Pulmonary Hypertension in 2025;

AONP conference

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Relevant Disclosure and Mitigation Report

Syed Talal Hussain MD

I have no financial relationships or affiliations with commercial interests/ineligible companies to disclose.

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Learning Objectives

Upon completion of this session, participants will improve their competence and performance by being able to:

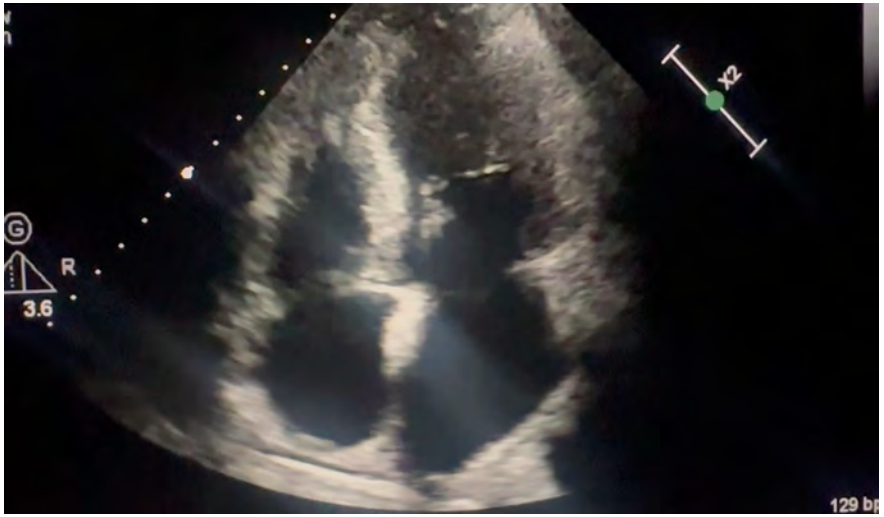
- Evaluate and diagnose patients with pulmonary hypertension
- Understand indications of doing acute vasodilatory testing
- Better understand classification of pulmonary hypertension
- Better understand new pulmonary hypertension treatment strategies

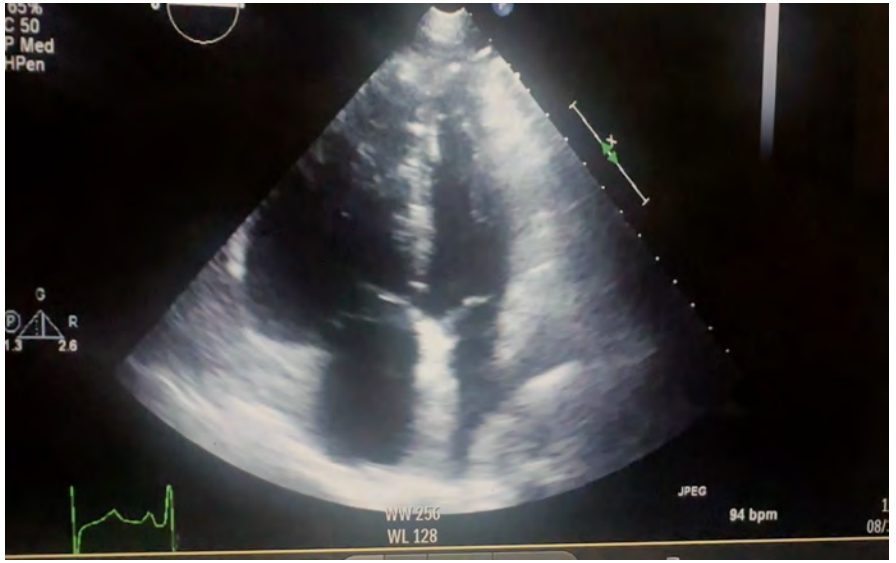
Case Scenario

A 46-year-old female with history of prior methamphetamine use is admitted to the hospital due to syncope and shortness of breath.

FC III
ProBNP is 10,000 pg/ml

Echocardiogram





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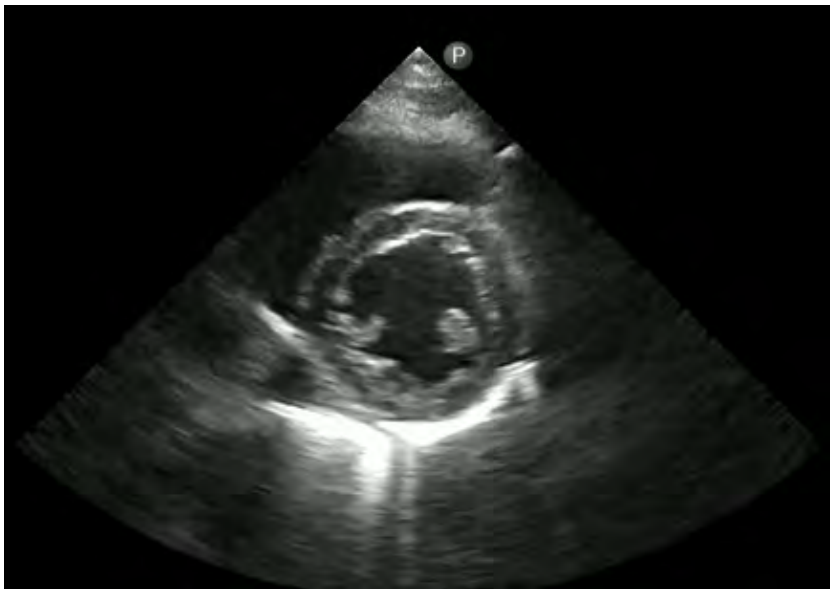
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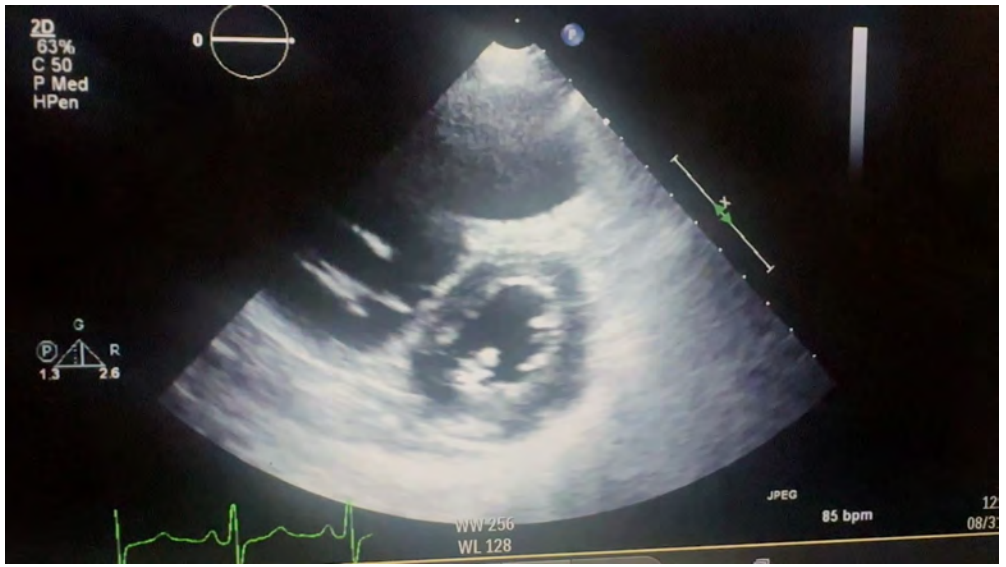
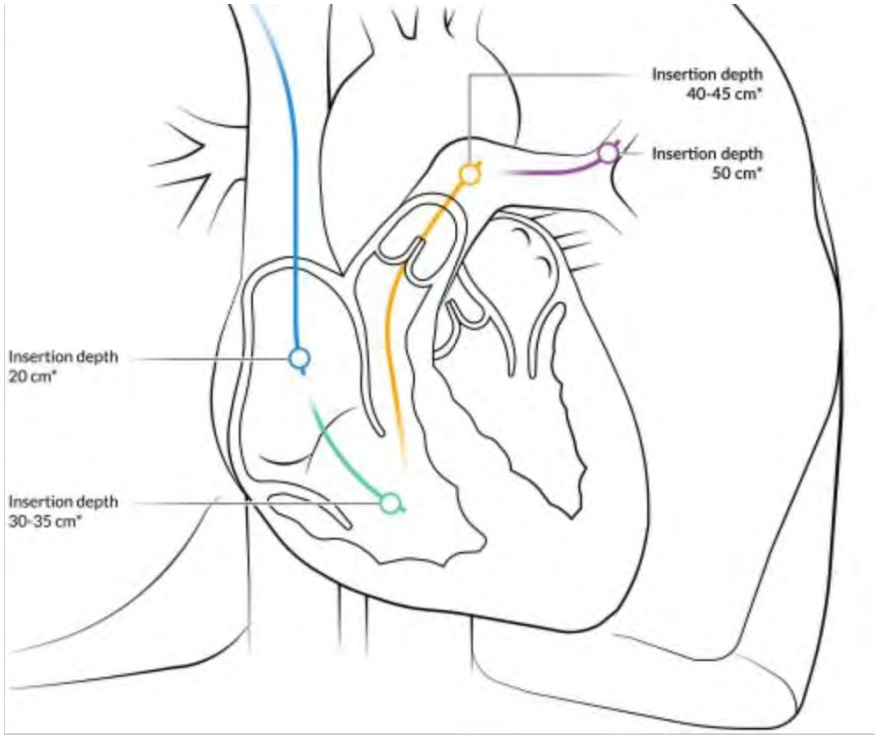

2D
63%
C 50
P Med
HPen
0
G
P
R
1.3
2.6
JPEG
85 bpm
WW 256
WL 128

Right heart catheterization

- *On milnirone 0.25 mcg/kg/min*

- PA 100/40 mm Hg
- mPAP: 60 mm Hg
- PCWP: 6 mm Hg
- CO : 3.7 L/min, CI: 1.9
- PVR : 15 WU



Boostma et al 2021

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Hemodynamic Definitions

Definition	Hemodynamic profile	Typical clinical group
PH	mPAP >20 mm Hg	All
Precapillary PH	mPAP >20 mm Hg PVR >2 WU PAWP ≤15 mm Hg	Pulmonary arterial hypertension PH attributable to lung disease CTEPH
Combined precapillary+postcapillary PH	mPAP >20 mm Hg PVR >2 WU PAWP >15 mm Hg	Left heart disease Left heart+lung disease overlap
Isolated postcapillary PH	mPAP >20 mm Hg PVR ≤2 WU	Left heart disease

ERS 2022

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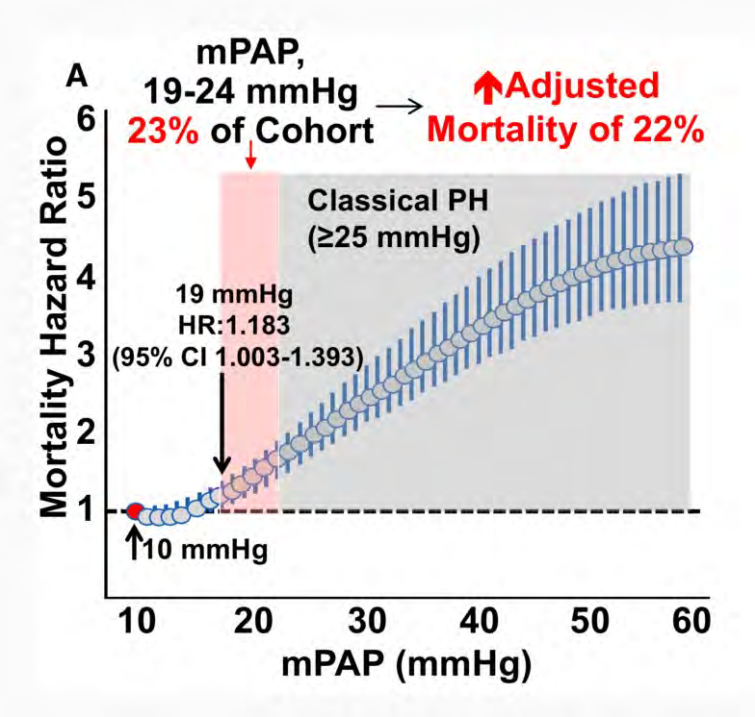
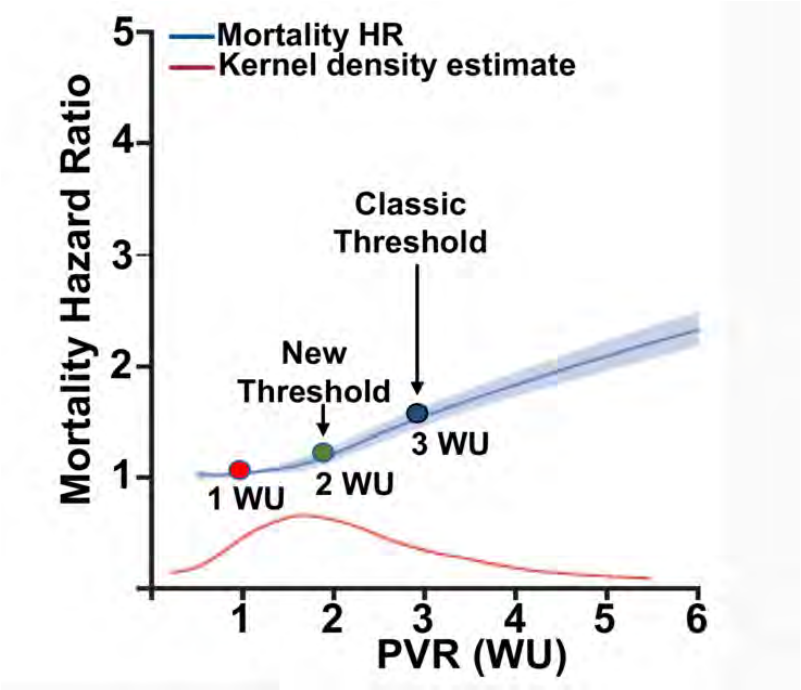
Why the change ?





Maron JAHA 2023

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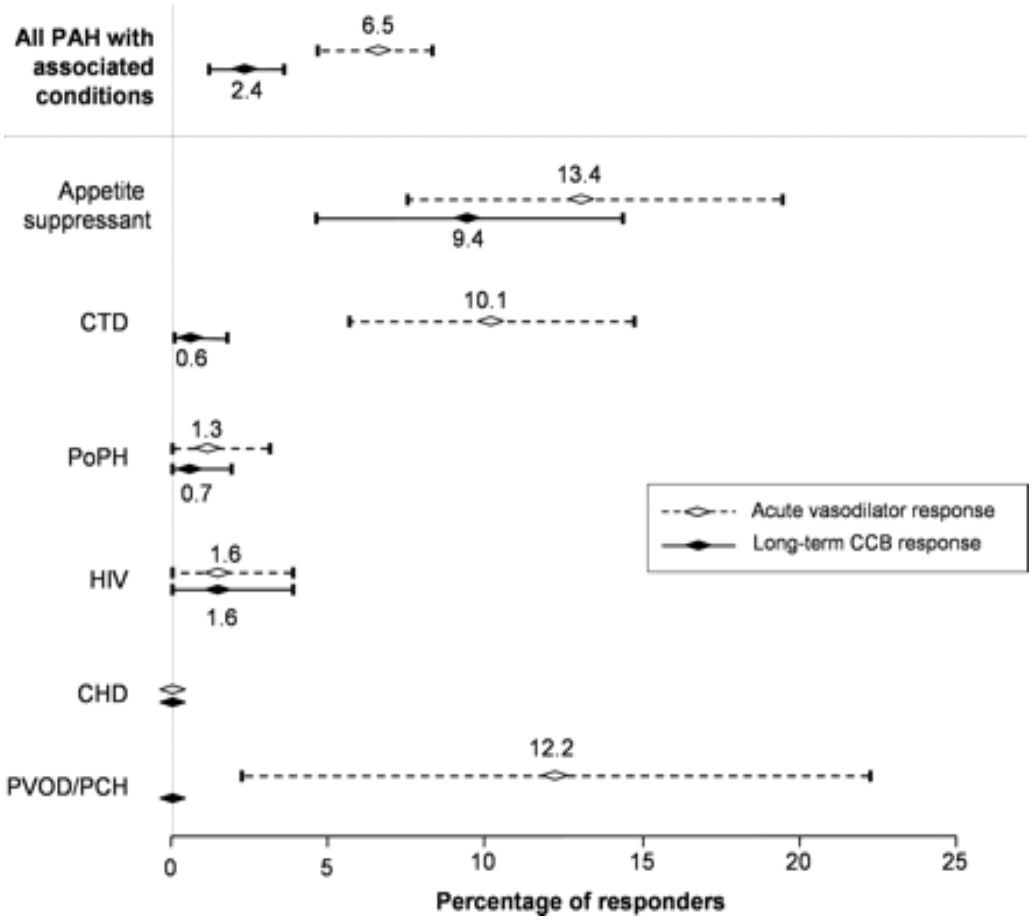
Vasoreactivity Testing

The purpose of vasoreactivity testing in PAH is to identify acute vaso-responders who may be candidates for treatment with high-dose calcium channel blockers (CCBs).

Pulmonary vasoreactivity testing is only recommended in patients with IPAH, HPAH, or DPAH.

A positive acute response is defined as a reduction in mPAP by ≥10 mmHg to reach an absolute value ≤40 mmHg, with increased or unchanged CO



Agent	Route	Dosage
iNO	Inhaled	10-20 ppm
Iloprost	Inhaled	5-10 ug
Epoprostenol	IV	2-12 ng/kg/min

*Adenosine not recommended due to side effect profile

Montani et al EHJ 2010

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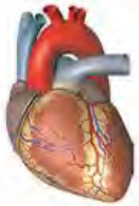
Classification Of Pulmonary Hypertension

Pulmonary arterial hypertension (PAH)

- Idiopathic/heritable
- Associated conditions

PH associated with left heart disease



- IpcPH
- CpcPH

PH associated with lung disease

- Non-severe PH
- Severe PH

PH associated with pulmonary artery obstructions

- CTEPH
- Other pulmonary obstructions

PH with unclear and/or multifactorial mechanisms

- Haematologic disorders
- Systemic disorders

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1. Pulmonary arterial hypertension

- Idiopathic
- Heritable
  - BMPR2
  - ALK1, Endoglin
  - Unknown
- Drug and toxin-induced
- Associated with PAH
  - Connective tissue diseases
  - HIV infection
  - Portal hypertension
  - Congenital heart disease
  - Schistosomiasis
  - Chronic hemolytic anemia
- 1′. Pulmonary Veno-occlusive disease and/or capillary hemangiomatosis
- 1″. Persistent pulmonary hypertension of the newborn (PPHN)

2. Pulmonary hypertension due to left heart disease

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

4. Chronic thromboembolic pulmonary hypertension (CTEPH)

- Complication of pulmonary embolism
- Large or proximal vessel disorders
- High blood pressure, blood clots
- Reduced compliance and luminal narrowing

3. Pulmonary hypertension due to lung diseases and/or hypoxia

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

5. Pulmonary hypertension with unclear and/or multi-factorial mechanisms

- Hematologic disorders (myeloproliferative disorders, splenectomy)
- Systemic disorders (Vasculitis sarcoidosis, pulmonary Langerhans cell, histiocytosis LAM, neurofibromatosis)
- Metabolic disorders (Glycogen storage disease, thyroid disorders)
- Congenital heart disease
- Cancer-related, renal failure on dialysis

Rare but Lethal Forms !!

PVOD

Pulmonary tumor thrombotic microangiopathy

Bisserier et al. Vascular Biology 2020

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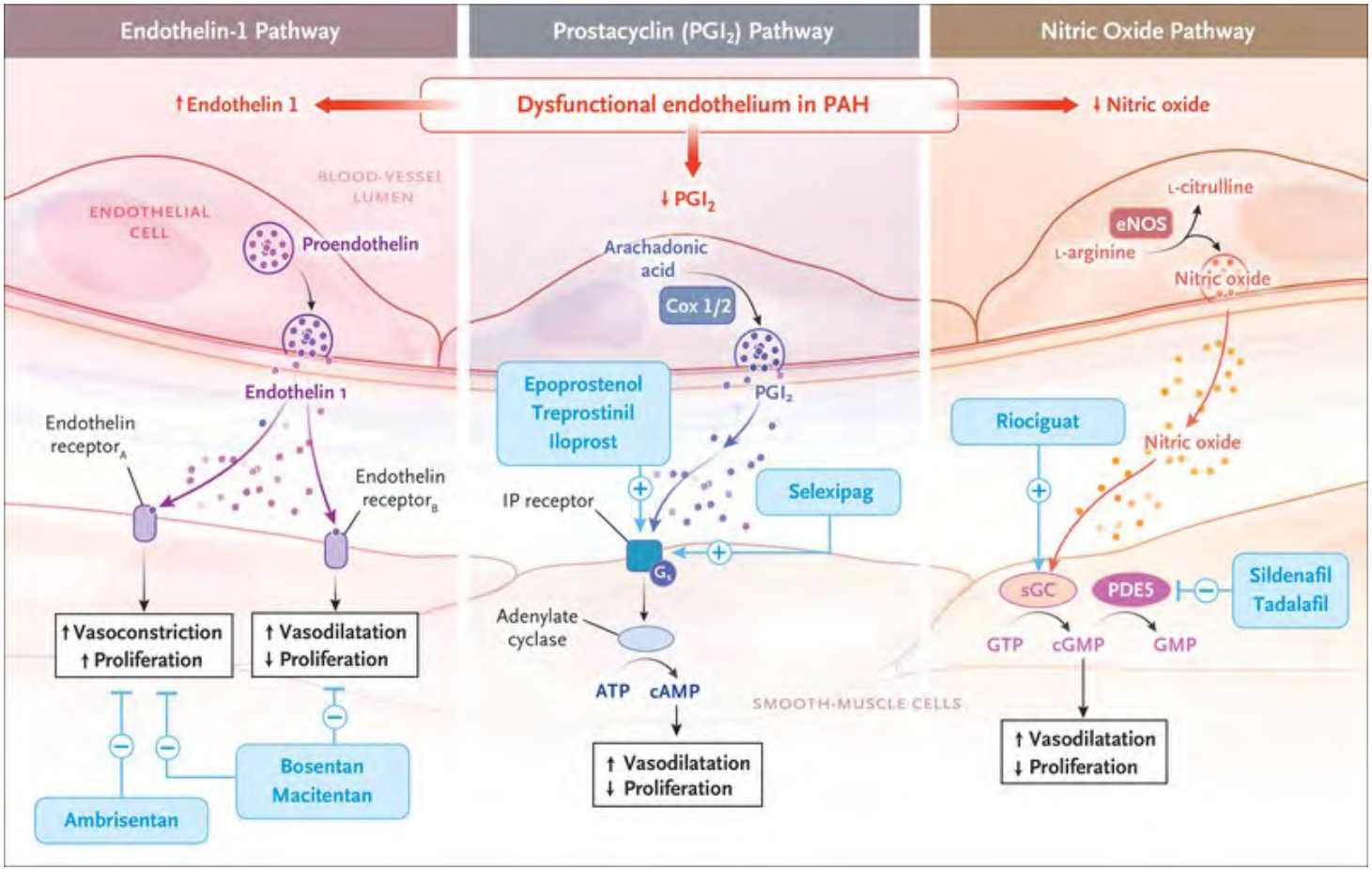
Risk Stratification

Determinants of prognosis (estimated 1-year mortality)	Low risk (<5%)	Intermediate risk (5–20%)	High risk (>20%)
Clinical observations and modifiable variables			
Signs of right HF	Absent	Absent	Present
Progression of symptoms and clinical manifestations	No	Slow	Rapid
Syncope	No	Occasional syncope[a]	Repeated syncope[b]
WHO-FC	I, II	III	IV
6MWD[c]	>440 m	165–440 m	<165 m
CPET	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	Peak VO_2 <11 mL/min/kg (<35% pred.) VE/VCO_2 slope >44
Biomarkers: BNP or NT-proBNP[d]	BNP <50 ng/L NT-proBNP <300 ng/L	BNP 50–800 ng/L NT-proBNP 300–1100 ng/L	BNP >800 ng/L NT-proBNP >1100 ng/L
Echocardiography	RA area <18 cm^2 TAPSE/sPAP >0.32 mm/mmHg No pericardial effusion	RA area 18–26 cm^2 TAPSE/sPAP 0.19–0.32 mm/mmHg Minimal pericardial effusion	RA area >26 cm^2 TAPSE/sPAP <0.19 mm/mmHg Moderate or large pericardial effusion
cMRI[e]	RVEF >54% SVI >40 mL/m^2 RVESVI <42 mL/m^2	RVEF 37–54% SVI 26–40 mL/m^2 RVESVI 42–54 mL/m^2	RVEF <37% SVI <26 mL/m^2 RVESVI >54 mL/m^2
Haemodynamics	RAP <8 mmHg CI ≥2.5 $L/min/m^2$ SVI >38 mL/m^2 SvO_2 >65%	RAP 8–14 mmHg CI 2.0–2.4 $L/min/m^2$ SVI 31–38 mL/m^2 SvO_2 60–65%	RAP >14 mmHg CI <2.0 $L/min/m^2$ SVI <31 mL/m^2 SvO_2 <60%

Pharmacotherapy



Hassoun NEJM 2021

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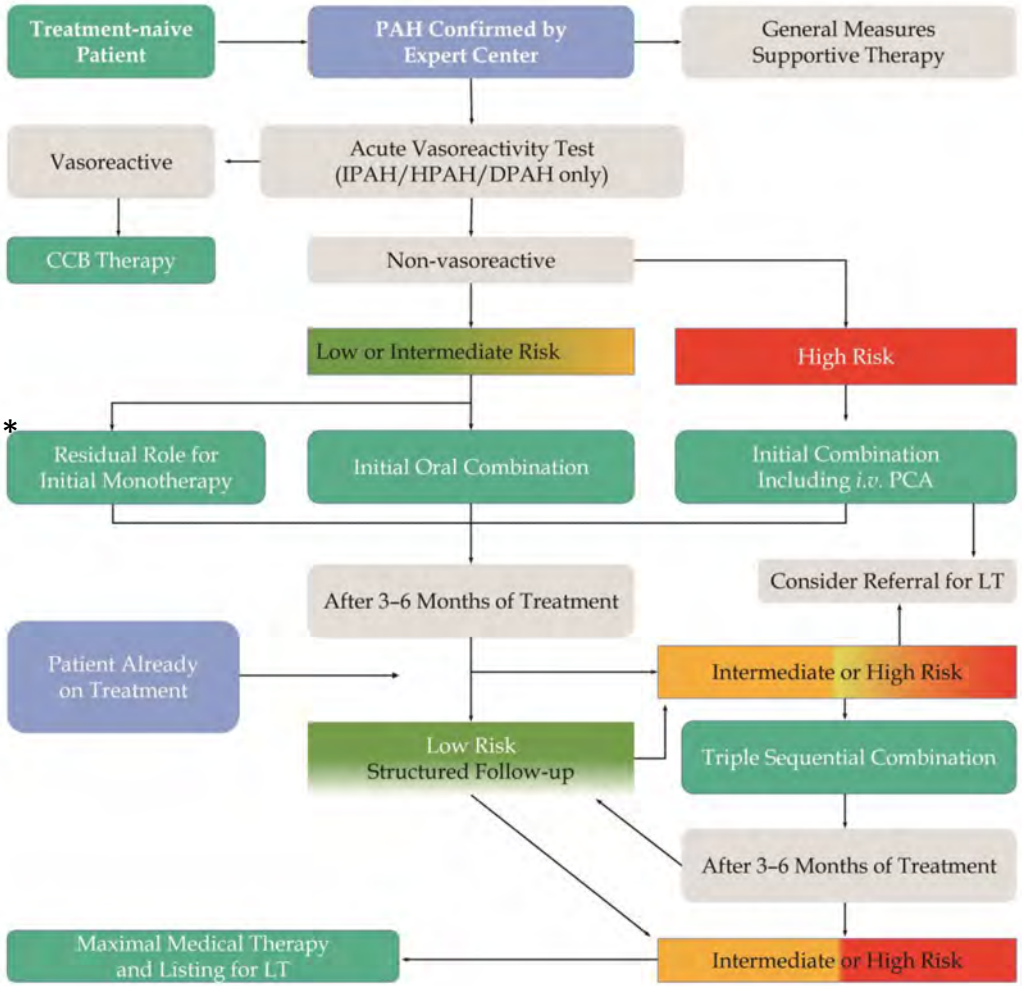
Co-morbid Conditions such as LHD, Lung disease



Jin et al. Pharmaceutics ***2023***

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Looking Beyond the Three Pathways

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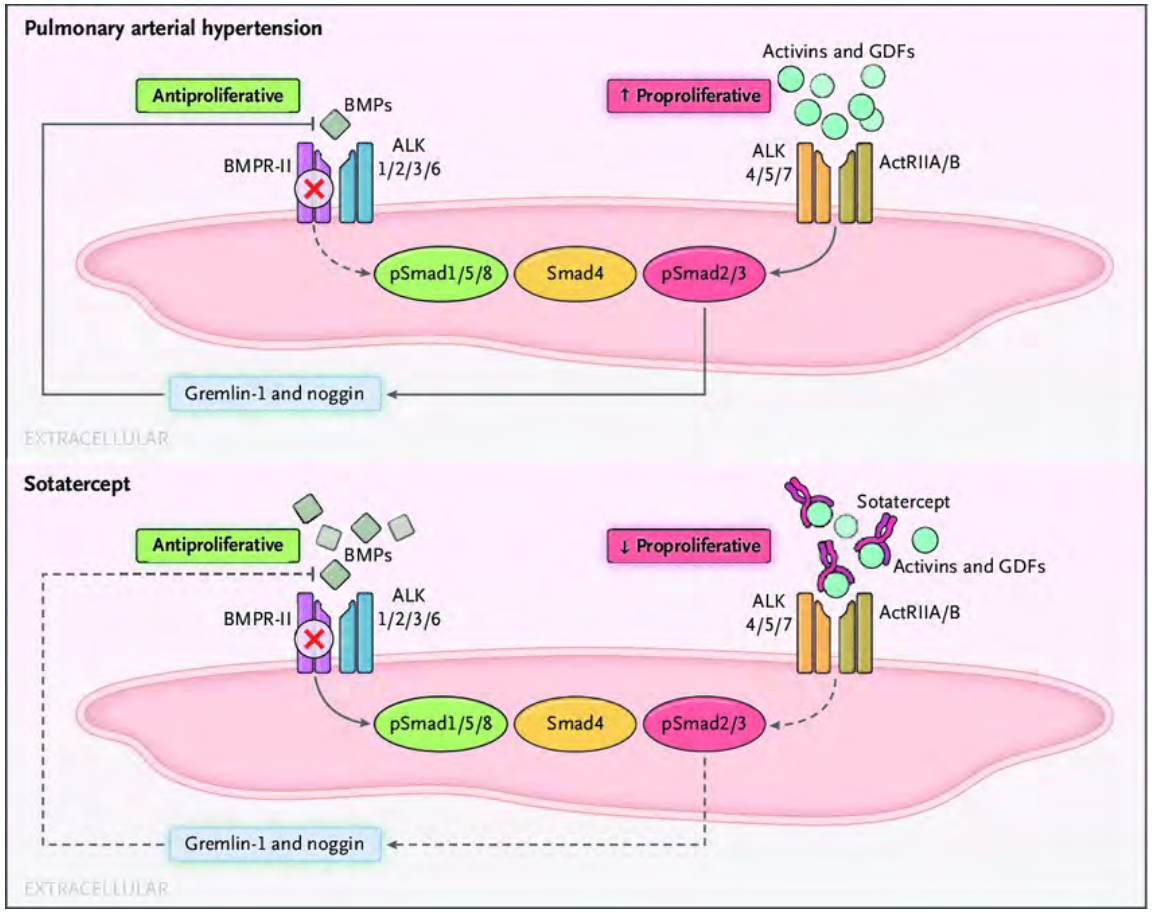
Sotatercept



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RESEARCH SUMMARY

Phase 3 Trial of Sotatercept for Treatment of Pulmonary Arterial Hypertension

Hoeper MM et al. DOI: 10.1056/NEJMoa2213558

CLINICAL PROBLEM

Pulmonary arterial hypertension is characterized by proliferative remodeling of the small pulmonary arteries and progressive luminal narrowing. Morbidity and mortality are high, and new therapeutic approaches are needed. Sotatercept — a first-in-class fusion protein that inhibits activins and growth differentiation factors implicated in pulmonary arterial hypertension — improved pulmonary hemodynamics and exercise capacity in a phase 2 trial, but additional data are needed.

CLINICAL TRIAL

Design: A phase 3, multinational, double-blind, randomized, placebo-controlled trial evaluated the efficacy and safety of sotatercept in adults with symptomatic pulmonary arterial hypertension receiving stable background therapy.

Intervention: 323 patients with pulmonary arterial hypertension (World Health Organization [WHO] functional class II or III) who had been receiving stable background therapy for ≥90 days were assigned to add sotatercept or placebo, administered by subcutaneous injection every 21 days. The primary end point was the change in the 6-minute walk distance at week 24.

RESULTS

Efficacy: The median change in the 6-minute walk distance was significantly greater in the sotatercept group than in the placebo group.

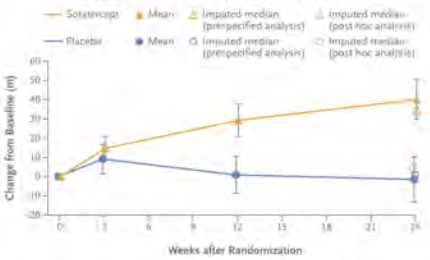
Safety: Sotatercept recipients were more likely than placebo recipients to have an increased hemoglobin level, thrombocytopenia, bleeding events (mostly nonserious epistaxis and gingival bleeding), increased blood pressure, and telangiectasia.

LIMITATIONS AND REMAINING QUESTIONS

- The trial was limited to patients with pulmonary arterial hypertension in WHO functional class II or III.
- Non-White patients were underrepresented, as were those outside North America or Europe.
- The long-term durability of the treatment response is unknown.

Links: Full Article | NEJM Quick Take | Editorial

Change in 6-Minute Walk Distance through Week 24



	Sotatercept	Placebo
Median change in 6-minute walk distance	34.4 m (95% CI, 33.0 to 35.5)	1.0 m (95% CI, −0.3 to 3.5)
Hodges–Lehmann estimate of the difference in change from baseline	40.8 m (95% CI, 37.5 to 54.1); P<0.001	

Adverse Events of Interest or Special Interest

	Sotatercept (N=163)	Placebo (N=160)
	no. of patients (%)	
Increased hemoglobin	9 (5.5)	0
Thrombocytopenia	10 (6.1)	4 (2.5)
Bleeding events	35 (21.5)	20 (12.5)
Increased blood pressure	6 (3.7)	1 (0.6)
Telangiectasia	17 (10.4)	5 (3.1)

CONCLUSIONS

In adults with pulmonary arterial hypertension receiving stable background therapy, the addition of subcutaneous sotatercept every 21 days resulted in a greater improvement in exercise capacity over a period of 24 weeks than placebo.

STELLAR TRIAL

Q21 days dosing

Need CBC monitoring

End Point	Sotatercept (N=163)	Placebo (N=160)
Primary end point		
6-Minute walk distance — m		
Median change estimate (95% CI) from baseline at wk 24†	34.4 (33.0 to 35.5)	1.0 (−0.3 to 3.5)
Hodges–Lehmann location shift from placebo estimate (95% CI)‡	40.8 (27.5 to 54.1)§¶	
Secondary end points		
Multicomponent improvement		
Patients who met all three criteria for 6-min walk distance, NT-proBNP level, and WHO functional class — no./total no.	63/162‖	16/159‖
Percentage of patients (95% CI)	38.9 (31.3 to 46.9)¶**	10.1 (5.9 to 15.8)
Pulmonary vascular resistance — dyn-sec-cm^{-5}		
Median change estimate (95% CI) from baseline at wk 24†	−165.1 (−176.0 to −152.0)	32.8 (26.5 to 40.0)
Hodges–Lehmann location shift from placebo estimate (95% CI)‡	−234.6 (−288.4 to −180.8)§¶	
NT-proBNP — pg/ml		
Median change estimate (95% CI) from baseline at wk 24†	−230.3 (−236.0 to −223.0)	58.6 (46.0 to 67.0)
Hodges–Lehmann location shift from placebo estimate (95% CI)‡	−441.6 (−573.5 to −309.6)§¶	
WHO functional class		
Patients with improvement at wk 24 from baseline — no./total no.	48/163¶**	22/159‖
Percentage of patients (95% CI)	29.4 (22.6 to 37.1)	13.8 (8.9 to 20.2)
Time to first occurrence of death or nonfatal clinical worsening event		
Hazard ratio (95% CI)††	0.16 (0.08 to 0.35)¶‡‡	
French risk score§§		
Patients with a low-risk score with the use of the simplified French model at wk 24 — no./total no.	64/162‖	29/159‖
Percentage of patients (95% CI)	39.5 (31.9 to 47.5)¶**	18.2 (12.6 to 25.1)
PAH-SYMPACT Physical Impacts domain score¶¶		
Median change estimate (95% CI) from baseline at week 24†	−0.13 (−0.15 to 0.00)	0.01 (0.00 to 0.13)
Hodges–Lehmann location shift from placebo estimate (95% CI)‡	−0.26 (−0.49 to −0.04)¶‖	
PAH-SYMPACT Cardiopulmonary Symptoms domain score¶¶		
Median change estimate (95% CI) from baseline at week 24†	−0.12 (−0.14 to −0.08)	−0.01 (−0.03 to 0.00)
Hodges–Lehmann location shift from placebo estimate (95% CI)‡	−0.13 (−0.26 to −0.01)¶‖	
PAH-SYMPACT Cognitive/Emotional Impacts domain score¶¶		
Median change estimate (95% CI) from baseline at week 24†	0.00 (0.00 to 0.00)	0.00 (0.00 to 0.00)
Hodges–Lehmann location shift from placebo estimate (95% CI)‡	−0.16 (−0.40 to 0.08)	

Hoeper et al. NEJM 2023

Our Patient Update

- Patient is now on PDE5i, IV Prostacyclin (developed pulmonary edema with ERA)
- FC is II, Pro BNP 140 pg/ml, PVR has dropped from 15 WU to 6 WU.
- No syncope.
- RHC few days ago- PA 60/28 mm Hg, CO 5.5 L/min, PVR. 6 WU.

Thank You

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