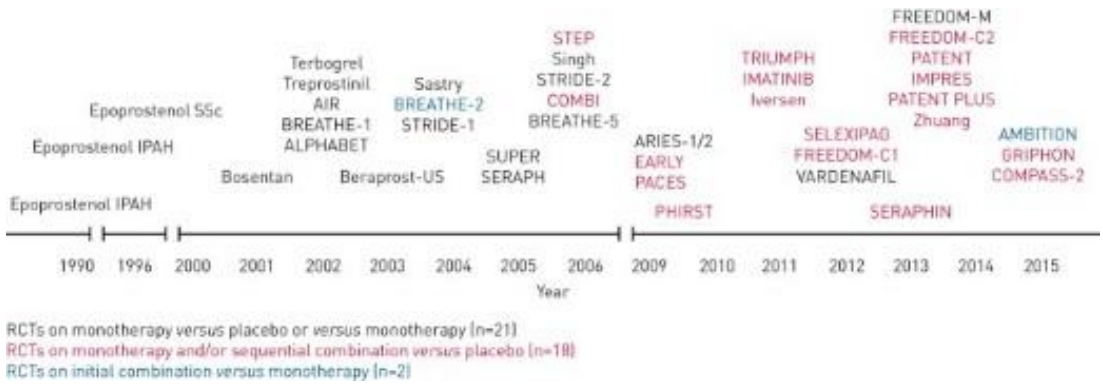
a) IPAH
b) HPAH
c) Connective Tissue Disease – SSc, MCTD, SLE and RA
d) Porto-pulmonary HTN
e) Congenital Heart Disease
f) HIV
g) Drug and toxin-induced
h) Schistosomiasis

General Measures in Treatment of PAH

- Supportive therapy – Diuretics, O_2, Anti-coagulation
- Pulmonary Rehabilitation
- Referral to a PH Center
- Vasoreactivity testing – can consider for IPAH patients – determines CCB responsiveness
- Approximately 8% of IPAH patients are vasoreactive – can be treated with high dose calcium channel blockers but need very close follow-up

Galie N, et al. Updated Treatment Algorithm of Pulmonary Arterial Hypertension. JACC 2013;62: D60-D72.

A Timeline of PAH Clinical Trials



Galie N, et al. Eur Respir J 2019 Jan; 53(1): 1801889.

Trends in PAH Clinical Trials: An Overview

- Length of trial – Increased
- Clinical trial endpoints – Mortality, 6MWD, composite endpoints
- Time to clinical worsening: PAH hospitalizations, need for IV therapy/transplant, mortality
- Caveat: IPAH, HPAH, PAH-CTD, and Toxin induced – only patients in clinical trials
- Porto-pulmonary HTN and HIV-PAH – always included in recommendations but we really don't know

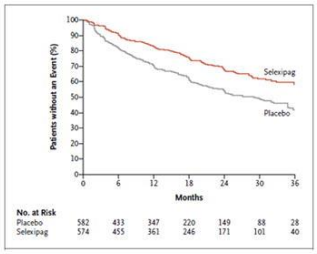
What have we learned from all these trials

- Treatment Naïve patients: Initial monotherapy improves exercise capacity, hemodynamics and outcome compared with untreated patients
- Initial combination therapy better than monotherapy

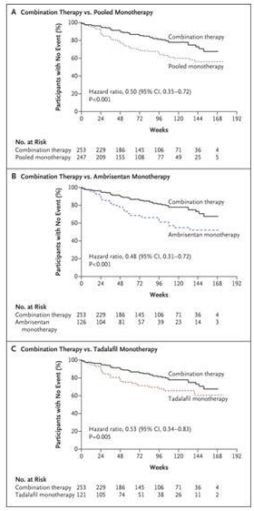
In already treated PAH patients, sequential therapy is better than just continuing background therapy

The Rationale for Combination Therapy in PAH

A.



B.



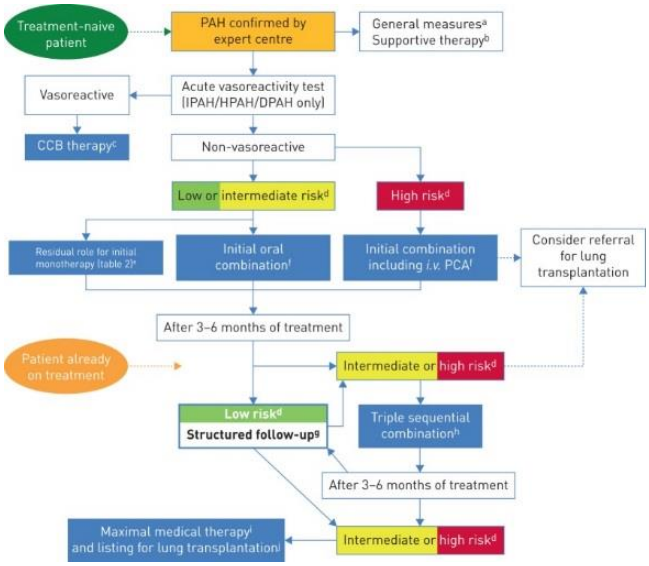
Maron BA and Galie N JAMA Cardiol 2016 Dec 1;1(9):1056-1065

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%

Galie N, et al. *European Heart Journal*, 2016; 37:67–119.

Treatment Algorithm for PAH



Galie N, et al. Eur Respir J 2019 Jan; 53(1): 1801889.

PAH Treatment in 2024

- Currently 14 medications FDA approved for treatment of PAH:

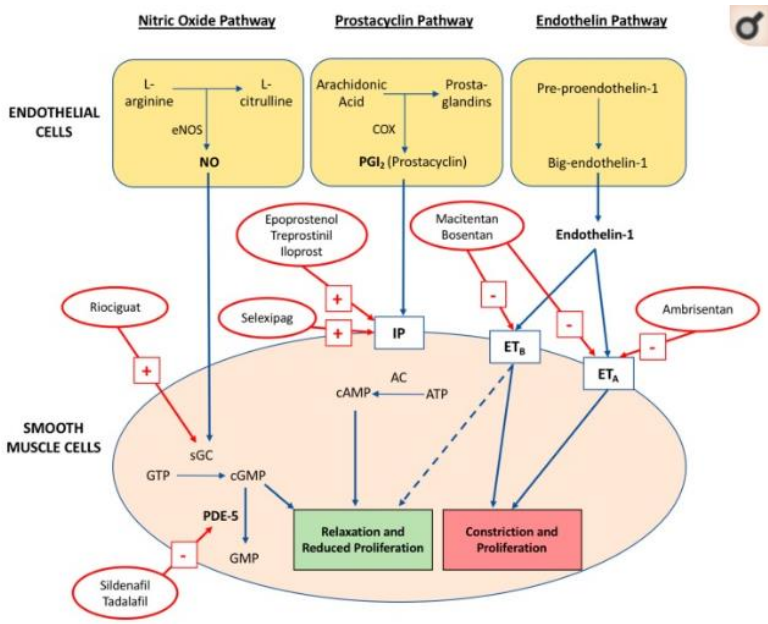
a) Prostaglandins: Epoprostenol, Treprostinil (subq/IV, inhaled, oral) , Iloprost, Selexipag

b) ERA's: Bosentan, Ambrisentan, Macitentan

c) PDE5 Inhibitors: Sildenafil, Tadalafil

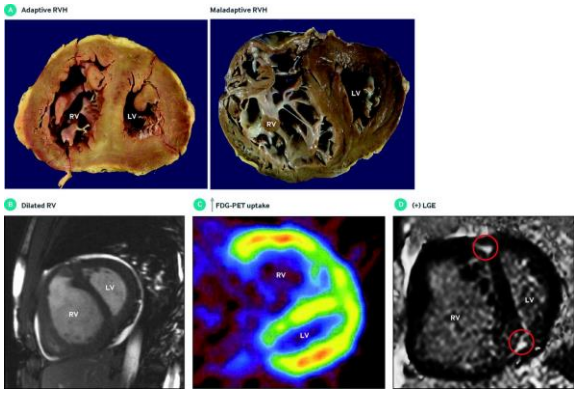
d) Soluble guanylate cyclase agonists: Riociguat

Sotatercept – not a pulmonary vasodilator – FDA approved in April 2024



Lan, NSH et al. Diseases 2018; 6(2): 38.

Impact of pulmonary hypertension on RV size and function



- ☐ Complex ellipsoidal/crescentic shape
- ☐ Anatomica and functional dependence with the left ventricle by shared septum, pericardium, epicardial fibers
- ☐ Less muscular thickness than the left ventricle
- ☐ Pumps against a low resistance circuit
- ☐ Poor adaptive mechanism for acute increases in afterload
- ☐ Sequential contraction pattern (from inlet to infundibulum)
- ☐ Poor tolerance of arrhythmia

Thenappan T et al. B*MJ* 2018;360:j5492 doi: 10.1136/bmj.j5492

Factors Impacting Medication Selection

- Try to start everyone with orals if possible
- Everyone gets vasodilation symptoms
- Once a day vs multiple doses per day
- Generics are coming fast and furious
- Think about class specific toxicities:

ERAs – hepatotoxicity, LE edema

PDE5i – Can't use with nitrates, nasal/sinus symptoms

Subcutaneous treprostinol: pain at injection site

Case Follow-up

Started on Ambrisentan and tadalafil – Jan 2020

Optimal length of follow-up: Every 1-3 months
Sept 2020 – RHC
RA 9/7 4
RV 44/0
PA 44/11 (25)
PAWP 17/22, 13
CO/CI 7.44/3.88
PVR 129

August 2023: 6MWT – 427 meters with normal oxygenation, now NYHA II-III, but also back smoking
Echocardiogram – Normal LV and RV function, PASP 22 mmHg (Nov 2023)

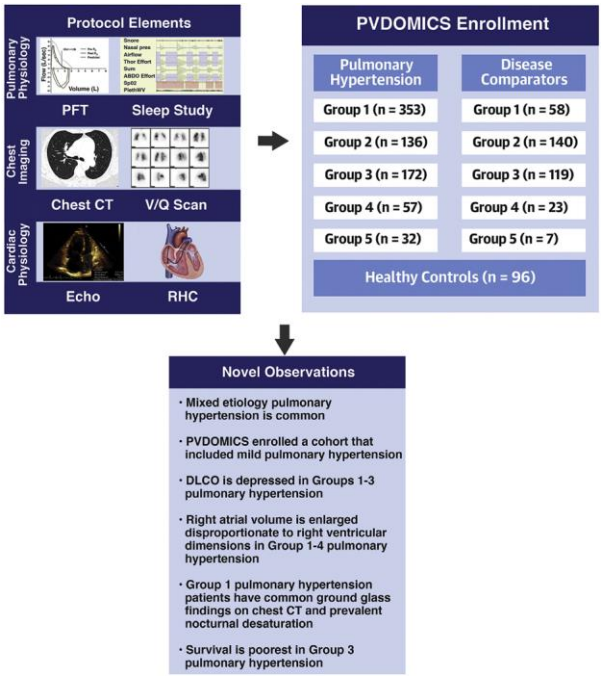
Newer Directions in PH

- Many patients actually do not fit neatly into 1 group
- Combined pre- and post-capillary PH incredibly common
- Need more options for the most common forms of PH – Group 2 and Group 3 PH
- The current therapies only target vasodilation, yet the biology of the disease is more complex

PVDOMICs

- NHLBI funded multicenter initiative – Vanderbilt, B and W, Columbia/Cornell, Mayo, U of Arizona and Hopkins
- Prospective clinical and genomic/proteomic/metabolomic studies on PH patients across WHO groups – goal to enroll 1500 patients
- Clinical data starting to be presented – expect published data this academic year

Hemnes A, et al Circ Res 2017; 121: 1136-9.



Hemnes AR, et al. JACC 2022; 80:697-718.

Can PAH Therapies Work in Group 3 PH?

- Worsening V/Q mismatch limits use of most agents
- INCREASE Study – Randomized, placebo controlled – 326 patients with PH-ILD – Inhaled treprostinil vs placebo
- 16 week study – change in 6MWD primary endpoint
- Treprostinil increased 6MWD by 31.1 meters (95% CI 16.85-45.39, p=0.001)
- Post-hoc analysis – increased benefit in those who received ≥9 puffs QID

Waxman A, et al. N Engl J Med 2021; 384: 325-334.
Nathan SD, et al. Chest 2023; 163:398-406.

Sotatercept

- Acts via modulation of TGF-beta signaling – Endothelial/smooth muscle cell proliferation
- Phase 3 trial: 323 PAH patients, NYHA Class II or III, 1:1 randomization, subcutaneous sotatercept (starting dose, 0.3 mg per kilogram of body weight; target dose, 0.7 mg per kilogram) or placebo every 3 weeks
- Primary end point: Change in 6-minute walk distance at 24 wks: improved 40.8 meters ($p< 0.001$)
- Secondary endpoints – reduced PVR, decreased NT-pro-BNP levels, improved NYHA Class, increased time to death/clinical worsening
- Big issues – telangectasias, thrombocytopenia, epistaxis
- FDA approved April 2024

Humbert M, et al. NEJM 2021; 384: 1204-1215.

Summary

- Pulmonary hypertension increasing in frequency due to improved echocardiography
- PH due to left-sided heart disease and chronic lung disease remains most common
- Delays in diagnosis and referral to PH centers are common and lead to poor outcomes
- Progressive dyspnea, chest pain – keep in your differential
- Syncope – ominous, needs an emergent referral